The Evidence-Based Prescription Drug Program (EBRx)

Prior Authorization Criteria

March 1st 2022

EBRx Prior Authorization Call Center

Phone (Toll Free): (866) 564-8258

Please call for most recent information about criteria and Prior Authorization forms

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Abemaciclib (Verzenio®)

50, 100, 150, and 200 mg tablets

EBRx PA Criteria

FDA-approved for:

- in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA approved test.
- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. (NOT COVERED) overall survival benefit has not been demonstrated at this time (see criteria for ribociclib)
- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. SEE CRITERIA
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. (NOT COVERED)

Criteria for new users (early breast cancer—adjuvant therapy)
1. Diagnosis of breast cancer
2. Tumor is hormone receptor positive (e.g. HR+, ER+ and/or PR+)

3. Tumor is HER2/neu negative
4. Tumor Ki-67 score is 20% or greater
5. Tumor is node positive
6. Abemaciclib will be used in combination with endocrine therapy (e.g. tamoxifen, anastrozole, letrozole).
If all criteria met, approve x 1 year. PA may be renewed 1 time for 1 year for maximum duration of treatment of 2 years.
Note: Dose: 150 mg PO BID Compared to placebo, abemaciclib improved invasive disease free survival (iDFS). The 36-mo iDFS was 86% in the abemaciclib group and 79% in the control arm (HR 0.626 95% CI 0.488, 0.803). ESMO clinical benefit scoring: A (highest rating). Reference Johnston SRD et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol. 2020 Dec 1;38(34):3987-3998. doi: 10.1200/JCO.20.02514. Epub 2020 Sep 20. PMID: 32954927; PMCID: PMC7768339.

Criteria for new users (advanced/metastatic disease)
1. Diagnosis of advanced or metastatic breast cancer
2. Tumor is hormone receptor positive (e.g. HR+, ER+ and/or PR+)
3. Tumor is HER2 negative
4. Progression of disease on or within 12 months of completion of adjuvant endocrine therapy OR progression of disease while receiving endocrine therapy for advanced/metastatic breast cancer. (endocrine therapy = tamoxifen, anastrozole, letrozole, or exemestane)
5. No prior treatment with fulvestrant or CDK 4/6 inhibitors for advanced disease.
6. Abemaciclib will be used in combination with fulvestrant.
If all criteria met, approve x 1 year.
Note: Dose is 150 mg bid EBRx covers for this patient population described in criteria due to overall survival benefit

demonstrated in the MONARCH-2 trial. This trial enrolled women with advanced/metastatic HR+ and HER2- breast cancer. Patient were given either abemaciclib+fulvestrant or placebo+fulvestrant. The overall survival benefit of abemaciclib was demonstrated in the overall population (median OS 46.7 mo in the abemaciclib group vs 37.4 mo in the placebo group).

Reference:

Sledge GW Jr et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA Oncol. 2019 Sep 29. doi: 10.1001/jamaoncol.2019.4782. [Epub ahead of print] PMID 31563959 NCT02107703

Quantity Limits:

50, 100, and 150 mg tablets: #60 tabs/30 days

200 mg tablets: used for monotherapy dosing which is not covered.

Revision History:

Date	What changed	Pharmacist's initials
10/28/19	Criteria written.	SK
7/7/2020	Criteria reviewed. No change.	SK
1/13/2021	Changed criteria #5 from No prior treatment with fulvestrant, chemotherapy, everolimus, or CDK 4/6 inhibitors TO No prior treatment with fulvestrant, **cytotoxic** chemotherapy **(such as doxorubicin, cyclophophosphamide, or taxane)**, everolimus, or CDK 4/6 inhibitors **for advanced disease**.	SK
9/28/2021	Criteria reviewed. No change	SK
12/16/2021	Added criteria for new adjuvant breast cancer indication	SK
1/26/2022	In **Criteria for new users (advanced/metastatic disease),** removed "everolimus, cytotoxic chemotherapy (such as doxorubicin, cyclophophosphamide, or taxane)." Patients are unlikely to have received these therapies previously for advanced disease.	SK

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Abiraterone (Zytiga®)

250 mg tablets

EBRx PA Criteria

Note: 500 mg tablet is not covered. Prefer 250 mg tablet.

Note: Yonsa is not covered

FDA approved indication:

- in combination with prednisone for the treatment of patients with metastatic castration-*resistant* prostate cancer (mCRPC)
- in combination with prednisone for the treatment of patients with metastatic high-risk castration-*sensitive* prostate cancer (m-hr-CSPC)

Note: Castration-*resistant* prostate cancer (CRPC) is defined as progression of disease (rising PSA or increase in tumor size on imaging) when testosterone level is <50 ng/dl (due to LHRH agonist/antagonist OR orchiectomy).

Criteria for new users
1. Diagnosis of **metastatic** prostate cancer.
2. LHRH agonist/antagonist will be given with abiraterone OR patient has undergone orchiectomy
3. Abiraterone acetate will be given with prednisone
4. If disease is castration-sensitive, patient has not received prior docetaxel.
If above criteria are fulfilled, approve for 12 months Note: Do not approve for NON-metastatic prostate cancer.
QL: 250 mg tablets: 120 tablets/30d. [250 mg tablet is generic] **Note: *500mg tablet is not generic and is not covered** **Yonsa is a micronized formulation of abiraterone and remains brand only and is not covered by EBRx**

Evidence:

Metastatic castration-***resistant*** prostate cancer:

-Abiraterone improves overall survival compared with prednisone alone before and after docetaxel.[1,2]

Metastatic castration-***sensitive*** prostate cancer:

-Abiraterone improves overall survival compared to placebo in high-risk metastatic disease per LATITUDE study. Abiraterone additionally was shown to prolong time to pain progression and time to symptomatic skeletal events.[3,4]

-Abiraterone also improves overall survival in patients with locally advanced AND metastatic disease (regardless of risk factors) per the STAMPEDE trial. However, the benefit was driven by metastatic subgroup.[5]

-Two meta-analyses have confirmed the benefit of abiraterone in patients with metastatic disease.[6,7]

Zytiga dose: 1000mg (#4 of the 250 mg tablets) daily on an empty stomach. Concomitant prednisone is required to prevent mineralocorticoid excess and adrenal insufficiency.

References:

1. De Bono JS et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011 May 26;364(21):1995-2005. PMID21612468 NCT00638690
2. Ryan CJ et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015 Feb;16(2):152-60. PMID 25601341 NCT00887198
3. Fizazi K et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med. 2017 Jul 27;377(4):352-360. PMID 28578607
4. Fizizi K et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol. 2019 Apr 12. PMID 30987939
5. James ND et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017 Jul 27;377(4):338-351. PMID 28578639 NCT00268479
6. Rydzewska LHM et al. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: A systematic review and meta-analysis. Eur J Cancer. 2017 Oct;84:88-101. PMID 28800492
7. Tan PS et al. Addition of abiraterone, docetaxel, bisphosphonate, celecoxib or combinations to androgen-deprivation therapy (ADT) for metastatic hormone-sensitive prostate cancer (mHSPC): a network meta-analysis. Prostate Cancer Prostatic Dis. 2018 Nov;21(4):516-523. PMID 29875432

Date	Notes	Pharmacist Initials
5/26/11	Criteria were written	JJ
5/14/14	Diagnosis was changed to require “castration-resistant”; contraindication to docetaxel is an acceptable way to answer number 2, and ECOG performance status was added. No 3 or 4 should gain access, as it has not been studied.	JJ
7/7/17	I added reference 3. I also added the requirement for concomitant prednisone 5mg BID as was done in the trials. We recognize abiraterone has been shown effective in 1st line prostate CA use.	JJ

<table>
<tr><td></td><td>However, abiraterone has not yet been compared to docetaxel (another NCCN-Category 1), the previous and current drug for 1st line use.</td><td></td></tr>
<tr><td>7/10/17</td><td>I added reference 4 regarding the need for prednisone. Since some types of patients could be harmed by prednisone (or equivalent corticosteroid) and since the OS outcomes for prednisone and non-prednisone users were not affected, I removed the requirement for corticosteroids for patients seeking to use abiraterone for prostate CA.</td><td>JJ</td></tr>
<tr><td>7/17/17</td><td>I added reference 5, which shows docetaxel provides an OS in 1st line therapy after hormone therapy. Abiraterone should be compared to docetaxel in 1st line therapy after hormone therapy.</td><td>JJ</td></tr>
<tr><td>10/24/17</td><td>FOR mCSPC, I added back the requirement for docetaxel after reviewing the data (ref 6). There appears to be no significant difference between abiraterone and docetaxel except cost.

The pooled hazard ratio (HR) for OS was 0.75 (95% confidence interval [CI]: 0.63–0.91, I 2 = 51%, 3 trials, 2951 patients) for Doce-ADT versus ADT-alone,

HR=0.63 (95% CI: 0.55–0.72, I 2 = 0%, 2 trials, 3116 patients) for Abi-ADT versus ADT-alone.

The indirect comparison of Abi-ADT to Doce-ADT demonstrated no statistically significant difference in OS between these approaches (HR: 0.84, 95% CI: 0.67– 1.06).

Supplementary Table 2: Summary of Grade 3-5 Adverse Events among included trials in the network meta-analysis
<table>
<tr><td></td><td>Grade 3-5 AE</td></tr>
<tr><td>Docetaxel Trils</td><td></td></tr>
<tr><td>STAMPEDE [16]</td><td></td></tr>
<tr><td>ADT</td><td>399/1228 (32%)</td></tr>
<tr><td>ADT + ZA</td><td>197/608 (32%)</td></tr>
<tr><td>ADT + Docetaxel</td><td>288/550 (52%)</td></tr>
<tr><td>ADT + ZA + Docetaxel</td><td>269/516 (52%)</td></tr>
<tr><td>CHAARTED [15]</td><td></td></tr>
<tr><td>ADT</td><td>Not reported</td></tr>
</table>
</td><td>JJ</td></tr>
</table>

	<table><tr><td>ADT + Docetaxel</td><td>115/390 (29%)</td></tr><tr><td>*GETUG* [14]</td><td>Not reported</td></tr><tr><td>Abiraterone Trials</td><td></td></tr><tr><td>*STAMPEDE* [17]</td><td></td></tr><tr><td>ADT</td><td>315/960 (33%)</td></tr><tr><td>ADT + Abiraterone</td><td>443/948 (47%)</td></tr><tr><td>*LATITUDE* [18]</td><td></td></tr><tr><td>ADT</td><td>311/602 (52%)</td></tr><tr><td>ADT + Abiraterone</td><td>402/597 (67%)</td></tr><tr><td colspan="2">AE: adverse event; ADT: androgen deprivation therapy; ZA: zoledronic acid.</td></tr></table> Although ref 3 shows abiraterone +ADT improves OS vs ADT alone in men with newly diagnosed and metastatic, node+ or high-risk locally advanced, or disease that was previously treated w/ radical surgery or radiotherapy and was now relapsing, NCCN for Prostate CA 2.2017 shows for systemic therapy for progressive castration-naïve disease to give ADT + docetaxel w/ or w/o prednisone.	
07/25/2018	Added Yonsa to PA criteria based on being interchangeable with Zytiga in its ability to reduce testosterone (STARR trial for therapeutic equivalence: reference 7-also added); No HTH trials of Zytiga vs Yonsa for OS in mCRPC.	ALM
5/20/19	Full criteria reviewed. Adjusted criteria to allow for use for castration sensitive as well as resistant disease regardless of docetaxel status due to consistent overall survival improvement compared with ADT alone.	Sk
10/28/19	Criteria reviewed. Added that no prior docetaxel should have been used if request is for use in the castration sensitive treatment setting.	SK
7/7/2020	Criteria reviewed. No change. Added notes that 250 mg tablet is preferred over 500 mg tablet.	SK
9/28/2021	Criteria reviewed. No change. Watch for STAMPEDE data in non metastatic PC. Adjusted wording re: 500 mg tab—it is now generic but cost remains high.	SK

Acalabrutinib (Calquence)

100 mg capsules

EBRx PA Criteria

is FDA-approved for adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy (accelerated approval)
- Chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) APPROVED FOR RELAPSED/REFRACTORY DISEASE ONLY
    - The benefit of acalabrutinib in the first line setting is limited to progression free survival only.

Sharman JP et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020 Apr 18;395(10232):1278-1291. doi: 10.1016/S0140-6736(20)30262-2. Erratum in: Lancet. 2020 May 30;395(10238):1694. PMID: 32305093; PMCID: PMC8151619.

Criteria for new users
1. Diagnosis of mantle cell lymphoma or chronic lymphocytic leukemia
2. Disease has been treated with at least one prior therapy with progression or relapsed of disease on or after that therapy
3. No prior BTK inhibitor (ibrutinib, zanubrutinib, acalabrutinib)
If all criteria met, approve for 12 months.

Mantle Cell Lymphoma References:

1. Wang M et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet. 2018 Feb 17;391(10121):659-667. PMID: 29241979; PMCID: PMC7864374.
2. Wang M et al. Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Long-Term Efficacy and Safety Results from a Phase 2 Study. https://ash.confex.com/ash/2020/webprogram/Paper134824.html. Accessed 10/26/2021.

Chronic Lymphocytic Lymphoma References:

1. Ghia P et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. J Clin Oncol. 2020 Sep 1;38(25):2849-2861. doi: 10.1200/JCO.19.03355. Epub 2020 May 27. PMID: 32459600.

2. Byrd JC et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. J Clin Oncol. 2021 Jul 26:JCO2101210. doi: 10.1200/JCO.21.01210. Epub ahead of print. PMID: 34310172.

Quantity Limits: 2/1

Revision History:

Date	What changed	Pharmacist's initials
11/18/2021	Criteria written	SK

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Alectinib (Alecensa®)

150mg capsules

EBRx PA Criteria

FDA approved indication:

Non-small cell lung cancer, metastatic: Treatment of anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) as detected by an approved test.

Dosing: 600mg PO BID

Non-small cell lung cancer (NSCLC)
1. Diagnosis of advanced or metastatic non-small cell lung cancer
2. Must be ALK-positive as detected by an FDA approved test
3. Performance status (ECOG) 0-2
4. No prior ALK inhibitor (e.g. crizotinib, ceritinib, lorlatinib)
5. Alectinib will be used as single agent.
If criteria met, approve for 6 months
Note: Dose is 600mg BID (supplied in 150mg caps); treat to progression or unacceptable toxicity.

QL: 240/30

References:

1. Clinicaltrials.gov NCT02075840, NCT02604342
   (Data in Shaw, Alice T., et al. "Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial." *The lancet oncology*18.12 (2017): 1590-1599.)
2. LexiComp: alectinib. Accessed 12/10/2018.
3. NCCN.org. NSCLC. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf Accessed 1/28/19.

Date	Notes	Pharmacist's initials
12/19/2018	I created criteria for alectinib in NSCLC.	ALM
1/28/19	I added the NCCN.org reference	JJ
7/18/19	Criteria reviewed. Added that patient should not have prior ALK inhibitor and that alectinib should be used as single agent	SK
3/29/2021	Criteria reviewed. No change.	SK

CONFIDENTIAL

Alemtuzumab (Lemtrada®)

Vial 12mg/1.2mL, 1.2mL

EBRx Medical PA Criteria

FDA-approved indication: relapsing forms of multiple sclerosis (RRMS)

Alemtuzumab is marketed as Lemtrada (12mg/1.2mL, 1.2mL). Campath (30mg/mL, 1mL) was once FDA-approved and marketed as Campath, indicated for B-cell chronic lymphocytic leukemia.

Lemtrada is approved for relapsing forms of MS, generally who have had an inadequate response to 2 or more MS meds. It binds to CD52, a nonmodulating antigen present on the surface of B and T lymphocytes, monocytes, macrophages, NK cells, and some granulocytes. After binding, an antibody-dependent lysis of malignant cells occurs.

Criteria
1. The patient must have a diagnosis of relapsing multiple sclerosis, defined as at least two relapses in the previous 2 years and at least one in the previous year.
2. At first request, EDSS (see bottom of page) should be 0-5.
3. At first request, disease duration should be < 10 y.
4. The patient should be free of any thyroid disease.
5. The patient should have normal liver transaminases prior to and during administration of alemtuzumab.
6. The patient has discussed the risks with their prescriber for the potential rare but serious cases of ischemic or hemorrhagic stroke and cervicocephalic arterial dissection associated with alemtuzumab, immune activation up to 4 years after alemtuzumab possibly resulting in a diagnosis of hemophagocytic lymphohistiocytosis.

Dosing is IV 12mg daily for 5 consecutive days (total 60mg), then 12 months later: 12mg daily for 3 days (total 36mg). Most patients (73-78%) do not require subsequent MS drug therapy.[2, figure 1]

Quantity Limits: 5 doses/365 days for the first year, 3 doses/365 subsequent years after the 1st year.

References:

1. Coles, AJ, et al. Alemtuzumab for patients with relapsing MS after disease-modifying therapy: a RC phase 3 trial. Lancet. 2012;380:1829-1839.

2. Coles, AJ, et al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 Clinical Trial. Neurology. 2012;78:1069-78.
3. EDSS. http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/10-2-3-29-EDSS_Form.pdf . Accessed 2/5/15.
4. Cohen JA, Coles AJ, et al. Alemtuzumab versus interferon beta 1a as first-line treatment ofr patients with RRMS; A RCT phase 3. Lancet. 2012;380:1819-28.
5. Medscape on new risk with alemtuzumab. https://www.medscape.com/viewarticle/911741?nlid=129300_4822&src=WNL_mdplsfeat_190416_mscpedit_phar&uac=126299PK&spon=30&impID=1938647&faf=1

Date	Notes	Pharmacist's initials
2/5/15	I wrote the criteria.	JJ
3-10-15	Discussed at DCWG. QL of 5doses 1st year and 3 doses each subsequent year.	JJ
4/16/19	In 2018, the FDA warned of rare but serious cases of ischemic and hemorrhagic stroke and cervicocephalic arterial dissection associated with alemtuzumab. The European Medicines Agency (EMA) advises to initiate alemtuzumab only in adults with RRMS that is highly active despite treatment with at least 2 other disease-modifying therapies or in those who cannot take other therapies. Also to monitor ECG and vitals during the infusions, LFTs prior to treatment. A pathological immune activation and diagnosis of hemophagocytic lymphohistiocytosis could occur up to 4 y after the start of therapy. Pts being treated w/ alemtuzumab who are benefiting may continue treatment in consultation with their physician.	JJ
7/13/2020	I reviewed the criteria. No changes	JJ

EDSS scale for MS:

0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).

1.0 - No disability, minimal signs in one FS* (i.e., grade 1).

1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).

2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).

2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).

3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.

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3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).

4.0 - Fully ambulatory w/o aid, self-sufficient, up and about some 12 h/d despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk w/o aid or rest some 500 m.

4.5 - Fully ambulatory w/o aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk w/o aid or rest some 300 m.

5.0 - Ambulatory w/o aid or rest for about 200 m; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).

5.5 - Ambulatory w/o aid for about 100 m; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).

6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+). ❑ 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).

7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).

8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).

8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).

9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).

9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).

10.0 - Death due to MS.

*Excludes cerebral function grade 1.

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Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Sources:

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.

Haber A, LaRocca NG. eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society; 1985.

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Alglucosidase Alfa (Lumizyme®)

Vial 50mg

EBRx PA Criteria

FDA-approved indication: Pompe disease (acid alpha-glucosidase [GAA] deficiency).

Criteria for new users
1. The patient must have the diagnosis of Pompe disease.

Note: If yes, approve for 1 year.

References:

1. Amalfitano A, Bengur AR, and Morse RP, “Recombinant Human Acid Alpha-Glucosidase Enzyme Therapy for Infantile Glycogen Disease Type II: Results of a Phase I/II Clinical Trial,” *Genet Med*, 2001, 3(2):132-8.
2. Klinge L, Straub V, Neudorf U, et al, “Enzyme Replacement Therapy in Classical Infantile Pompe Disease: Results of a Ten-Month Follow-up Study,” *Neuropediatrics*, 2005, 36(1):6-11.
3. Klinge L, Straub V, Neudorf U, et al, “Safety and Efficacy of Recombinant Acid Alpha-Glucosidase (rhGAA) in Patients With Classical Infantile Pompe Disease: Results of a Phase II Clinical Trial,” *Neuromuscular Disorders*, 2005, 15(1):24-31.
4. Van der Ploeg AT, Clemens PR, Corzo D, et al, “A Randomized Study of Alglucosidase Alfa in Late-Onset Pompe’s Disease, *N Engl J Med*, 2010, 362(15):1396-406.
5. Kishnani PS, Corzo D, Nicolino M, et al, "Recombinant Human Acid [Alpha]-Glucosidase: Major Clinical Benefits in Infantile-Onset Pompe Disease," *Neurology*, 2007, 68(2):99-109.
6. Kishnani PS, Nicolino M, Voit T, et al, "Chinese Hamster Ovary Cell-Derived Recombinant Human Acid Alpha-Glucosidase in Infantile-Onset Pompe Disease," *J Pediatr*, 2006, 149(1):89-97.
7. Schoser B, Hill V, and Raben N, "Therapeutic Approaches in Glycogen Storage Disease Type II/Pompe Disease," *Neurotherapeutics*, 2008, 5(4):569-78.
8. UpToDate. Pompe Disease. Accessed 9/24/19.

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Date	Notes	Pharmacist's initials
8/7/06	T2PA approved & criteria written.	JJ
10/19/11	Lumizyme added. Someone (not I) inserted references and age specifications.	JJ
5/18/12	Revision hx table added	JJ
9/24/19	I revised the criteria and removed Myozyme since it is no longer available. Added reference 7.	JJ

CONFIDENTIAL

Alirocumab (Praluent™)

Vial 75 and 150 mg/mL

EBRx PA Criteria

FDA-approved: as adjunct to diet and maximally tolerated statin therapy for tx of adults requiring additional lowering of LDL-C and with either

1. Heterozygous familial hypercholesterolemia (heFH) with or without established CHD or CHD risk equivalents who are not adequately controlled with a maximally tolerated stable daily dose of statin**
2. Clinical ASCVD, who require additional lowering of LDL-C

Criteria for new users
1. The patient must be age ≥ 40 years AND
EITHER: 2. Hospitalized for ACS with MI or unstable angina within the last 12 months OR have the diagnosis of heFH made by either genotyping or by clinical criteria$^{\phi}$
AND
3. The patient must be on maximally tolerated dose of high intensity statin (**atorvastatin 40-80 mg or rosuvastatin 20-40 mg or simvastatin 80mg if already on this for >1y) for 3 months OR is statin intolerant based off the below supplement on statin intolerance AND
4. The patient must have LDL ≥ 100 mg/dL despite the patient being on high intensity statin or intolerant to statin therapy
If the patient meets criteria 1-4 above, approve alirocumab 75 mg q2wks for 1 year. • Provider may request alirocumab 150 mg q2wks. • Approval of alirocumab 150 mg q2wks is contingent on the patient having LDL ≥ 100 mg/dL despite alirocumab 75 mg q2wks.
Continuation Criteria
1. Approve alirocumab 75-150 mg q2weeks for 1 year if the patient has remained on high intensity statin during alirocumab treatment or has clinical documentation of intolerance based off supplement below.
Dosing: 75 mg q2wks or 300 mg q4wks. May increase to max of 150 mg q2wks. (q2wks were used in clinical trials)
$^{\phi}$HeFH clinical criteria may be based on either the WHO criteria/dutch Lipid Clinical Network criteria with a score of >8 points or the Simon Broome register diagnostic criteria with a criterion for definite FH. (See Appendices A &/or B)
CHD risk equivalents **include 4 or more of the following criteria**: 1) Documented peripheral arterial disease a) Current intermittent claudication (muscle discomfort in the lower limb that is both reproducible and produced by exercise and relieved by rest within 10 minutes) of presumed atherosclerotic origin TOGETHER WITH ankle-brachial index ≤ 0.90 in either leg at rest, OR b) History of intermittent claudication (muscle discomfort in the lower limb that is both reproducible and produced by exercise and relieved by rest within 10 minutes) TOGETHER

WITH endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease OR
   c) History of critical limb ischemia TOGETHER WITH thrombolysis, endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease.
2) Documented previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. CT or MRI must have ruled out hemorrhage and non-ischemic neurological disease.
3) Documented moderate chronic kidney disease, estimated GFR >30mL/min/1.73 m^2 or <60, for at least 3 months
4) Known history of diabetes mellitus AND 2 or more additional risk factors
   a) History of hypertension (established on antihypertensive medication)
   b) Documented history of ankle-brachial index ≤0.90
   c) Documented history of microalbuminuria or macroalbuminuria OR current dipstick urinalysis with >2+ protein
   d) Documented history of pre-proliferative or proliferative retinopathy or laser treatment for retinopathy
   e) Known family history of premature CHD (CHD in father or brother before age 55y or in mother or sister before age 65y)

Definition of Statin Intolerance

4/2/18

- Patients are defined as having a true intolerance or contraindication to statins if they **fulfill criteria 1, 2a, OR all of criteria 3a-d.**
- **Criteria 2b-c are guidelines** to assess transient elevations in LFT and their relation to statin use. **Transient elevations in LFTs accompanied with statin use are NON COVERED indications to define statin intolerance or contraindication to therapy.**

1) The patient has acute liver failure or decompensated cirrhosis.
2) The National Lipid Association Statin Safety Task Force recommends the following:
   a. If there is a high clinical suspicion that there is statin-induced rhabdomyolysis (rhabdo), discontinue statin therapy (**diagnosed with elevated CK,** not elevated ALT/AST). This is an acute issue and wouldn't be of high suspicion on a regular outpatient basis. If the patient does have clinically diagnosed statin-induced rhabdomyolysis, **this would be a permanent contraindication to statins.**
   b. If a patient has ALT/AST < 3 x ULN and newly diagnosed acute elevation in bilirubin, the statin should be discontinued **temporarily** to identify underlying etiology.
      i. If no acute elevation in bilirubin, the statin should be continued.
   c. In patients with ALT/AST > 3 x ULN, the statin should be d/c **temporarily** to identify underlying etiology. In both instances based on ALT/AST elevation, the statin is discontinued temporarily to identify if it is a contributing factor.
      i. It is encouraged to re-evaluate statin therapy after underlying cause of AST/ALT elevation is identified.
      ii. Bottom Line – It is encouraged for patients to continue on statin therapy for ASCVD benefit even in instances of ALT/AST elevation. Discontinuation should be done only on an acute basis to identify

underlying etiology. In patients with statin related myopathy, several algorithms exist for management in order to get a patient on a tolerated agent.

3) According to UpToDate, pravastatin, fluvastatin XL, and pitavastatin have the lowest incidence of myalgias among statins. So, for patients to claim intolerance to statins due to myalgias there should be:
    a. ≥1 fill for rosuvastatin, atorvastatin, or simva 80mg (if started over 1 year ago) AND
    b. ≥1 fill for 2 out of 3 of either pravastatin, fluvastatin XL, and pitavastatin AND
    c. Clinical documentation of myalgias in chart notes AND
    d. If clinical documentation of myalgias using treatment algorithm in 3a-c, there should also be > 3-month trial of ezetimibe 10 mg daily with documented, sustained LDL-C > 100 mg/dL.

Revision History:

Date	What changed	Pharmacist's initials
4/5/18	I wrote the criteria	JK
4/17/18	I determined 3 months of high potency statin use was sufficient since Lexicomp says a fasting lipid profile within 4 and 12 weeks after initiation or dose adjustment and every 3-12 months thereafter. The clinical trial recruited those on high potency statins for 4-16 weeks.	JJ
5/14/18	I added heFH as a criteria and as defined by the Odyssey protocol, however the CV event reduction publication still has not been published and we are going on ICER's data; in addition, the current online PI does not reflect Praluent causes fewer events. I also added simva 80mg as a high potency statin group that could have been tried. I did not reduce the eligible age to 18 instead of 40 per the Odyssey protocol because the baseline characteristics showed the mean age to be 60 with a SD of 10y, so 18 year old patients, although invited, are not representative of the population that produced the Odyssey results.	JJ

Ref:

1. Farnier, Michel, et al. "Long-term treatment adherence to the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab in 6 ODYSSEY Phase III clinical studies with treatment duration of 1 to 2 years." *Journal of clinical lipidology* 11.4 (2017): 986-997.
2. ICER Prelimiinary New Evidence Update. Alirocumab for High Cholesterol. March 2018
3. Jacobson, Terry A. "NLA task force on statin safety-2014 update." *Journal of clinical lipidology* 8.3 (2014): S1-S4.
4. Stone, Neil J., et al. "2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of

Cardiology/American Heart Association Task Force on Practice Guidelines." *Journal of the American College of Cardiology* 63.25 Part B (2014): 2889-2934.
5. McKenney, J. M., et al. "National Lipid Association Statin Safety Assessment Task Force. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force." *Am J Cardiol* 97.8A (2006): 89C-94C.
6. Odyssey Protocol. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1501031/suppl_file/nejmoa1501031_protocol.pdf Accessed 5/14/18.

APPENDIX A WHO Criteria (Dutch Lipid Network clinical criteria) for diagnosis of HeFH

Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia	
Family history	
a. First degree relative with known premature (men <55y, women <60y coronary and vascular disease) OR b. First degree relative with known LDL-C >95th percentile for age and sex	1
AND/OR a. First degree relative with tendon xanthomata and/or arcus cornealis b. Children below 18y with LDL-C >95th percentile for age and sex	2
Clinical history	
a. Patient has premature (men <55y, women <60y) coronary artery disease	2
b. Patient has premature (men <55y, women <60y) cerebral or peripheral vascular disease	1
Physical examination	
a. Tendon xanthomata	6
b. Arcus cornealis below the age of 45 y	4
Lab analysis	
a. LDL >330 mg/dL	8
b. LDL 250-329 mg/dL	5
c. LDL 190-249 mg/dL	3
d. LDL 155-189	1

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DNA-analysis	
a. Functional mutation LDL receptor gene present	8
Diagnosis of heFH is: Certain when >8 points Probable when 6-8 points Possible when 3-5 points	

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APPENDIX B Simon Broome Register Diagnostic Criteria for Heterozygous Familial Hypercholesterolemia

Definite familial hypercholesterolemia is defined as:

- Total-C >260 mg/dL or LDL cholesterol above 155 mg/dL in a child 290 mg/dL or LDL cholesterol above 190 mg/dL in an adult. (Levels either pre-treatment or highest on treatment)

PLUS

- Tendon xanthomas in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt)

OR

- DNA-based evidence of an LDL receptor mutation or familial defective apo B-100

Possible familial hypercholesterolemia is defined as:

- Total-C >260 mg/dL)or LDL cholesterol above 155 mg/dL in a child 290 mg/dL or LDL cholesterol above 190 mg/dL in an adult. (Levels either pre-treatment or highest on treatment)

And at least one of the following:

- Family history of myocardial infarction below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative.
- Family history of raised cholesterols >290 mg/dL in adult 1st or 2nd degree relative or >260 mg/dL in child or sibling under 16 years of age.

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Alosetron (Lotronex®)

0.5, 1 mg tablets [available generically]

EBRx PA Criteria

FDA-approved indication: IBS-D in women with symptoms for 6m or longer, have had anatomic or biochemical abnormalities of the GI tract excluded, and who have not responded adequately to conventional therapy.

Criteria for new users
1. The patient must have the diagnosis of irritable bowel syndrome with severe diarrhea and have not responded adequately to conventional therapy.
2. Symptoms must have existed for 6 months prior to initial use.
3. There is evidence of having tried conventional therapy as 1st line use (dicyclomine, amitriptyline, hyoscyamine, desipramine). If not, there should be some mention of OTC loperamide being used in the chart notes. Also, second line drugs should have also failed (bile acid sequestrants)
4. No recent history of constipation, ischemic colitis, intestinal obstruction, stricture, toxic megacolon, GI perforation, adhesions, diverticulitis, Crohn's disease, ulcerative colitis, or severe hepatic impairment, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state.
5. There should be no history of bloody diarrhea.
If all of the above criteria are satisfied, approve for 2 months initially.

Criteria for continuation
1. An adequate response is required to continue. The dose should be 1mg BID. If no response, treatment should be discontinued. If adequate response, approve for 1 year.

Note: Alosetron is available only through REMS.

References:

1. American Gastroenterological Association Institute Guideline on the Pharmacological Management of IBS, 2014.
2. UpToDate. IBS-D. Accessed 9/24/2019.

Date	What changed	Pharmacist's initials
3/25/10	Created revision history; JJ did not create these criteria	JJ
9/24/2019	I revised the criteria and added continuation criteria per prescribing guidelines.	JJ
7/13/2020	Reviewed. No changes	JJ

CONFIDENTIAL

Alpha 1-Proteinase Inhibitor (Zemaira®)

Vial 1000 mg

EBRx PA Criteria

Criteria
1. Patient must have the diagnosis of emphysema and hereditary, severe alpha-1 antitrypsin deficiency, confirmed by genetic testing for alpha-1 antitrypsin deficiency.
2. Alpha-1 antitrypsin level must be documented at <11 micromoles or <80 mg/dL.
3. Upon initial request, the patient must have pulmonary function tests within the previous three months showing a FEV1 of 30-65% predicted. **OR** A rapid decline in lung function of a decrease in FEV1 of more than 120 mL/year
4. Must be a non-smoker

If yes, approve 6 months, for requests outside of the above diagnosis, a manual review will be required.

Date	What was changed	Pharmacist's initials
5/8/12	Created revision history; JJ did not create this criteria.	JJ
3/1/18	After realizing other alpha 1 proteinases are on the market and with the emergence of Prolastin-C, we are revising the criteria. Previously, the only criteria was: "Does the patient have congenital alpha$_1$-antitrypsin deficiency, with clinical emphysema?" These products include Zemaira, Prolastin-C, Glassia, and Aralast NP.	JJ

CONFIDENTIAL

Ambrisentan (Letairis™)

5mg, 10mg oral tablets

EBRx PA Criteria

FDA-approved indication: Treatment of pulmonary artery hypertension (PAH) World Health Organization (WHO) Group I to improve exercise ability and delay clinical worsening; in combo with tadalafil to dreduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability. Studies establishing effectiveness included predominantly patients with WHO Functional Class II to III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

Note: According to treatment guidelines from the Fifth World Symposium on Pulmonary Hypertension (WSPH), only a small number of PAH patients with WHO-FC IV symptoms (ie, severely ill patients) were included in clinical trials, therefore, most experts consider ambrisentan second-line therapy in these patients (WSPH [Gailè 2013]).

Criteria
1. The patient must have the diagnosis of PAH (Group I) and either be taking a CCB and still having symptoms, or have failed a CCB.
OR
2. The patient must have the diagnosis of pulmonary hypertension (Group 5)
Dosing: 5mg QD. Max dose is 10mg QD. Special consideration: If given with cyclosporine, the dose should not exceed 5mg/day.

Quantity Limits: 1 tabs/1 day (30 tabs/30).

Addendum:

Diagnostic Criteria and WHO categorization of PH						
	All Groups	Group 1	Group 2	Group 3	Group 4	Group 5
Description	Elevated PAP	Pulmonary arterial hypertension	Pulmonary venous hypertension	PH due to hypoxemia	Chronic thromboembolic PH	Miscellaneous or multifactorial PH
Estimated prevalence	Up to 10-20% of the general population	15 cases/1,000,000 overall; 6 cases per 1mil for idiopathic PAH	>3-4 mil in US	20% in COPD pts w/ a prior hospitalization for COPD	0.5-2% (up to 3.8%) in survivors of acute PE	Unclear
Diagnostic criteria						

Mean PA pressure, mmHg	≥25	≥25	≥25	≥25	≥25	≥25
PCWP or LVEDP, mmHg		≤15	>15	≤15	≤15	≤15
PVR, dynes/s/cm		>240		>240	>240	>240

References:

1. Galie N, Barbera, Frost AE, et al. Initial use of ambrisentan plus tadalafil in PAH. N Engl J Med 2015;373:834
2. Lexicomp. Ambrisentan. Accessed 9/24/19.

Date	What changed	Pharmacist's initials
2-6-15	I wrote the criteria.	JJ
2-22-16	I removed the requirement to fail a PDE5inh. Due to the "AMBITION" trial, evaluating initial use of ambrisentan + tadalafil in PAH, which showed an improvement in the time to the first event of clinical failure, defined as the 1st occurrence of a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response.	JJ
9/24/19	I reviewed the criteria. No changes.	JJ

CONFIDENTIAL

Amikacin liposomal (Arikayce®)

590/8.4mL by nebulization

EBRx PA Criteria

is FDA-approved for: treatment of *Mycobacterium avium* complex (MAC) lung disease in adults who have limited or no alternative treatment options, as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy.

Criteria for new users
1. Diagnosis of pulmonary NONtuberculous (*Mycobacterium avium* complex (MAC), or *Mycobacterium abscessus*)
2. Patient must have received combination antibacterial drug therapy including a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).
3. The patient must have had a failure to convert sputum to AFB culture negative after at least 6 months of the combination therapy (above).
4. The patient must have limited or no other treatment options.
5. The prescriber must be an infectious disease physician or in be working in coordination with one.
6. The patient must be 18y or older.
If all 6 criteria above are satisified, approve for 6 months.

Criteria for CONTINUATION after 6 months of initial access
1. The patient must have at least 1 negative sputum culture conversion by 6 months of Arikayce use.
2. The prescriber must attest to improvement in the patient's condition.
If both of the INITIAL CONTINUATION criteria are satisfied, approve for 6 months.

Quantity Limits: 590mg daily by nebulization.

Revision History:

Date	What changed	Pharmacist's initials
2/10/19	I wrote the criteria.	JJ

3/10/21	I added continuation criteria.	JJ

References:

1. https://www.arikayce.com/ Prescribing information accessed 2/10/19.

2. Griffith, David E., et al. "An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases." *American journal of respiratory and critical care medicine* 175.4 (2007): 367-416.

3. Griffith, David E., and Timothy R. Aksamit. "Therapy of refractory nontuberculous mycobacterial lung disease." *Current opinion in infectious diseases* 25.2 (2012): 218-227.

4. Olivier, Kenneth N., et al. "Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung disease." *American journal of respiratory and critical care medicine* 195.6 (2017): 814-823.

CONFIDENTIAL

Antihemophilic factor (recombinant), pegylated-- (Adynovate™, Jivi™)

Factor VIII replacement

Adynovate: ~250, ~500, ~750, ~1500, ~2000, ~1000, ~3000 units

Jivi: ~500, ~1000, ~2000, ~3000 units

EBRx PA Criteria

FDA-approved indication:

- Perioperative management during surgery in adults and children with hemophilia A.
- Treatment and control of bleeding episodes on-demand treatment in patients with hemophilia A.
- Routine prophylaxis to reduce the frequency of bleeding in patients with hemophilia A
- IT IS NOT INDICATED FOR THE TREATMENT OF VON WILLEBRAND DISEASE; JIVI is not indicated for previously untreated patients.

Criteria for new users
1. The patient has the diagnosis of hemophilia A (congenital factor VIII deficiency).

References:

1. Lexicomp. Antihemophilic Factor (Recombinant [Pegylated]). Accessed 9/24/19.

Date	What changed	Pharmacist's initials
2/5/16	I wrote the criteria.	JJ
9/24/19	I revised the criteria and added the information about Jivi.	JJ

CONFIDENTIAL

Apalutamide (Erleada™)

60 mg tablets

EBRx PA Criteria

FDA-approved indications:

- Treatment of patients with metastatic castration-sensitive prostate cancer (NOT COVERED-prefer abiraterone due to cost and additional data showing improvement in symptoms)
    - Apalutamide improves overall survival compared to placebo in this setting. However, abiraterone also shows improved overall survival and is less expensive. Therefore, abiraterone is preferred. Reference: Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med*. 2019;381(1):13-24. PMID 31150574 NCT02489318
- Treatment of patients with non-metastatic castration-resistant prostate cancer (CRPC)

Note: CRPC is defined as progression of disease (rising PSA or increase in tumor size on imaging) when testosterone level is <50 ng/dl (due to LHRH antagonist/agonist OR orchiectomy).

Criteria for new users (non-metastatic CRPC)
Diagnosis of prostate cancer without evidence of metastatic disease
The patient has castrate level of testosterone (<50 ng/dl)
PSA doubling time is </= 10 months
Minimum of three rising PSA values at an interval of at least 1 week apart
At time of first request, PSA is 2 ng/ml or greater
If all of the above criteria are met, approve for 1 year
Notes: Apalutamide was compared to placebo in men with castration resistant prostate cancer WITHOUT metastasis. Time to development of metastasis or death was longer with apalutamide (40.5 mo) compared with placebo (16.2 mo). Enzalutamide is also approved for this indication.[1] In an updated analysis (52 mo f/u), median overall survival was improved in the apalutamide group (73.9 mo vs 59.9mo; HR 0.784; p=0.016).[2] Two meta-analyses indicate an improvement in overall survival compared to placebo when the results of apalutamide, enzalutamide, and darolutamide studies were pooled [3,4] Although it is not an absolute contraindication, patients with history of or predisposition to seizures were NOT allowed in this study. These patients WERE allowed in the darolutamide study.

Criteria developed with guidance of study protocol located at https://www.nejm.org/doi/suppl/10.1056/NEJMoa1715546/suppl_file/nejmoa1715546_protocol.pdf (accessed 3/18/19).

Dose: 240 mg PO once daily until progression of disease or unacceptable toxicity.

References:

1. Smith MR et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. NEJM. 2018 Apr 12;378(15):1408-1418. [NCT01946204, PMID 29420164]
2. Small EJ et al. Final survival results from SPARTAN, a phase III study of apalutamide (APA) versus placebo (PBO) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC). J Clin Oncol 38: 2020 (suppl; abstr 5516). https://meetinglibrary.asco.org/record/187437/abstract. Accessed 6/16/2020.
3. Di Nunno V et al. New Hormonal Agents in Patients With Nonmetastatic Castration-Resistant Prostate Cancer: Meta-Analysis of Efficacy and Safety Outcomes. Clin Genitourin Cancer. 2019 Jul 8. pii: S1558-7673(19)30207-1. doi: 10.1016/j.clgc.2019.07.001. [Epub ahead of print] PMID 31378578
4. Hird AE, Magee DE, Bhindi B, et al. A Systematic Review and Network Meta-analysis of Novel Androgen Receptor Inhibitors in Non-metastatic Castration-resistant Prostate Cancer [published online ahead of print, 2020 Mar 6]. Clin Genitourin Cancer. 2020;S1558-7673(20)30039-2. PMID 32278840
5. Mori, Keiichiro, et al. "Apalutamide, enzalutamide, and darolutamide for non-metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis." International journal of clinical oncology (2020): 1-9.

Date	What changed	Pharmacist's initials
3/18/19	Criteria written	sk
9/23/19	Added definition of CRPC. Added meta-analysis data and reference.	Sk
10/28/19	Added new indication (metastatic CSPC). It will not be covered per 10/19/19 EBRx committee meeting.	Sk
4/15/2020	Added reference for second meta-analysis to show improvement in overall survival of antiandrogens (including enzaluatmide) vs placebo in non-metastatic prostate cancer	SK
6/16/2020	Criteria reviewed. Added reference for mCRPC indication (not preferred). Added new overall survival data for nmCRPC indication. No change in criteria	SK
5/25/21	Added 5th reference. Criteria reviewed no change.	SK

Apomorphine SC (Apokyn®)

EBRx PA Criteria

FDA-approved for: Treatment of acute, intermittent hypomobility "off" episodes in patients with advanced Parkinson disease.

Criteria for new users
1. The patient must have the diagnosis of Parkinson's Disease with hypomobility due to "off" episodes.
2. The Kynmobi (sublingual) form of apomorphine must not be an option for the patient. The Kynmobi form is less costly.

Note: Dose for Apokyn is based on tolerance and response to the initial test dose. Start with 0.2mL (2mg) as needed. Max dose is 0.6mL (6mg). there is limited experience with dosing >5x/d, single doses >0.6mL (6mg), and with total daily doses >2mL (20mg).

References:

1. LexiComp. Accessed 10/14/21.

2. Olanow CW, Factor SA, Espay AJ, et al. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Neurol*. 2020;19(2):135-144. doi:10.1016/S1474-4422(19)30396-5.

3. Clinicaltrials.gov. NCT03391882.

Revision History:

Date	What changed	Pharmacist's initials
10/14/21	I wrote the criteria.	JJ

CONFIDENTIAL

Apremilast (Otezla®)

10, 20, 30mg tablets

EBRx PA Criteria

Plaque Psoriasis
1. The patient must have the diagnosis moderate to severe (affecting ≥5% BSA) plaque psoriasis.
2. The patient must have either failed 3 months of phototherapy or systemic therapy, or not be a candidate for it. [Prescriber must state a reasonable reason, in the opinion of the call center pharmacist, why the patient is not a candidate for either phototherapy or other systemic therapy listed below.] Examples include: • systemic therapy: methotrexate or cyclosporine or acitretin systemic therapy • phototherapy (broadband ultraviolet B (UVB), narrowband UVB, and psoralen with ultraviolet A (PUVA) • topical treatments (calcineurin inhibitors (tacrolimus or pimecrolimus), topical corticosteroids, vitamin D analogs (calcipotriene), topical retinoids (tazarotene))

Note: Concurrent TIMs with apremilast are not recommended.

If approved, only 30 day fills are available through this pharmacy plan. The PA is good for 1 year.

Psoriatic Arthritis
1. The patient must have the diagnosis “active psoriatic arthritis”.
2. The patient must have failed at least 2 NSAIDs at therapeutic doses. Each trial should be 1 month in length.
3. The patient must have failed or not be a candidate for methotrexate (MTX) and must have tried 25mg/week for 8 weeks before being deemed a MTX failure. Reasons for not being a MTX candidate include underlying liver disease, interstitial lung disease or bone marrow suppression.
4. In the case the patient is not a candidate for MTX, the patient must try leflunomide 20mg daily for 3 months before access to apremilast would be approved. If the patient did not get a satisfactory response from MTX, they do NOT have to try leflunomide.

Note: Concurrent TIMs with apremilast are not recommended.

If approved, only 30 day fills are available through this pharmacy plan. The PA is good for 1 year.

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Behcet's Syndrome/Disease
1. The patient must have the diagnosis of Behcet's síndrome and have recurrent oral or genital ulcers.
2. The patient must have at least 2 months of colchicine at 1.2-1.8mg per day on the profile in the previous 12 months.
3. In the case the patient has been receiving apremilast for Behcet's, they do not have to have colchicine use in the previous 12 months. (Assume they already satisfied that requirement.)
If approved, the PA is good for 12 months.

References:

1. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomized, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor *Ann Rheum Dis 2014;73:1020–1026.*
2. Otezla PI. www.otezla.com. Accessed 6/11/14.
3. Loos, Anne M., et al. "Comparative effectiveness of targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis." *Journal of the American Academy of Dermatology* 79.1 (2018): 135-144.
4. Cui, Lian, et al. "Efficacy and safety of biologics targeting IL-17 and IL-23 in the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials." *International immunopharmacology* 62 (2018): 46-58.
5. UpToDate. Plaque Psoriasis. Accessed 4/10/19. https://www.uptodate.com/contents/treatment-of-psoriasis-in-adults
6. UpToDate. Psoriatic Arthritis. Accessed 4/10/19. https://www.uptodate.com/contents/treatment-of-psoriatic-arthritis?search=psoriatic%20arthritis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2
7. The American College of Rheumatology Psoriatic Arthritis 2018 Guidelines. https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Psoriatic-Arthritis
8. UpToDate. Treatment of Behcet syndrome. Accessed 2/25/2020.
9. Hatemi, Gulen, et al. "Apremilast for Behçet's syndrome—a phase 2, placebo-controlled study." *New England Journal of Medicine* 372.16 (2015): 1510-1518.
10. Yurdakul, Sebahattin, et al. "A double- blind trial of colchicine in Behçet's syndrome." *Arthritis & Rheumatism* 44.11 (2001): 2686-2692.

11. Davatchi, Fereydoun, et al. "Colchicine versus placebo in Behçet's disease: randomized, double-blind, controlled crossover trial." *Modern Rheumatology* 19.5 (2009): 542-549.

Date	What changed	PharmD's initials
6/11/2014	JJ created criteria	JJ
8/19/14	Insurance Board adopted the drug at T4PA	JJ
1/15/15	I added plaque psoriasis as an indication.	JJ
4/10/19	I updated the PA to be consistent with updated guidelines. I added references 3-7. The 2019 American Academy of Dermatology is putting out new psoriasis guidelines for non-biologics expected in the 4th quarter 2019. https://www.aad.org/practicecenter/quality/clinical-guidelines	JJ
2/26/2020	I updated the PA to include the FDA approval Behcet's Disease and I included references 9-11. There are not comparative data to date and therefore we do not know whether colchicine is superior to apremilast, however, in the case they have tried and failed an adequate trial of colchicine, it is reasonable to allow apremilast. The QL should be 30mg BID.	JJ

CONFIDENTIAL

Aprepitant (Emend®)

40, 80, 125 mg capsules

EBRx PA Criteria

Note: generic now available

FDA approved indications:

In combination with other antiemetic agents, in patients 6 months of age and older for prevention of:

- Acute and delayed nausea and vomiting associated with initial and repeat courses of highly-emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
- Nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
- For prevention of postoperative nausea and vomiting in adults

Dosing:

- For prevention of chemotherapy-induced nausea/vomiting: 125 mg on day 1 and 80 mg on days 2 and 3
- For postoperative nausea and vomiting in adults: 40 mg within 3 hours prior to induction of anesthesia

Note: the only restriction for Emend capsules is quantity limits as below.

Strength/Product	QL:
40 mg capsule	2 caps/month
80 mg capsule	4 caps /month
125 mg capsule	2 caps /month
Tri-Pack	2 packs/month

Date	What changed	Pharmacist's initials
5/20/19	QL updated to match what is programmed into MedAccess.	sk

CONFIDENTIAL

Aripiprazole IM, ER 1-month injection (Abilify Maintena©)

300, 400mg suspension for IM administration

EBRx PA Criteria

FDA-approved indications:

- Bipolar I disorder maintenance, monotherapy
- Schizophrenia treatment

Criteria for new users
1. The patient must have the diagnosis of either schizophrenia or bipolar I disorder.
2. Must have a history of intolerable extrapyramidal symptoms from taking haloperidol decanoate or fluphenazine decanoate long-acting injections not responsive to benztropine, trihexyphenidyl, or propranolol in the medical records; look back 5 y or as long as our profile's history and as long a history available in the medical records available to us.
If all of these criteria are fulfilled, approve for 12 months.
• Concurrent use of other forms of olanzapine, quetiapine, ziprasidone, chlorpromazine, haloperidol, trifluoperazine, prochlorperazine, thioridazine, thiothixene, aripiprazole, or risperidone should be given concurrently for **ONLY the first 2 weeks or when there is a mixed dose. Permanent combination therapy is not indicated.** • Max dose is 400mg once monthly.

Criteria for continuation
1. At least 26 days must have elapsed since the previous dose to get another long-acting injection.

Note: Doses:

- Bipolar I disorder maintenance, monotherapy
  - 400mg once monthly, separated by >26d; Note: tolerability should be established using oral aripiprazole prior to initiation of parenteral therapy. Continue oral aripiprazole or other oral antipsychotic for 14 days during initiation of parenteral therapy.
- Schizophrenia treatment
  - 400mg once monthly, separated by >26d; Note: tolerability should be established using oral aripiprazole prior to initiation of parenteral therapy. Continue oral aripiprazole or other oral antipsychotic for 14 days during initiation of parenteral therapy.
  - Missed doses:
    - 2nd or 3rd doses missed:
      - >4w but <5w since last dose: Administer next dose ASAP.

- >5w since last dose: Administer oral aripiprazole for next 14d with injection.
- 4th or subsequent doses missed:
  - >4w but <6w since last dose: Administer next dose ASAP.
  - >6w since last dose: Administer oral aripiprazole for 14 d with next injection.

- Dosage adjustment for adverse effects: Consider reducing dose to 300mg QM.

Quantity Limits: 400mg q26 days

References:

1. UpToDate. Bipolar I treatment. Also Schizophrenia treatment guidelines. Accessed 6/24/19.
2. LexiComp, dosing info. Accessed 6/24/19.

Revision History:

Date	What changed	Pharmacist's initials
10/30/15	I wrote the criteria.	JJ
6/24/19	I added bipolar I indication.	JJ

CONFIDENTIAL

Ascminib (Scemblix)

20 mg and 40 mg tablets

EBRx PA Criteria

FDA-approved for:

- Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs). (Accelerated approval based on major molecular response (MMR). SEE CRITERIA
- Ph+ CML in CP with the T315I mutation. NOT COVERED see ponatinib criteria
  - A single arm trial (CABL001X2101; NCT02081378) in CP-CML patients with T315I mutation found a major molecular response rate of 49%. Although asciminib appears effective, ponatinib is also an effective option that is less expensive (as of 12/16/2021: AWP ~$100,000/mo versus ~$20,000/mo).
    - Reference: asciminib package insert. https://www.novartis.us/sites/www.novartis.us/files/scemblix.pdf

Criteria for new users
Ph+ chronic myeloid leukemia (CML) in chronic phase with resistance*, intolerance, or contraindication to imatinib AND dasatinib (note: Ph+ may also be denoted as t(9;22) or BCR/ABL)
*Resistance to CML therapy is generally defined as any of the following: a. Inadequate response (defined as one of the following): i. After 3 months of therapy: Lack of complete hematologic response (Platelets <450 x10^9/L; leukocyte count <10 x 10^9/L) ii. After 3 months of therapy: Cytogenetic analysis shows >95% Ph+ metaphases iii. After 6 months of therapy: BCR-ABL1 (IS) >10% by quantitative PCR (qPCR) iv. After 6 months of therapy: Cytogenetic analysis shows >35% Ph+ metaphases v. After 12 months of therapy: BCR-ABL1 (IS) >1% by quantitative PCR (qPCR) vi. After 12 months of therapy: Cytogenetic analysis shows >0% Ph+ metaphases b. Progression of disease after a cytogenetic/hematologic response was achieved c. Documentation of mutation associated with drug resistance (typically checked after failure of first-line therapy—see below)
If criteria 1 is fulfilled, approve for 12 months

Notes:

General CML information:

1. Cytogenetic monitoring: Chromosomes are examined directly for BCR-ABL chromosomal translocation. Number of cells in metaphase are examined. The number of metaphase cells that contain BCR-ABL are divided by total number of metaphase cells to get a percentage. Test requires bone marrow aspirate.
2. Molecular monitoring: Transcripts for BCR-ABL mRNA are quantified via real time PCR. “IS” denotes that the result is obtained via a standardized method. Test requires

peripheral blood sample.

3. Cytogenetic and molecular monitoring are both valid. Since cytogenetic monitoring requires bone marrow biopsy, molecular monitoring may be preferred.
4. Analysis of BCR-ABL mutations is typically not done until failure of first-line therapy for chronic phase CML but may be checked sooner in advanced phase. If a mutation is documented that predicts resistance to imatinib or other therapy, an alternative agent should be used. NCCN has guide for treatment options according to which mutation is identified.

Treatment recommendations based on BCR-ABL1 mutation profile (NCCN CML version 2.2022)	
Contraindicated Mutations	Drugs
T315I/A, F317L/V/I/C, V299L	Dasatinib
T315I, Y253H, E255K/V, F359V/C/I	Nilotinib
T315I, V299L, G250E, F317L	Bosutinib
None	Asciminib, Ponatinib, Omacetaxine, stem cell transplant, clinical trial

Notes regarding EBRx criteria:

1. Above criteria for resistance/failure of imatinib were obtained from NCCN guidelines Early Treatment Response Milestones page CML-3 in version 1.2019 and guideline published by European LeukemiaNet (ELN).[1] ELN proposes more restrictive resistance/failure definitions for second line therapy, however, NCCN has no specific guidelines. Therefore, will leave resistance/failure definitions as listed above.
2. After failure of first line therapy, there are no randomized trials showing one TKI to be superior to another.

Ascminib dosing:

After failure of at least 2 prior TKIs: 80 mg PO once daily or 40 mg PO twice daily

Asciminib was compared to bosutinib in this patient population and found to have a higher major molecular response rate (25% vs. 13%) and lower incidence of adverse events.

REFERENCES:

1. Baccarani M et al. Blood. 2013 Aug 8;122(6):872-84. PMID 23803709
2. Asciminib package insert. https://www.novartis.us/sites/www.novartis.us/files/scemblix.pdf. Accessed 12/16/2021
3. Réa D et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021 Nov 25;138(21):2031-2041. doi: 10.1182/blood.2020009984. PMID: 34407542. https://ashpublications-org.libproxy.uams.edu/blood/article/138/21/2031/476601/A-phase-3-open-label-randomized-study-of-asciminib
4. Hughes TP et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. N Engl J Med. 2019 Dec 12;381(24):2315-2326. doi: 10.1056/NEJMoa1902328. PMID: 31826340; PMCID: PMC7724923. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7724923/

Quantity Limits: 30 day supply

Revision History:

Date	What changed	Pharmacist's initials
12/16/2021	Criteria written	SK

CONFIDENTIAL

Atezolizumab (Tecentriq©)

840 mg/14 mL and 1200 mg/20 mL vials

EBRx PA Criteria

FDA-approved for:

- **Non-small cell lung cancer, metastatic (NSCLC)**
  - As monotherapy for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (**EITHER** PD-L1 stained ≥50% of tumor cells [TC ≥50%] **OR** PD-L1 stained tumor-infiltrating immune cells covering ≥10% of the tumor area [IC ≥10%]), with no EGFR or ALK genomic tumor aberrations
  - In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations
  - In combination with paclitaxel protein-bound (Abraxane) and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations
  - As monotherapy in patients with disease progression during or following platinum-containing chemotherapy. Patients should have disease progression on approved therapy for EGFR or ALK genomic tumor mutations (if present) prior to receiving atezolizumab
- **Urothelial carcinoma, locally advanced or metastatic**
  - patients not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-inflitrating immune cells [IC] covering ≥5% of the tumor area) NOT COVERED: single arm trial only
  - patients not eligible for any platinum-containing chemotherapy regardless of PD-L1 status NOT COVERED: single arm trial only
  - Patients who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy. NOT COVERED (see pembrolizumab-Keytruda): RCT showed fewer side effect but no overall survival benefit with atezolizumab vs. chemo (Powles et al. Lancet 2018;391(10122):748-757; only 6% of chemo pt received post-trial immunotherapy). PEMBROLIZUMAB has shown overall survival benefit in this setting with fewer severe adverse effects versus chemotherapy.
- **Triple-Negative Breast Cancer (TNBC)**
  - In combination with paclitaxel protein-bound (Abraxane) for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA approved test (**accelerated approval based on progression free survival**). NOT COVERED

    ****PLEASE READ****
    - As of 5/20/2021 EBRx P&T meeting, TNBC indication will no longer be covered. ***Current users will be grandfathered.***

  - In IMPOWER130, benefit was limited to progression free survival only.
  - In confirmatory trial (IMPOWER131), PFS benefit was NOT confirmed, and an overall survival benefit was not evident.
  - References:
    - IMPOWER130: Schmid P et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 Nov 29;379(22):2108-2121. doi: 10.1056/NEJMoa1809615. Epub 2018 Oct 20. PMID: 30345906.
    - IMPOWER130 (updated results): Schmid P et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020 Jan;21(1):44-59. doi: 10.1016/S1470-2045(19)30689-8. Epub 2019 Nov 27. PMID: 31786121.
    - IMPOWER 131: https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/primary-results-from-impassion131-a-double-blind-placebo-controlled-randomised-phase-iii-trial-of-first-line-paclitaxel-pac-atezolizumab-atez Accessed 4/27/2021 [NCT03125902 impassion 131]

- **Small Cell Lung Cancer (SCLC)**
  - In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage SCLC.
- **Hepatocellular Carcinoma (HCC)**
  - in combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy
- **Melanoma**
  - in combination with cobimetinib and vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma NOT COVERED
    - Benefit of this combination is limited to progression free survival. Overall survival nor quality of life have been shown to be improved at this time.
    - Reference: Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;395(10240):1835-1844. doi:10.1016/S0140-6736(20)30934-X PMID 32534646

Non-Small Cell Lung Cancer (NSCLC)
PATIENTS WITH PREVIOUSLY-TREATED ADVANCED/METASTATIC DISEASE:

1. Patient must have diagnosis of metastatic NSCLC diagnosis (squamous or non-squamous)
2. Patient must have been treated previously with platinum-based chemotherapy.
3. If patient is ALK/EGFR mutation positive, patient also has previously been treated with targeted therapy (e.g. erlotinib, afatinib, dacomitinib, gefitinib, osimertinib, alectinib, crizotinib, brigatinib, ceritinib)
4. At initial request, patient must be ECOG performance status 0-1.
5. No prior PD-L1 or PD-1 inhibitor
If all criteria met, approve for 12 months
PATIENTS WITH NO PRIOR THERAPY FOR ADVANCED/METASTATIC DISEASE:
1. Patient must have diagnosis of metastatic NSCLC
2. Tumor does NOT harbor EGFR or ALK mutations.
3. At initial request, patient must be ECOG performance status 0-1.
4. If atezolizumab monotherapy will be used, tumor has high PD-L1 expression (TC ≥50% or IC ≥10%) [tumor histology can be squamous or non squamous]
5. If atezolizumab combination therapy will be used, both of the following criteria are met: • Tumor histology is non squamous (e.g. adenocarcinoma, large cell) AND • Atezolizumab will be used in combination with bevacizumab, carboplatin, and conventional paclitaxel **OR** in combination with carboplatin and nab-paclitaxel (Abraxane). [PD-L1 expression can be present or absent]
If 1, 2, 3, and either 4 or 5 are met, approve for 12 months
Note: -In patients previously treated with platinum-based chemotherapy (and targeted therapy if EGFR/ALK mutation +), atezolizumab improved OS compared to docetaxel with median OS 13.8 mo vs 9.6 mo (HR 0.73 95% CI 0.62-0.87). 1-2 prior chemo regimens with one being platinum based were required prior to enrollment.[1] Fewer severe adverse events were observed in atezolizumab arm (15% vs 43%) -If newly-diagnosed, untreated, and non-squamous histology, atezolizumab/bevacizumab/carboplatin/paclitaxel improved OS vs bevacizumab/carboplatin/paclitaxel with median OS of 19.2 mo vs. 14.7 mo (HR 0.78; 95% CI, 0.64 to 0.96).[2] Atezolizumab/carboplatin/nab-paclitaxel also improved OS vs carboplatin/nab-paclitaxel with median OS of 18.6 mo vs. 13.9 mo.[3] -If newly-diagnosed, untreated, any histology, and high PD-L1 expression (TC >50% or IC >10%), atezolizumab monotherapy improved overall survival compared with platinum-based doublet (median OS 20 mo vs 13 mo).[4] [data from trial Impower 110 study, NCT02409342—results published in PI only as of 6/2/2020]

References:

1. Rittmeyer A et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017 Jan 21;389(10066):255-265. NCT02008227 PMID27979383
2. Socinski MA et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med. 2018 Jun 14;378(24):2288-2301. NCT02366143 PMID 29863955
3. West H et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019 May 20. pii: S1470-2045(19)30167-6. doi: 10.1016/S1470-2045(19)30167-6. [Epub ahead of print] NCT02367781 PMID 31122901
4. Tecentriq PI. https://www.gene.com/download/pdf/tecentriq_prescribing.pdf. Accessed 5/22/2020.

Small Cell Lung Cancer
1. Diagnosis of extensive stage small cell lung cancer
2. Atezolizumab will be given in combination with carboplatin and etoposide
3. The patient has received no prior systemic therapy
If all criteria met, approve for 12 months

Note:

Atezolizumab+carboplatin+etoposide was compared to carboplatin+etoposide. Median overall survival (atez+chemo vs chemo) was 12.3 mo versus 10.3 mo (HR 0.7; 95% CI 0.54-0.91; p=0.007). 12-month overall survival: 51.7% vs. 38.2%.

Atezolizumab+chemo is given for 4 cycles, then atezolizumab is continued as maintenance therapy until disease progression or unacceptable toxicity.

Reference:

Horn L et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018 Dec 6;379(23):2220-2229. PMID 30280641 NCT02763579

Hepatocellular Carcinoma
1. Diagnosis of advanced/unresectable hepatocellular carcinoma
2. Atezolizumab will be given in combination with bevacizumab
3. The patient has received no prior systemic therapy
4. No variceal bleeding 6 months prior to initiation of treatment
5. Child Pugh score = A
If all criteria met, approve for 12 months

Note:

Atezolizumab+bevacizumab was compared to sorafenib. Median overall survival was improved in the atezo/bev group compared to sorafenib (median not reached in atezo/bev group versus 13.2 mo; HR 0.58; 95% CI 0.42-0.79; p=0.0006).

Time to deterioration of overall quality of life using EORTC-QLQ C30) was also prolonged in the atezo/bev group (median 11.2 mo vs 3.6 mo; HR 0.63; 95% CI 0.46-0.85). Time to deterioration of physical functioning and role functioning was also prolonged in the atezo/bev group.

Reference:

Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382(20):1894-1905. doi:10.1056/NEJMoa1915745. PMID 32402160 NCT03434379

Revision History:

Date	What changed	Pharmacist's initials
3/2/17	I wrote the criteria.	JJ
5/10/17	IMvigor211, the confirmatory trial, seeking an OS benefit over chemotherapy, failed to show a benefit, putting the FDA-approval for urothelial carcinoma in jeopardy. Awaiting the actual reference from the peer-reviewed publication.	JJ
2/26/2019	Added first line use criteria in combination with bevacizumab/carboplatin/paclitaxel per study criteria.	Sk
7/18/19	Added TNBC and small cell lung cancer indications. Simplified NSCLC criteria	SK
12/9/19	Added new FDA approved indication under FDA approvals (no change to criteria—this indication was already covered--data was released months ago): In combination with paclitaxel protein-bound (Abraxane) and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations	Sk
1/29/2020	Reviewed all criteria. No change	Sk
5/27/2020	Added coverage for monotherapy indication for non small cell lung cancer with high PD-L1 expression.	SK
6/24/2020	Added coverage for hepatocellular carcinoma	SK
8/7/2020	New indication reviewed (melanoma). Do not cover.	SK
5/21/2021	PER 5/20/2021 P&T meeting, do not cover mTNBC indication. Criteria removed. Details above.	SK

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Avelumab (Bavencio®)

200 mg/10 ml solution

EBRx PA Criteria

FDA-approved for:

Merkel Cell Carcinoma (MCC)[1]

• Adults and pediatric patients 12 years and older with metastatic MCC. NOT COVERED: Data limited to single arm trial with no report of overall survival or quality of life benefit. (See pembrolizumab criteria)

References (two reports of same study):

- Kaufman HL et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(10):1374-1385. PMID 27592805 NCT02155647
- D'Angelo SP et al. Efficacy and Safety of First-line Avelumab Treatment in Patients With Stage IV Metastatic Merkel Cell Carcinoma: A Preplanned Interim Analysis of a Clinical Trial. *JAMA Oncol*. 2018;4(9):e180077. PMID 29566106 NCT02155647

Urothelial Carcinoma (UC)

• Maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with first-line platinum-containing chemotherapy (SEE CRITERIA)

• Patients with locally advanced or metastatic UC who meet one of the following conditions:

- Have disease progression during or following platinum-containing chemotherapy. NOT COVERED: Data limited to single arm trial with no report of overall survival or quality of life benefit. (See pembrolizumab criteria)
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. NOT COVERED: Data limited to single arm trial with no report of overall survival or quality of life benefit. (See pembrolizumab criteria)

Reference:

Patel MR et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial *Lancet Oncol*. 2018;19(1):51-64. PMID 29217288 NCT01772004

Renal Cell Carcinoma (RCC)

• First-line treatment, in combination with axitinib, of patients with advanced RCC. NOT COVERED: Benefit limited to progression free survival. (See pembrolizumab + axitinib criteria).

Reference:

Motzer RJ et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380(12):1103-1115. PMID 30779531 NCT02684006

[1]This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Criteria for urothelial carcinoma (maintenance therapy after first-line chemotherapy)
1. Diagnosis of unresectable, locally advanced or metastatic urothelial (bladder) carcinoma
2. In the first-line setting, patient was treated with platinum-based chemotherapy, and disease did not progress on or after therapy. [platinum-based chemotherapy typically consists of cisplatin/gemcitabine or carboplatin/gemcitabine]
4. Avelumab will be initiated within 10 weeks of last dose of chemotherapy.
If all criteria met, approve for 12 months. Avelumab continues until disease progression or unacceptable toxicity.

Note:

Avelumab was compared to placebo in this treatment setting. Overall survival was significant prolonged in the avelumab group (median 21.4 mo vs 14.3 mo; HR 0.69).

Dose: 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.

Reference:

1. Bevancio PI. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf. Accessed 7/7/2020.

Quantity Limits: n/a

Revision History:

Date	What changed	Pharmacist's initials
7/22/2020	Criteria written	SK

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Axitinib (Inlyta®)

1 mg, 5 mg tablets

EBRx PA Criteria

FDA-approved indications:

- Treatment of advanced renal cell carcinoma after failure of one prior systemic therapy NOT COVERED
  - In patients who progressed on first-line therapy (sunitinib, cytokines, bevacizumab, or temsirolimus), axitinib improved PFS but not OS compared to sorafenib. Crossover was not allowed in this study. Quality of life was not significantly improved.

References:

1. Rini BI et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011 Dec 3;378(9807):1931-9. PMID 22056247 NCT00678392
2. Cella D et al. Patient-reported outcomes for axitinib vs sorafenib in metastatic renal cell carcinoma: phase III (AXIS) trial. Br J Cancer. 2013 Apr 30;108(8):1571-8. PMID 23579211 NCT00678392
3. Motzer RJ et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol. 2013 May;14(6):552-62. PMID 23598172 NCT00678392

- In combination with pembrolizumab, for the first-line treatment of patients with advanced renal cell carcinoma (note: this indication is listed in the pembrolizumab package insert, not the axitinib package insert).

Renal Cell Carcinoma
1. Advanced or metastatic clear cell renal cell carcinoma
2. No prior therapy for advanced disease
3. Axitinib must be given in combination with pembrolizumab
4. Patient must have Karnofsky performance status of ≥70% (see below)
5. Patient must have intermediate or poor risk disease as measured by IMDC criteria (see below)
If all criteria fulfilled, approve for 6 months.
QL: **5 mg tabs: #120/30d** **1 mg tabs: #180/30d**
Dose: Initial: 5 mg twice daily (in combination with pembrolizumab); increase to 7 mg twice daily and then 10

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mg twice daily if tolerated.

Evidence:

In the first line setting, pembrolizumab+axitinib improved overall survival regardless of IMDC risk (12-month OS: 89.9% vs 78.3%). No difference was found in subgroup with favorable risk per IMDC criteria below indicating that benefit was driven by intermediate/poor risk subgroup. The lack of benefit seen in the favorable risk subgroup is consistent with the ipilimumab/nivolumab data.

IMDC risk:

Favorable risk: no risk factors

Intermediate risk: 1-2 risk factors

Poor risk: 3 or more risk factors

Risk factors:

- Less than 1 year from time of diagnosis to systemic therapy
- Performance status <80% (Karnofsky—see guide below)
- Hemoglobin < lower limit of normal (LLN)
- calcium > upper limit of normal (ULN)
- Neutrophil > ULN
- Platelets > ULN

Reference

Rini et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019 Mar 21;380(12):1116-1127. NCT02853331 PMID 30779529

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Karnofsky Score (KS)	Definition
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Date	What changed	Pharmacist's initials
5/20/19	Criteria written	sk
10/31/19	Criteria reviewed. No changes	SK
12/29/2020	Criteria reviewed. No changes	SK

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Azacitidine (Onureg®)

200 mg, 300 mg tablets

EBRx PA Criteria

is FDA-approved for:

Nucleoside metabolic inhibitor indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy

Criteria for new users
1. Age ≥ 55 y/o
2. Diagnosis of acute myeloid leukemia (AML)
3. AML is intermediate or high risk*
4. AML has not been previously treated with a hypomethylating agent (e.g. azacitidine or decitabine)
5. Patient has achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi)** following intensive induction chemotherapy***
6. Time of first request is within 4 months of attainment of first remission
7. Patient remains in CR or CRi at time of first request
8. Patient is unable to complete intensive curative therapy****
9. Patient is not a candidate for hematopoietic stem cell transplantation

***AML Risk Stratification**

RISK STRATIFICATION BY GENETICS IN NON-APL AML[1,2]

Risk Category*	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Biallelic mutated *CEBPA* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,§ monosomal karyotype‖ Wild-type *NPM1* and *FLT3*-ITD^{high}† Mutated *RUNX1*¶ Mutated *ASXL1*¶ Mutated *TP53*#

****CR = patient independent of transfusion AND absolute neutrophil count (ANC) >1000/mcL (blasts <5%) AND platelets ≥100,000/mcL**

CRi = patient independent of transfusion but ANC <1000/mcL and platelets <100,000/mcL

*****Intensive induction chemotherapy regimens include, but are not limited to the following:**

- 7+3 (idarubicin/cytarabine or daunorubicin/cytarabine)
- FLAG-IDA (fludarabine, idarubicin, cytarabine, GCSF)
- Vyxeos (liposomal daunorubicin/cytarabine)
- ADE (cytarabine, daunorubicin, etoposide)
- AIE (cytarabine, idarubicin, etoposide)
- MEC (mitoxantrone, etoposide, cytarabine)

******Intensive consolidation therapy regimens include, but are not limited to the following:**

- High dose cytarabine
- Vyxeos
- 7+3 (idarubicin/cytarabine or daunorubicin/cytarabine)
- 5+2 (idarubicin/cytarabine or daunorubicin/cytarabine)
- Allogeneic stem cell transplant

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Trial	Population	Key Outcomes	Key Results (Onureg vs placebo)	
A QUAZAR AML-001[1-4] NCT01757535 RCT, DB, PB, P3 Onureg vs placebo 1:1 randomization	Key Inclusion/Exclusion Criteria • ≥ 55 years of age • Newly diagnosed AML or AML secondary to prior myelodysplastic disease • Within 4 months of first complete remission (CR) or complete remission with incomplete blood count (CRi) recovery with induction therapy • Consolidation therapy could have been given but not required • Not a candidate for stem cell transplantation • Hypomethylating agent not used to achieve CR/CRi. POPULATION ENROLLED N = 472 patients • Median age: 68 years • ECOG 1 or 2: ~91% • Intermediate risk: ~85% • Poor risk: ~15% •Consolidation after induction: •None: ~20% •1 cycle: ~45% •2 cycles: ~30% •3 cycles: ~5%	1º: OS 2º: RFS & Safety	Median f/u 41.2 months: **OS:** **24.7 months vs. 14.8 months** **(HR 0.69; 95% CI: 0.55-0.86; p = 0.0009)** RFS: 10.2 months vs. 4.8 months (HR 0.65; 95% CI 0.52-0.81; p = 0.0001] Safety •15% had severe side effects (pneumonia & low WBC counts) •5% vs. 0.4% stopped medication •Median exposure was 12 cycles for azacitidine and 6 cycles for placebo OS/RFS benefit demonstrated regardless of baseline cytogenetic risk, the number of prior consolidation cycles received, and remission status (CR/CRi).	
RCT: randomized controlled trial, PB: placebo controlled, DB: double blind, P3: phase III, OS: overall survival, RFS: relapse free survival				

Notes:

-The FDA approval is stricter than the study criteria in that the FDA requires the patient not to be a candidate for intensive consolidation therapy. This is reasonable since it likely was unethical to give placebo to patients who were candidates for intensive consolidation therapy in the study. That being said, it is unclear what the best consolidation therapy is and for how long it should be continued.

-Intravenous azacitidine is also available and much cheaper, but overall survival data have not been demonstrated in this setting[5]

-The following statement is made in **NCCN guidelines** regarding oral azacitidine:

"This is a maintenance therapy and is not intended to replace consolidation chemotherapy, which can be curative in

some cases. In addition, fit patients with intermediate- and/or adverse-risk cytogenetics may benefit from HCT in first CR, and there are no data to suggest that maintenance therapy with oral azacitidine can replace HCT. The panel also notes that the trial did not include younger patients or those with CBF-AM; it was restricted to patients >55 years of age with intermediate or adverse cytogenetics who were not felt to be candidates for HCT. Most patients received at least 1 cycle of consolidation prior to starting azacitidine."[5]

-Dose: 300 mg PO daily on days 1 to 14 of a 28-day cycle. Continue until disease progression or unacceptable toxicity.

REFERENCES:

1. Roboz, Gail J., et al. "Design of the randomized, Phase III, QUAZAR AML Maintenance trial of CC-486 (oral azacitidine) maintenance therapy in acute myeloid leukemia." Future Oncology 12.3 (2016): 293-302.

2. ONUREG (azacitidine) [package insert] Summit. NJ: Celgene Corporation; 2020.

3. Wei, Andrew H., et al. "The QUAZAR AML-001 Maintenance Trial: results of a phase III international, randomized, double-blind, placebo-controlled study of CC-486 (oral formulation of azacitidine) in patients with acute myeloid leukemia (AML) in first remission." (2019): LBA-3. https://ashpublications.org/blood/article/134/Supplement_2/LBA-3/428840/The-QUAZAR-AML-001-Maintenance-Trial-Results-of-a.

4. Huls G et al. Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients Blood (2019) 133 (13): 1457–1464. https://ashpublications.org/blood/article/133/13/1457/261475/Azacitidine-maintenance-after-intensive

5. NCCN AML guidelines Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

Quantity Limits: 14 tabs/28 days

Revision History:

Date	What changed	Pharmacist's initials
10/22/2020	Criteria written	SK
1/26/2021	Criteria reviewed. No change.	SK

Aztreonam inhaled (Cayston®)

Vial 75 mg

EBRx PA Criteria

FDA-approved indication: improvement of respiratory symptoms in cystic fibrosis patients with pulmonary Pseudomonas aeruginosa infections.

Criteria for new users
1. The patient must have a diagnosis of cystic fibrosis.
2. the patient must have a known pulmonary infection with Pseudomonas aeruginosa.
3. The patient must be receiving bronchodilator therapy.
4. The patient should not have overlapping days supply of inhaled tobramycin (therapeutic duplication).

Note: Dosing is 75mg TID for 28 days followed by 28 days off.

Quantity Limits: 6-28d supplies in a year.

References:

1. Kirkby, Stephen, Kimberly Novak, and Karen McCoy. "Aztreonam (for inhalation solution) for the treatment of chronic lung infections in patients with cystic fibrosis: an evidence-based review." *Core evidence* 6 (2011): 59.
2. Assael, Baroukh M., et al. "Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: a comparative efficacy trial." *Journal of Cystic fibrosis* 12.2 (2013): 130-140.
3. Flume, Patrick A., et al. "Continuous alternating inhaled antibiotics for chronic pseudomonal infection in cystic fibrosis." *Journal of Cystic Fibrosis* 15.6 (2016): 809-815.

Revision History:

Date	Notes	Pharmacist's initials
4/2010	JJ created the criteria	JJ
5/8/12	JJ inserted revision history	JJ
9/24/19	I reviewed the criteria. Formatted. I added references 1-3.	JJ
7/16/2020	I added TD with TOBI and to avoid allowing this.	JJ
3/30/21	Reviewed. No changes.	JJ

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Bedaquiline (Sirturo®)

100mg tablets

EBRx PA Criteria

FDA-approved indication: treating multidrug resistant TB in combination with other drugs; in pediatric patients ≥5 y weighing ≥15kg and adults when an effective treatment regimen cannot otherwise be provided.

Criteria for new users
1. The patient must have the diagnosis of multidrug resistant tuberculosis.
2. The Arkansas Health Department should be consulted on the appropriate regimen.
If approved, allow the AR Dept of Health to determine the length of treatment and approve the PA accordingly.

Note: Max treatment regimen is 24 weeks.

Dose is 400mg daily for 2 weeks, then 200mg 3x/w up to 24 weeks. At least 3 other effective antiTB drugs must be taken along with bedaquiline.

It should be noted mortality was increased with bedaquiline vs placebo and is thus far unexplained.

QT prolongation is caused by the drug and is additive with other drugs (see PI) including quinolones which are often used in the combination therapy. Frequent EKGs should be performed. Stop drug if QT interval exceeds 500ms.

References:

1. Lexicomp. Bedaquiline. Accessed 5/28/13.
2. Diacon AH, Dawson R, vonGroote-Bidlingmaier F, et al. 140day bactericidal activity of PA-824,bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomized trial. Lancet. 2012;380(9846):986-93.
3. Sirturo PI. http://www.sirturo.com/sirturo-clinical-trials. Accessed 5/28/13.
4. World Health Organization. "WHO consolidated guidelines on drug-resistant tuberculosis treatment." (2019).

   https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1%20(Accessed%20on%20March%2028,%202019).

Date	What changed	Pharmacist's initials
5/28/13	Criteria written	JJ
9/24/19	I reviewed the criteria. I updated and simplified the criteria. Added reference 4.	JJ
3/10/21	Criteria reviewed. Changed FDA-approval on criteria down from 12y to 5y and from 30kg to 15kg.	JJ

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Belantamab mafodotin-blmf (Blenrep®)

100 mg single dose vial for reconstitution

EBRx PA Criteria

FDA-approved for: Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Criteria for new users
1. Diagnosis of multiple myeloma
2. Prior treatment with at least 4 prior regimens
3. Prior regimens included all of the following: a. at least one anti-CD38 monoclonal antibody (e.g. siltuximab [Sarclisa], daratumumab [Darzalex]) b. at least one proteasome inhibitor (e.g. carfilzomib [Kyprolis], bortezomib [Velcade], ixazomib [Ninlaro]) c. at least one immunomodulatory agent (e.g. lenalidomide [Revlimid], pomalidomide [Pomalyst], thalidomide [Thalomid]
If all criteria are met, approve for 12 months.

Note:

Dose: 2.5 mg/kg IV every 3 weeks

Belantamab mafodotin has not been directly compared to another agent and exhibited a low response rates in the DREAMM2 trial (~31%). However, indirect comparison of the DREAMM-2 trial to MAMMOTH data reveals a possible prolongation in overall survival compared to usual care.

DREAMM-2 trial (single arm trial)[1,2]

-response rate: 31%

-median overall survival: 13.7 mo

MAMMOTH (included patients with relapsed/refractory multiple myeloma not treated with novel agents, such as belantamab)[3,4]

-triple and quad refractory subgroup: Median overall survival: 9.2 mo

References:

1. Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol. 2020;21(2):207-221. doi:10.1016/S1470-2045(19)30788-0. PMID 31859245
2. Lonial et al. MM-219: Pivotal DREAMM-2 Study: Single-Agent Belantamab Mafodotin (Belamaf; GSK2857916) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to Proteasome Inhibitors and Immunomodulatory Agents, and Refractory and/or Intolerant to Anti-CD38 Monoclonal Antibodies (mAbs), Including Subgroups with Renal Impairment (RI) and High-Risk (HR) Cytogenetics. Clinical Lymphoma Myeloma and Leukemia. Volume 20, Supplement 1, September 2020, Pages S301-S302. https://www.sciencedirect.com/science/article/abs/pii/S2152265020309435. Accessed 5/17/2021.
3. LJ Costa et al. https://ashpublications.org/blood/article/134/Supplement_1/3125/423837/Overall-Survival-of-Triple-Class-Refractory-Penta. Accessed 11/18/19 [mammoth]
4. Cornell R et al. Overall survival of patients with triple-class refractory multiple myeloma treated with selinexor plus dexamethasone vs standard of care in MAMMOTH. Am J Hematol. 2021 Jan;96(1):E5-E8. doi: 10.1002/ajh.26010. Epub 2020 Oct 21. PMID: 32974944.

Quantity Limits: n/a (medical drug)

Revision History:

Date	What changed	Pharmacist's initials
5/21/2021	Criteria written	SK

Belatacept (Nulojix™)

Vial 250mg

EBRx PA Criteria

FDA-approved indication: Prophylaxis of organ rejection concomitantly with basiliximab induction, mycophenolate, and corticosteroids in adult Epstein-Barr virus (EBV) seropositive kidney transplant recipients.

Criteria for new users
1. The patient must be status post kidney transplant and currently taking mycophenolate mofexit and corticosteroids.
2. The patient must be known to be seropositive for Epstein-Barr virus.
If approved, PA is for 1 year.

Note: The dose is 10mg/kg initially dosed on Day 1, on day 5, at the end of week 2, at the end of weeks 4, 8, & 12. Then the dose is changed to a maintenance dose of 5mg/kg at the end of week 16 and every 4 weeks thereafter.

References:

1. Nulojix website. http://packageinserts.bms.com/pi/pi_nulojix.pdf Accessed 8/3/11.

2. Vincenti F, Blancho G, Durrbach A, Friend P, et al. Five year safety and efficacy of belatacept in renal transplantation. J Am Soc Nephrol. 2010. 21:1587-96.

3. Neuberger, James M., et al. "Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and clinical checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group." *Transplantation* 101.4S (2017): S1-S56.

Revision History

Date	What changed	PharmD's initials
10/11/11	JJ created criteria	JJ
5/8/12	JJ created revision history box	JJ
9/24/19	I updated the criteria, formatted, added reference 3.	JJ
07/16/2020	Reviewed. No changes	JJ

Belimumab (Benlysta®)

EBRx PA Criteria

FDA-approved for:

- **Lupus nephritis, treatment of adults with active LN who are receiving standard therapy**
- Systemic lupus erythematosus, treatment of adults and children >5y old with active, autoantibody-positive SLE who are receiving standard therapy (NOT COVERED due to lack of clinical endpoint data)

Criteria for new users with LN
1. The patient must be 18 y+.
2. The patient must have a diagnosis of autoantibody+ SLE (antinuclear antibody titers >1:80, anti-double-stranded DNA antibodies, or both) that fulfilled the 1982 (updated 1997) ACR classification criteria for SLE active lupus nephritis.
3. The patient must have a ratio of urinary protein to creatinine of 1 or more within the past 3 months. (time frame was at screening in the clinical trial; 3 months is generous but arbitrary)
4. The patient must have biopsy-proven lupus nephritis of International Society of Nephrology and Renal Pathology Society class III (focal lupus nephritis) or IV (diffuse LN) within the past 6 months.
5. The patient must not be receiving dialysis.
6. The patient **must be receiving standard therapy for LN including cyclophosphamide-azathioprine, or mycophenolate** mofetil. [Patients may also receive ACEi or ARB, hydroxychloroquine.]
If the criteria above are satisfied, approve PA for 1 year.

ACR= American College of Rheumatology

Note: Belimumab dose was 10mg/kg of body weight on days 1, 15, 29, and q28d thereafter.

Quantity Limits: 30ds limit

References:

1. Furie, Richard, et al. "Two-year, randomized, controlled trial of belimumab in lupus nephritis." *New England Journal of Medicine* 383.12 (2020): 1117-1128.

Revision History:

Date	What changed	Pharmacist's initials
4/14/21	I wrote the criteria. EBRx reconsidered coverage due to the BLISS-LN trial that measured clinical endpoints. Previously the drug was not covered by EBRx plans and still does not cover it for people not qualifying with LN, due to lack of clinical endpoint data. SELENA-SLEDAI was measured in the BLISS trials that includes lab values to help patients qualify as responders where clinical improvement in health was not independently established or where the benefit of belimumab waned (was not durable). For EBRx plans for which we do not manage medically-administered drugs, belimumab would likely not be provided on the pharmacy benefit.	JJ

CONFIDENTIAL

Belumosudil (Rezurock®)

200 mg Tablet

EBRx PA Criteria

FDA-approved for:

Treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.\

Criteria for new users
1. Diagnosis of chronic graft versus host disease (cGVHD)
2. Patient has been treated with at least two prior lines of systemic therapy with persistent manifestations of cGVHD
3. Patient's age is 12 years or older
Approve for 12 months if all criteria met.

Dose: 200 mg PO once daily. Treatment continues until progression of GVHD or unacceptable toxicity.

References:

1. Cutler, Corey, et al. "Belumosudil for Chronic Graft-versus-Host Disease (cGVHD) After 2 or More Prior Lines of Therapy: The ROCKstar Study." Blood (2021).
2. NIH response criteria for cGVHD: https://www.sciencedirect.com/science/article/pii/S108387911500155X
3. Rezurock PI: https://www.rezurock.com/full-prescribing-information.pdf

Quantity Limits: 1/1

Revision History:

Date	What changed	Pharmacist's initials
9/21/21	Criteria written	SK

Belzutifan (Welireg©)

40 mg tablet

EBRx PA Criteria

FDA-approved for:

Treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

Criteria for new users
1. Diagnosis renal cell carcinoma, central nervous system hemangioblastoma, or pancreatic neuroendocrine tumor
2. Diagnosis of von Hippel-Lindau (VHL) disease with documentation of germline VHL alteration
3. Disease does not require immediate surgery
4. No metastatic disease

Notes:

Dose 120 mg PO daily until disease progression or unacceptable toxicity.

Reference:

Belzutifan package insert. https://www.merck.com/product/usa/pi_circulars/w/welireg/welireg_pi.pdf.

Quantity Limits: 3/1

Revision History:

Date	What changed	Pharmacist's initials
10/21/2021	Criteria written. Drug discussed in EBRx P&T	SK

CONFIDENTIAL

Binimetinib (Mektovi™)

15 mg tablets

EBRx PA Criteria

Mektovi (binimetinib) is FDA approved in combination with Braftovi (encorafenib) for:
Melanoma, unresectable or metastatic with BRAF V600E V600K mutation.

Criteria for new users
1. Patient must have histologically confirmed, unresectable or metastatic cutaneous melanoma or unknown primary melanoma.
2. Tumor must be BRAF V600E or BRAF V600k mutation positive
3. Patient must be ECOG 0 or 1.
4. Binimetinib MUST be used in combination with encorafenib
5. No prior BRAF or MEK inhibitor.
If all criteria met, approved for 6 months QL: Binimetinib: 6 tabs/day
Note: Treatment continues until progression or unacceptable toxicity.
Doses -binimetinib 45mg BID **Evidence:** Encorafenib + Binimetinib improved overall survival compared to vemurafenib (34 mo versus 17 mo, HR 0.61 95% CI 0.47-0.79) in patients with advanced/metastatic melanoma who were either treatment naïve or had progressed on or after immunotherapy. **References:** 1. Dummer R et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018 May;19(5):603-615. NCT01909453 PMID 29573941 2. Dummer R et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018 Oct;19(10):1315-1327. NCT01909453 PMID 30219628

Revision History:

Date	What changed	Pharmacist's initials
9/25/18	I wrote criteria.	JJ
4/18/19	Reviewed criteria (no major change) and added references and evidence summary	SK
9/30/19	Reviewed criteria. No change in criteria. Added quantity limits.	SK
4/27/2020	Divided encorafenib and binimetinib criteria into two documents due to new encorafenib indication for colorectal cancer that does not require binimetinib co-therapy. **No change in binimetinib criteria**.	SK
7/26/2021	Criteria reviewed. Clarified criteria 5. No other changes.	SK

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Blinatumomab (Blincyto®)

35 mcg vial

EBRx PA Criteria

is FDA-approved for:

- CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.
    - This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
    - NOT COVERED Data limited to single arm trial demonstrating response rates only.
        - Reference: Gökbuget N et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood. 2018 Apr 5;131(14):1522-1531. doi: 10.1182/blood-2017-08-798322. Epub 2018 Jan 22. Erratum in: Blood. 2019 Jun 13;133(24):2625. PMID: 29358182; PMCID: PMC6027091. [BLAST]
- Relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL). SEE CRITERIA

Criteria for new users
1. Diagnosis of relapsed or refractory acute lymphocytic leukemia (ALL)
2. Leukemia is CD19 positive
3. Disease has relapsed or is refractory [e.g. patient has been treated with at least one prior therapy with no response OR disease has relapsed or progressed after response]
If criteria are met, approve x 16 months. No renewals without justification. Maximum duration of therapy is 9 cycles (see dosing below).

Adult dosing (see PI for pediatric dosing):

Note: Hospitalization is recommended for the first 9 days of cycle 1, and the first 2 days of cycle 2.

Cycle 1: IV: 9 mcg daily administered as a continuous infusion on days 1 to 7, followed by 28 mcg daily as a continuous infusion on days 8 to 28 of a 6-week treatment cycle.

Cycles 2 through 5: 28 mcg daily administered as a continuous infusion on days 1 to 28 of a 6-week treatment cycle.

Cycles 6 through 9: 28 mcg daily administered as a continuous infusion on days 1 to 28 of a 12-week treatment cycle.

The TOWER trial randomized patients with relapsed/refractory ALL to either blinatumomab or standard chemotherapy. Overall survival was significantly improved in the blinatumomab group (7.7 mo vs 4 mo; HR 0.71; 95% CI, 0.55 to 0.93; P = 0.01) as well complete response rate (78% vs 41%).[1] Health-related quality of life was also improved in the blinatumomab group.[2]

A cost-effectiveness analysis estimated the ICER for blinatumomab vs chemo to be $110,108/QALY gained, and blinatumomab has a 74% chance of being cost effective based on threshold of $150,000/QALY gained.[3]

References:

1. Kantarjian H et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med. 2017 Mar 2;376(9):836-847. doi: 10.1056/NEJMoa1609783. PMID: 28249141; PMCID: PMC5881572.
2. Topp MS et al. Health-related quality of life in adults with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab. Blood. 2018 Jun 28;131(26):2906-2914. PMID 29739753
3. Delea TE. Cost-effectiveness of blinatumomab versus salvage chemotherapy in relapsed or refractory Philadelphia-chromosome-negative B-precursor acute lymphoblastic leukemia from a US payer perspective J Med Econ. 2017 Sep;20(9):911-922. doi: 10.1080/13696998.2017.1344127. Epub 2017 Jul 11. PMID: 28631497.

Quantity Limits: n/a (medical benefit drug)

Revision History:

Date	What changed	Pharmacist's initials
6/17/2021	Criteria written	SK

Bosentan (Tracleer®)

62.5mg, 125mg oral tablets, 32mg soluble dispersible tablet (age≤12y)

EBRx PA Criteria

Bosentan (Tracleer) is FDA-approved for:

- treatment of PAH (WHO Group I) in patients with NYHA Class II, III, or IV symptoms to improve exercise capacity and decrease the rate of clinical deterioration;
- Treatment of PAH (WHO group 1) in pediatric patients >3 years with idiopathic or congenital PAH to improve pulmonary vascular resistance resulting in an improvement in exercise ability.

Criteria
1. The patient must have the diagnosis of PAH (Group I) and either be taking a CCB and still having symptoms, or have failed a CCB.
2. The patient must have tried and failed a PDE5 inhibitor (like sildenafil or tadalafil)
OR
3. The patient must have the diagnosis of pulmonary hypertension (Group 5)
To access 32mg dispersible tablets, the patient must be under age 12 AND under 25kg.
Dosing: <40kg, 62.5mg BID. >40kg, 62.5mg BID X4w, then 125mg BID. Doses >125mg BID do not appear to offer additional benefit but may increase liver toxicity risk. Pediatric dosing is weight-based.

Quantity Limits: 2 tabs/1 day (60 tabs/30d), either dosage form. Use dose optimization.

Addendum:

Diagnostic Criteria and WHO categorization of PH						
	All Groups	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 5**
Description	**Elevated PAP**	**Pulmonary arterial hypertension**	**Pulmonary venous hypertension**	**PH due to hypoxemia**	**Chronic thromboembolic PH**	**Miscellaneous or multifactorial PH**
Estimated prevalence	**Up to 10-20% of the general population**	**15 cases/1,000,000 overall; 6 cases per 1mil for idiopathic PAH**	**>3-4 mil in US**	**20% in COPD pts w/ a prior hospitalization for COPD**	**0.5-2% (up to 3.8%) in survivors of acute PE**	**Unclear**
Diagnostic criteria						
Mean PA	**≥25**	**≥25**	**≥25**	**≥25**	**≥25**	**≥25**

pressure, mmHg						
PCWP or LVEDP, mmHg		**≤15**	**>15**	**≤15**	**≤15**	**≤15**
PVR, dynes/s/cm		>240		>240	>240	>240

References:

1. Galiè, Nazzareno, et al. "2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)." *European heart journal* 37.1 (2015): 67-119. https://orbi.uliege.be/bitstream/2268/192756/1/eur%20h%20j%202016%2037%2067.full.pdf

Revision History:

Date	What changed	Pharmacist's initials
2-6-15	I wrote the criteria.	JJ
12/19/17	I added the 32mg dispersible tablet and included an age limit of 12 or younger and a weight limit based on Lexi-Comp dosing guidelines.	JJ
9/25/2019	I reviewed the criteria. I added reference 1.	JJ

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Bosutinib (Bosulif®)

100mg, 400 mg, 500 mg oral tablets

EBRx PA Criteria

FDA-approved for:

- Newly-diagnosed chronic phase Ph+ chronic myelogenous leukemia (CML). T NOT COVERED
- Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy.

Criteria for new users
1. Ph+ chronic myeloid leukemia (CML) in chronic phase, accelerated/advanced phase, or blast crisis with resistance*, intolerance, or contraindication to imatinib AND dasatinib (note: Ph+ may also be denoted as t(9;22) or BCR/ABL)
*Resistance to CML therapy is generally defined as any of the following: d. Inadequate response (defined as one of the following): i. After 3 months of therapy: Lack of complete hematologic response (Platelets <450 x10^9/L; leukocyte count <10 x 10^9/L) ii. After 3 months of therapy: Cytogenetic analysis shows >95% Ph+ metaphases iii. After 6 months of therapy: BCR-ABL1 (IS) >10% by quantitative PCR (qPCR) iv. After 6 months of therapy: Cytogenetic analysis shows >35% Ph+ metaphases v. After 12 months of therapy: BCR-ABL1 (IS) >1% by quantitative PCR (qPCR) vi. After 12 months of therapy: Cytogenetic analysis shows >0% Ph+ metaphases e. Progression of disease after a cytogenetic/hematologic response was achieved f. Documentation of mutation associated with drug resistance (typically checked after failure of first-line therapy—see below)
If criteria 1 is fulfilled, approve for 6 months
Criteria for continuation
Review of fill history indicates compliance with therapy
No progression of disease
No unacceptable toxicity
If continuation criteria fulfilled, approve for 1 year Quantity limits: 28 day supply max

Note about EBRx coverage: EBRx prefers imatinib for treatment of all phases of CML. Dasatinib is preferred after imatinib therapy due to cost advantage and impending patent expiration. Bosutinib may be covered if the patient experiences resistance or intolerance to imatinib and dasatinib. NCCN guidelines suggest using a non-imatinib agent for first line therapy for intermediate/high risk patients (risk determined by Sokal or Hasford methods) based on quicker time to response. Although quicker time to response has been associated with improved outcomes, non-imatinib agents have not been shown to improve overall survival compared to

imatinib in the first line setting. Therefore, EBRx recommends that non-imatinib agents be denied access for first line use unless there is documentation of resistance or intolerance to a trial of imatinib.

Notes:

General CML information:

5. Cytogenetic monitoring: Chromosomes are examined directly for BCR-ABL chromosomal translocation. Number of cells in metaphase are examined. The number of metaphase cells that contain BCR-ABL are divided by total number of metaphase cells to get a percentage. Test requires bone marrow aspirate.
6. Molecular monitoring: Transcripts for BCR-ABL mRNA are quantified via real time PCR. "IS" denotes that the result is obtained via a standardized method. Test requires peripheral blood sample.
7. Cytogenetic and molecular monitoring are both valid. Since cytogenetic monitoring requires bone marrow biopsy, molecular monitoring may be preferred.
8. Analysis of BCR-ABL mutations is typically not done until failure of first-line therapy for chronic phase CML but may be checked sooner in advanced phase. If a mutation is documented that predicts resistance to imatinib or other therapy, an alternative agent should be used. NCCN has guide for treatment options according to which mutation is identified.

Treatment recommendations based on BCR-ABL1 mutation profile (NCCN CML version 2.2022)	
Contraindicated Mutations	Drug
T315I/A, F317L/V/I/C, V299L	Dasatinib
T315I, Y253H, E255K/V, F359V/C/I	Nilotinib
T315I, V299L, G250E, F317L	Bosutinib
None	Asciminib, Ponatinib, Omacetaxine, stem cell transplant, clinical trial

Notes regarding EBRx criteria:

3. Above criteria for resistance/failure of imatinib were obtained from NCCN guidelines Early Treatment Response Milestones page CML-3 in version 1.2019 and guideline published by European LeukemiaNet (ELN).[1] ELN proposes more restrictive resistance/failure definitions for second line therapy, however, NCCN has no specific guidelines. Therefore, will leave resistance/failure definitions as listed above.
4. Bosutinib in the first line setting was shown to induce quicker responses as compared to imatinib. Though quicker responses have been associated with improved outcomes, no overall survival benefit has been demonstrated in the primary study.[2] Imatinib will be

preferred until more data is available.

5. After failure of first line therapy, there are no randomized trials showing one TKI to be superior to another.

Adult bosutinib dosing:

First-line treatment of CML: 400 mg PO daily

Second/subsequent-line treatment of CML: 500 mg PO daily

REFERENCES:

5. Baccarani M et al. Blood. 2013 Aug 8;122(6):872-84. PMID 23803709
6. Cortes JE et al. J Clin Oncol. 2018 Jan 20;36(3):231-237 NCT02130557

Revision History:

Date	Notes	Pharmacist's initials
3/6/13	Criteria created	JB
3/5/19	Criteria updated requiring imatinib and dasatinib trial before proceeding with bosutinib; also added general information about CML monitoring	SK
8/7/19	Criteria reviewed. No change.	SK
6/18/2020	Added "(note: Ph+ may also be denoted as t(9;22) or BCR/ABL)"	SK
8/20/2020	Criteria reviewed. No change	SK
10/2/2021	Criteria reviewed. No changes to criteria. Now has full approval for newly diagnosed indication—updated FDA approvals as such.	SK
12/6/2021	Updated Table re: treatments recs based on mutation	SK

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Botulinum toxins (various)
AbobotulinumtoxinA (Dysport®)
IncobotulinumtoxinA (Xeomin®)
OnabotulinumtoxinA (Botox®)
PrabotulinumtoxinA (Jeuvea®)
RimabotulinumtoxinB (Myobloc®)

Injectable

EBRx PA Criteria/ EBRx Medical PA Criteria

10/2/2019

Criteria for new users

1. The patient must have the diagnosis of:
   - Axillary hyperhidrosis OR
   - Cervical dystonia OR
   - Chronic migraine (>15 headache days/month for the previous 3 months, lasting >4 hours per day; AND still have an inadequate response to triptan therapy. OR
   - Spasticity OR
   - Sialorrhea

Note: EBRx will not approve use for strabismus. Please see subsection below.

If the criteria are fulfilled, approve PA for 1 year.

FDA-approved uses:	Axillary hyperhidrosis	Cervical dystonia	Chronic migraine	Glabellar lines	Forehead lines	Lateral canthal lines	Upper limb spasticity	Lower limb spasticity	Spasticity in adults	Overactive bladder	Strabismus and blepharospasm associated w/ dystonia	Urinary incontinence due to detrusor overactivity	Blepharospasm	Sialorrhea
Botox				Cosmetic	Cosmetic	Cosmetic	**2-17y**	**Adults**						
Dysport				Cosmetic				Age ≥2y						
Xeomin				Cosmetic										

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Jeuveau				Cosmetic										
Myobloc		[redacted]												[redacted]

Spasticity:

A meta-analysis of botulinumtoxinA products (Botox, Dysport, & Xeomin) showed they are effective and safe in adult patients with upper and lower limb spasticity after stroke. BTXA improves muscle tone, physician global assessment, and disability assessment scale in upper limb spasticity and increases the Fugl-Meyer score in lower limb spasticity. BTXA did not have a significant effect on active upper limb function and adverse events. For lower limb spasticity, BTXA had no effect on muscle tone or gait speed or adverse events.

- Dong, Y., et al. "Efficacy and safety of botulinum toxin type A for upper limb spasticity after stroke or traumatic brain injury: a systematic review with meta-analysis and trial sequential analysis." (2017): 256-267.

Urinary incontinence (Botox is the only one FDA-approved):

This NMA of 19 trials showed Botox was associated with improved outcomes, including reductions in the # of micturitions in 24 hrs and the number of incontinence episodes, compared to mirabegron. Mirabegron was associated with a lower risk of UTIs vs Botox, however.

- Lozano-Ortega G, Walker D, Rogula B, Deighton A, et al. The Relative Efficacy and Safety of Mirabegron and OnabotulinumtoxinA in Patients With Overactive Bladder who have previously been managed with an Antimuscarinic: A Network Meta-analysis. Urology 127:1-8, 2019.

Migraine:

This meta-analysis of 17 trials (6 chronic migraine, 11 episodic migraine attacks) and 3646 patients of botulinum toxin in reducing the frequency of migraine reported a tendency in favor of BTXA over placebo at 3 m, with a mean difference in the OVERALL change of migraine frequency of -0.23 (95%CI, -0.47 to 0.02; p=0.08). The reduction in CHRONIC migraine frequency was significant, with a mean differential change of -1.56 (95%CI, -3.05 to -0.07; p=0.04), significant after 2 months. There was not a significant improvement in episodic migraine reduction with a mean difference in change of migraine frequency per month of -0.17 (95%CI, -0.41 to 0.08; p=0.18), with statistical heterogeneity. There was also an improvement in the patient's QOL at 3 months in the BTXA group (p<0.0001). Further adverse events were significantly increased, RR=1.32 (p=0.002).

BOTTOM LINE: BTXA should not be used for episodic migraine. This MA as well as the American Academy of Neurology in 2008 led to acknowledgment of the inefficacy of BTXA for episodic migraines.

- Bruloy, Eva (01/2019). "Botulinum Toxin versus Placebo: A Meta-Analysis of Prophylactic Treatment for Migraine.". *Plastic and reconstructive surgery (1963)* (0032-1052), 143 (1), p. 239.

Herd, Clare P., et al. "Botulinum toxins for the prevention of migraine in adults." *Cochrane Database of Systematic Reviews* 6 (2018).

Sialorrhea (excessive salivation associated w/ neurological disorders or local anatomical abnormalities):

This mixed treatment NMA of 15 trials determined that compared to placebo, benztropine and BTX A & B are associated with drooling. **Benztropine showed to be substantially and statistically superior to BTX A &/or B**. In children with cerebral palsy or adults with Parkinson's disease, benztropine and BTXB and glycopyrrolate were superior to placebo, while BTXA was not.

Sridharan, Kannan, and Gowri Sivaramakrishnan. "Pharmacological interventions for treating sialorrhea associated with neurological disorders: A mixed treatment network meta-analysis of randomized controlled trials." *Journal of Clinical Neuroscience* 51 (2018): 12-17.

Blepharospasm (focal dystonia involving the orbicularis oculi muscles and other periocular muscles manifested by increased blinking and spasms of involuntary eye closure, usu bilateral, synchronous, and symmetric or asymmetric:

A systematic review by the American Academy of Ophthalmology identified two placebo-controlled randomized trials (n = 194) and four blinded comparative trials (n = 719) of different types of botulinum neurotoxin A (BoNT-A) for blepharospasm in adults [35]. The review concluded that periocular BoNT-A injections are more effective than placebo for reducing blepharospasm severity based on standardized rating scales and that the three types of BoNT-A (onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA) ***have similar efficacy***. In the largest placebo-controlled trial, patients treated with incobotulinumtoxinA improved by 0.8 points on a 4-point severity scale from a baseline score of 3.1 (adjusted mean difference compared with placebo 1.0 points, 95% CI 0.5-1.4) [36].

UpToDate. Treatment of dystonia. Blepharospasm. Accessed 2019 10 02.

Strabismus:

Cochrane Systematic Reviews-insufficient evidence. "Further high quality trials using robust methodologies are required to compare the clinical and cost effectiveness of various forms of botulinum toxin (e.g. Dysport, Xeomin, etc), to compare botulinum toxin with and without adjuvant solutions and to compare botulinum toxin to alternative surgical interventions in **strabismus** cases with and without potential for binocular vision."

Rowe, Fiona J., and Carmel P. Noonan. "Botulinum toxin for the treatment of strabismus." *Cochrane Database of Systematic Reviews* 3 (2017).

<u>Cervical dystonia</u>: involuntary activation of the muscles of the neck and shoulders; results in sustained abnormal posturing of the head, neck, and shoulders.

"Indirect comparisons between trials that used Dysport against placebo and trials that used Botox against placebo showed no significant differences between Dysport and Botox in terms of benefits or adverse events. A single injection cycle of BtA is effective and safe for treating cervical dystonia. Enriched trials (using patients previously treated with BtA), suggest that further injection cycles continue to work for most patients." It appears that BtA is more beneficial than trihexyphenidyl in cervical dystonia, but comparisons with other anticholinergics are lacking.

<u>Hyperhidrosis:</u>

Evidence for effectiveness and safety of treatments for primary hyperhidrosis is limited overall, and few firm conclusions can be drawn. There is moderate-quality evidence to support the use of botulinumtoxin for axillary hyperhidrosis. A trial comparing botulinumtoxin with iontophoresis for palmar hyperhidrosis is warranted.

Wade, R., et al. "Interventional management of hyperhidrosis in secondary care: a systematic review." *British Journal of Dermatology* 179.3 (2018): 599-608.

Revision History:

Date	Changes	
2/9/2011	Document Created	
7/17/12	Added migraine criteria; specified infantile esotropia as indication and requirement for 2 w of eye patching previous to botulinum	
7/31/12	Added medication overuse reference, definition, hyperlink; placed article/reference in the EBRx file on the network.	
2/25/16	Added upper limb spasticity data and allowed access to Xeomin for post stroke. No access for this with Botox because of lack of data.	
10/2/2019	I reviewed the evidence including meta-analyses and NMA for each indication as shown above. Currently, UAMS/EBRx has a contract on Xeomin. The evidence supports this is very likely to have a similar effect in most if not all the indications. I removed the info on this document regarding anal fissures, as current treatment does not support BTXA or B for this purpose.	

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Brentuximab vedotin (Adcetris®)

50mg IV vial

EBRx PA Criteria

Is FDA-approved for:

- *Classical Hodgkin lymphoma (cHL)* in the following treatment settings:
  - Previously untreated Stage III or IV cHL, in combination with doxorubicin, vinblastine, and dacarbazine NOT COVERED: ECHELON-1 study used unconventional primary endpoint (modified progression free survival) and no overall survival nor quality of life benefit has been demonstrated to date.
    - Reference: Connors JM et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. N Engl J Med. 2018 Jan 25;378(4):331-344. PMID 29224502 NCT01712490
  - cHL at high risk of relapse or progression as post autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation
  - cHL after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates
- *T cell lymphoma subtypes*
  - Previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone
  - Systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multiagent chemotherapy regimen
  - Primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) in patients who have received prior systemic therapy

Classical Hodgkin Lymphoma (relapsed/refractory)
1. Diagnosis of classical Hodgkin lymphoma that is progressing
2. Patient has undergone autologous stem cell transplant (ASCT) or, if the patient is not an ASCT candidate, he/she has failed at least two multi-agent chemotherapy regimens
3. No prior brentuximab
4. Brentuximab will be given as single agent

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If all of above criteria are met, approve x 1 year
Note: -Classical Hodgkin Lymphoma includes the following subtypes: nodular sclerosis, mixed cellularity, lymphocyte-predominant, and lymphocyte-rich, which are all treated similarly. - Nodular lymphocyte-predominant Hodgkin lymphoma is NOT a type of classical Hodgkin lymphoma and is not covered under this indication
Evidence: 1. Patients meeting the above criteria were given brentuximab, the response rate was 75% with a complete response rate of 34%. The median progression free survival (PFS) was 9.3 months. The 5-year overall survival (OS) was 41% with a median OS of 41 months. According to a registry study, patients treated with brentuximab after autologous transplant had improved OS compared with patients who were not treated with brentuximab (median 57 months vs 31 months).[1,2] 2. Dose: 1.8 mg/kg IV (max 180 mg) every 3 weeks x 16 doses total until disease progression or unacceptable toxicity. References: 1. Chen R et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2016 Sep 22;128(12):1562-6. PMID 274328752. 2. Tsirigotis P et al. Positive impact of brentuximab vedotin on overall survival of patients with classical Hodgkin lymphoma who relapse or progress after autologous stem cell transplantation: A nationwide analysis. Hematol Oncol. 2018 Oct;36(4):645-650. doi: 10.1002/hon.2521. PMID 298823634. 3. NCCN guidelines for Hodgkin Lymphoma: https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf

Classical Hodgkin Lymphoma (post-transplant consolidation therapy)
1. Diagnosis of classical Hodgkin lymphoma
2. Patient has undergone autologous stem cell transplant within the past 1-2 months and has no known progression of disease
3. Presence of *one* of the following high risk factors: a) Primary refractory Hodgkin lymphoma (i.e. failure to achieve complete remission after first line therapy OR progression of disease **during** first line therapy) b) Relapse or progression of disease within 12 months of initial remission

c) Extranodal involvement (e.g. liver, bone, lung, etc)
4. No prior brentuximab
5. Brentuximab will be given as single agent
If all of above criteria are met, approve x 1 year. Maximum duration of therapy for post-transplant consolidation is 16 doses or ~1 year.
Note: -Classical Hodgkin Lymphoma includes the following subtypes: nodular sclerosis, mixed cellularity, lymphocyte-predominant, and lymphocyte-rich, which are all treated similarly. - Nodular lymphocyte-predominant Hodgkin lymphoma is NOT a type of classical Hodgkin lymphoma and is not covered under this indication
Evidence: 1. The AETHERA trial randomized patients meeting above criteria to brentuximab or placebo. The primary endpoint of progression free survival (PFS) was improved in the brentuximab group (median 43 mo vs 24 mo). There was no statistical improvement in overall survival though the 85% crossover rate may have confounded the result.[1,2,3] 2. Dose 1.8 mg/kg IV (max 180 mg) every 3 weeks x 16 doses total. References: 1. Moskowitz CH et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015 May 9;385(9980):1853-62. PMID 25796459 NCT01100502 2. Moskowitz CH et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. Blood. 2018 Dec 20;132(25):2639-2642. PMID 30266774 NCT01100502 3. Ramsey S et al. Quality of life results from a phase 3 study of brentuximab vedotin consolidation following autologous haematopoietic stem cell transplant for persons with Hodgkin lymphoma. Br J Haematol. 2016 Dec;175(5):860-867. PMID 27649689 NCT01100502 4. NCCN guidelines for Hodgkin Lymphoma: https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf

T Cell Lymphoma (untreated)
1. Diagnosis of systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCLs) including angioimmunoblastic T-cell lymphoma and

PTCL not otherwise specified

2. No prior therapy for ALCL/PTCL

3. Brentuximab will be used in combination with cyclophosphamide, doxorubicin, and prednisone

4. Growth factor support will be used (i.e. filgrastim or pegfilgrastim)

If all of above criteria are met, approve x 6 months. Therapy consists of 6 cycles maximum.

Evidence:

1. The ECHELON-2 trial randomized patients meeting above criteria to brentuximab-cyclophosphamide-doxorubicin-prednisone or CHOP. The primary endpoint of overall survival was improved in the brentuximab group (HR 0.66, 95% CI 0.46-0.95) with similar rates of adverse events.[1]
2. Dose: 1.8 mg/kg IV (max 180 mg) every 3 weeks x 8 cycles maximum (in combination with cyclophosphamide, doxorubicin, and prednisone.

References:

1. Horwitz S et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019 Jan 19;393(10168):229-240. PMID 30522922 NCT017771524.
2. NCCN guidelines for T-cell lymphomas: https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf

T Cell Lymphoma (systemic/cutaneous ALCL or mycosis fungoides, relapsed/refractory)

1. Diagnosis of systemic anaplastic large cell lymphoma (ALCL) or primary cutaneous ALCL or CD30-expressing mycosis fungoides

2. No prior brentuximab

3. Progression of disease after at least one prior therapy

4. Brentuximab will be given as single agent

If all of above criteria are met, approve x 1 year.

Evidence:

1. In patients with systemic ALCL, brentuximab produced a response rate of 86% with a complete response rate of 57% in a single arm trial. The 5-year rate of overall survival was 60%. Of all patients, 82% had reduction in B symptoms.[1] The response rate with brentuximab is much high than those seen with other newer agents such Pralatrexate and Romidepsin.[2]
2. In patients with primary cutaneous ALCL or CD30-expressing mycosis fungoides who had received prior therapy, brentuximab was compared to investigator's choice of bexarotene or methotrexate. The primary endpoint of progression free survival was prolonged in the

brentuximab group (median 17 vs 3.5 months) along with a statistically and clinically greater improvement in the patient-reported burden of symptoms domain of the Skindex-29 score (MCID 10 points).[3]

3. Dose: 1.8 mg/kg IV (max 180 mg) every 3 weeks until progression of disease or unacceptable toxicity

References:

1. Pro B et al. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood. 2017 Dec 21;130(25):2709-2717. PMID 28974506 NCT00866047
2. NCCN guidelines for T-cell lymphomas: https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf
3. Prince HM et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet. 2017 Aug 5;390(10094):555-566. PMID 28600132

Date	Notes	Pharmacist's initials
6/10/14	JJ created PA criteria. SK's handout is in JJ's electronic file contracts/DUEC Drug Delivery/Brentuximab	JJ
6/17/19	Criteria reviewed: add new **covered** indications: • high-risk Hodgkin lymphoma patients after autologous stem cell transplant, • untreated ALCL or PTCL, • cutaneous ALCL or • mycosis fungoides. The following new indication will not be covered: untreated Hodgkin Lymphoma	SK
6/16/2020	Criteria reviewed. No changes	SK
9/1/2021	Criteria reviewed. No changes.	SK

Brexanolone (Zulresso®)

MEDICAL PA

100mg/20mL for IV infusion

EBRx PA Criteria

FDA-approved for: postpartum depression

Criteria for new users
1. Patient must be female, and be at least temporarily not breastfeeding for 4 days after receiving brexanolone.
2. Diagnosis of a major depressive episode with onset no later than 4 weeks after delivery
3. Currently 6 months or less postpartum.
4. HAM-D total score ≥26, before infusion.
5. Must have kidney function better than 15 mL/min/1.73m^2
If the criteria are met, the approved dose will be: 0-4h: 30mcg/kg/hour 4-24h: 60 mcg/kg/hour 24-52: 90 mcg/kg/hour; may reduce dose to 60 mcg/kg/hour based on tolerability 52-56 hours: 60 mcg/kg/hour 56-60 hours: 30 mcg/kg/hour

Quantity Limits: QL is 1-60 minute infusion.

References:

1. Meltzer-Brody, Samantha, et al. "Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials." *The Lancet* 392.10152 (2018): 1058-1070.

2. Lexi-Comp. Brexanolone. Accessed 10/14/19.

Revision History:

Date	What changed	Pharmacist's initials
10/14/19	I wrote the criteria based on the clinical trial. I excluded eligibility to patients with HAM-D scores of 25 or better (lower/less severe) as the trial showed there was not a significant improvement in those patients.	JJ
1/14/2021	I reviewed the criteria. No changes were made.	JJ

CONFIDENTIAL

Budesonide (Uceris®)

tab SR 24h 9mg

EBRx PA Criteria

FDA-approved for active Crohn's disease, mild-moderate involving the ileum and/or ascending colon; maintenance of remission of Crohn's disease, mild-mod involving the ileum and/or ascending colon; ulcerative colitis, active, mild-mod to induce remission:

Criteria for new users
1. Patient must have the diagnosis of ulcer colitis or Crohn's disease, and
2. Patient must have either failure of or be intolerant to sulfasalazine, and
3. patient must have either failure of or be intolerant to mesalamine oral or rectal.
4. Patient must not be taking concurrent systemic corticosteroids. (Systemic budesonide is intended to provide the effect.)

Note: From the Pharmacists' Letter 3/13: Uceris is budesonide like Entocort EC...but not interchangeable. Both work locally in the GI tract to reduce systemic steroid effects...but they target different areas. Entocort EC targets the ileum and right colon for Crohn's disease...Uceris targets the entire colon for ulcerative colitis. UC tx is based on disease location and severity...patient preferences...and cost. Pts w/ distal disease may achieve remission w/ rectal mesalamine (Rowasa, etc) or hydrocortisone (Cortenema, etc)...but pts w/ more extensive disease usu need oral therapy. 5-ASA products (mesalamine, etc) are still first-line for inducing and maintaining remission in mild-mod dz.

Uceris would be an alternative to oral prednisone if 5-ASA products aren't effective. Uceris will cost about $1200/m; vs as little as $4 per month for prednisone. But adrenal suppression is unlikely when Uceris is used short-term.

Efficacy in Crohn's:
14 studies (1805 patients) were included: --Nine (779 patients) compared budesonide to conventional corticosteroids, 3 (535 patients) were placebo-controlled, and 2 (491 patients) compared budesonide to mesalamine. Findings: Oral 9 mg budesonide X 8w was significantly **more effective** than placebo for induction of clinical remission.

- 47% (115/246) of budesonide pts achieved remission at 8 w compared to 22% (29/133) of placebo pts (RR 1.93, 95% CI 1.37 to 2.73; 3 studies, 379 patients).

Budesonide X8w was significantly **less effective** than conventional steroids for induction of remission.

- 52% budesonide pts achieved remission at week 8 compared to 61% of pts who received conventional steroids (RR 0.85, 95% CI 0.75 to 0.97; 8 studies, 750 patients).

Budesonide was significantly **less effective** than conventional steroids among patients with severe disease (CDAI > 300)

- (RR 0.52, 95% CI 0.28 to 0.95). Studies comparing budesonide to mesalamine were not pooled due to heterogeneity (I2 = 81%).

One study (n = 182) found budesonide X8w to be **superior to mesalamine** for induction of remission.

- 68% (63/93) of budesonide pts were in remission at 8w compared to 42% (37/89) of mesalamine pts (RR 1.63, 95%CI1.23-2.16).
- The other study found **no statistically significant difference** in remission rates at 8w.
- 69% (107/154) of budesonide pts were in remission at 8 w compared to 62% (132/242) of mesalamine patients (RR 1.12, 95% CI 0.95 to 1.32).
- **Fewer AEs** occurred in those treated with budesonide compared to conventional steroids (RR 0.64, 95% CI 0.54 to 0.76) and budesonide was better than conventional steroids in preserving adrenal function (RR for abnormal ACTH test **0.65**, 95% CI 0.55 to 0.78).
- Authors' conclusions: Budesonide is more effective than placebo for induction of remission in Crohn's disease. Although short-term efficacy with budesonide is < with conventional steroids, particularly in those with severe disease or more extensive colonic involvement, the likelihood of AEs and adrenal suppression with budesonide is lower. The current evidence does not allow for a firm conclusion on the relative efficacy of budesonide compared to 5-ASA products.

Efficacy of oral budesonide in UC:

- Oral budesonide was significantly less likely to induce clinical remission than oral mesalamine after 8 weeks of therapy (RR 0.72, 95% CI 0.57 to 0.91).
- There was no significant benefit of oral budesonide in comparison to placebo for inducing clinical remission after 4 weeks of treatment (RR 1.41, 95% CI 0.59 to 3.39).
- A small pilot study reported no statistically significant difference in endoscopic remission between budesonide and prednisolone (RR 0.75, 95% CI 0.23 to 2.42). The study was small and not powered to evaluate the impact of budesonide on clinical remission.
- Suppression of plasma cortisol was significantly more common in prednisolone treated patients (RR 0.02, 95% CI 0.0 to 0.33). Two multicenter studies are ongoing.
- Authors' conclusions: At present, there is no evidence to recommend the clinical use of oral budesonide for the induction of remission in active UC. Mesalamine is superior to budesonide for the treatment of active UC.

Efficacy of rectal foam budesonide in UC:

2 identically designed, R, DB, PC trials evaluated the efficacy of budesonide foam for induction of remission in 546 pts w/ mild-mod UC proctitis or ulcerative proctosigmoiditis who received

budesonide foam 2 mg/25 mL BID X2w, then QD X4w, or placebo.

RESULTS: Remission at w6 occurred significantly more frequently among pts receiving budesonide foam than placebo (Study 1: 38.3% vs 25.8%; P ¼ .0324; Study 2: 44.0% vs 22.4%; P < .0001). A significantly greater % of pts receiving budesonide foam vs placebo achieved rectal bleeding resolution (Study 1: 46.6% vs 28.0%; P ¼ .0022; Study 2: 50.0% vs 28.6%; P ¼ .0002) and endoscopic improvement (Study 1: 55.6% vs 43.2%; P ¼ .0486; Study 2: 56.0% vs 36.7%; P ¼ .0013) at week 6. Most AEs occurred at similar frequencies between groups, although events related to changes in cortisol values were reported more frequently with budesonide foam. There were no cases of clinically symptomatic adrenal insufficiency. CONCLUSIONS: Budesonide rectal foam was well tolerated and more efficacious than placebo in inducing remission in pts w/ mild-mod ulcerative proctitis and ulcerative proctosigmoiditis.

Revision History:

Date	What changed	Pharmacist's initials
12/22/2015	I wrote the criteria.	JJ

CONFIDENTIAL

Burosumab-twza (Crysvita®) SC injection

10, 20, 30mg/mL (1mL)

EBRx PA Criteria

FDA-approved for: treating adults and children ages 1y+ with x-linked hypophosphatemia, a rare, inherited form of rickets

Criteria for new users
1. Diagnosis of x-linked hypophosphatemia (XLH) confirmed either by the presence of the PHEX mutation in the patient or a directly related family member or by a serum intact FGF-23 level of >30 pg/mL.
2. Fasting serum phosphorus level of ≤2.8mg/dL (or a level below the lower level of normal for reference)
3. A standing height below the 50th percentile for age and sex on the basis of local normative data from the US.
4. Must have received oral phosphate plus active vitamin D therapy for: • >12 consecutive months (for children >3y) or • >6 consecutive months (for children <3y)
5. Must have an X-Ray confirming rickets @ the growth plates OR bowing of femur, tibia, or both femur and tibia.
6. Must be age 1-12 years.

Criteria for continuation
1. Must have a serum phosphate level in the normal range during burosumab therapy.
2. Must be adherent to burosumab therapy.

References:

1. Carpenter, Thomas O., et al. "Burosumab therapy in children with X-linked hypophosphatemia." *N Eng J Med* 378.21 (2018): 1987-1998.

2. UpToDate (accessed 6/12/19), XLH.

3. Clinicaltrials.gov. NCT02915705 Efficacy and safety of burosumab (KRN23) versus oral phosphate and active vitamin D treatment in pediatric patients with X-linked hypophosphatemia (XLH).

CONFIDENTIAL

Revision History:

Date	What changed	Pharmacist's initials
6/17/19	I wrote the criteria. Although the FDA approval includes adults, I omitted it per EBRx discussion and related information from UpToDate stating "for adults with XLH, burosumab therapy is more difficult to quantify because they do not manifest active rickets and their height is already established. However, there could be significant benefit to burosumab because the hypophosphatemia may contribute to bone and joint pain, failure to heal fractures, and symptoms such as muscle weakness and poor stamina." Therefore, I recommend EBRx have a low threshold for changing these criteria to include symptomatic adults who may have or may in the future gain benefit from this drug.	JJ

CONFIDENTIAL

C-1 esterase inhibitor (Haegarda®)

EBRx PA Criteria

***Haegarda is the covered product for EBD. Neither Ruconest nor Cinryze is covered due to higher cost. However, in times of FDA listed drug shortages, Ruconest has been used off-label when Haegarda or Cinryze are not available.

1. The patient must have a diagnosis* of hereditary angioedema. (see diagnosis criteria below)
2. The drug must be used as chronic prophylactic medication.
3. The patient must have had ≥2 severe (with abdominal or upper airway involvement that requires hospitalization) or life threatening HAE attacks per month that require acute treatment, medical attention in an ED, or caused significant functional impairment (must be documented in the medical record), in the past year.
4. The patient must have a contraindication or adverse event to attenuated androgen (Danazol 200mg QD or methyltestosterone, stanozolol, or oxandrolone) prophylaxis. Please state the contraindication. _____
5. If "no" to having contraindication or adverse effect to androgens, the patient must have failed androgen treatment.
6. The patient must remain off angiotensin-converting enzyme inhibitors (ACE-I's).
7. The patient must remain off any type of estrogen-containing medication.

Note doses:

Haegarda: 60IU/kg subQ twice a week [Dose should be rounded up or down per 500 units to nearest 1000-unit dose.]

Weight	Haegarda Dose Range	Haegarda Dose
</= 41	0-2460	2000
42-58	2520-3480	3000
59-74	3540-4440	4000
75-91	4500-5460	5000
92-108	5520-6480	6000
109-124	6540-7440	7000

Routine prophylaxis against hereditary angioedema (HAE) attacks (Cinryze): I.V.: 1000 units every 3-4 days. Administer intravenously at 1 mL/minute (over 10 minutes); use within 3 hours of reconstitution.

Self-administration: Following patient training and instructions on self-administration, patient may self-administer prophylaxis (Cinryze) therapy. Epinephrine should be available during self-administration in the event of an acute, severe hypersensitivity reaction. Patient suffering from an acute laryngeal HAE attack and self-administering should be informed to seek immediate medical attention following treatment (potential for airway obstruction to occur).

Please submit documentation of patient's attack history for review.

*The diagnosis requires one clinical criterion and one laboratory criterion:
Clinical criteria:
☐Self-limiting, noninflammatory subcutaneous angioedema without urticaria, recurrent, and lasting more than 12 hours.
☐Self-remitting abdominal pain without clear organic etiology, recurrent, and lasting more than six hours.
☐Recurrent laryngeal edema.
☐A family history of recurrent angioedema and/or abdominal pain and/or laryngeal edema, if present, supports the diagnosis of HAE, although it is not required because the patient may have a new mutation or an acquired disorder.
Laboratory criteria:
☐C1 inhibitor levels < 50% of the lower limit of normal at two separate determinations (at least 1 month apart) with the patient in their basal condition and after the first year of life and C4 antigen level below the laboratory reference range.
☐C1 inhibitor function of < 50% of normal at two separate determinations (at least one month apart) with the patient in their basal condition and after the first year of life and C4 antigen level below the laboratory reference range.
☐Mutation in C1 inhibitor gene altering protein synthesis and/or function. This is the only laboratory criterion that can be used to make the diagnosis in patients younger than one year of age.

- The criteria stipulate that C1 inhibitor antigenic levels and functional levels must be < 50%. In most cases of type I HAE, the levels are <30%, although some patients have levels slightly higher (30-50%).

References:

1. Xu YY, Buyantseva LV, Agarwal NS, et al. Update on treatment of heritary angioedema. Clinical & Experimental Allergy, 43:395-405.
2. Zuraw BL, Hereditary Angioedema. N Engl J Med. 2008;359:1027-36.
3. Kaplan AP, Greaves MW. Angioedema. J Am Acad Dermatol. 2005 (Sept);53(3):373-388.
4. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. N Engl J Med. 1996;334:1630-4.
5. Kunschak M, Dngl W, Maritsch F, Rosen FS, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. Transfusion. 1998;38:540-549.
6. Hereditary Angioedema. UpToDate online. Accessed 6/6/14.
7. Maurer, Marcus, et al. "The international WAO/EAACI guideline for the management of hereditary angioedema–the 2017 revision and update." *Allergy* (2018).
8.

Criteria History:

Date	What was changed	Pharmacist's initials
6/6/14	PA was already written by someone besides me. I reformatted and	JJ

	added examples of androgens. I also changed on question 5, that androgen failure meant still having symptoms as in question 3 while taking the androgen. I also added references. I also included the documentation that should be included for the diagnosis. The Drug Delivery Committee minimized the US HAE Association Medical Advisory Board 2013 recommendations to not require androgen failure because of the disclosed financial conflicts with the committee members and their relationship to Viro-Pharma (maker of Cinryze). Together with unconflicted authors who wrote a different article which state androgens are effective prophylaxis for HAE, it was the decision of our committee to require androgen failure prior to access to Cinryze for HAE prophylaxis.	
2/6/18	I added Haegarda's dosing for prophylaxis of attacks. The DUEC met 2/5/18 and approved covering Haegarda and excluding Cinryze due to cost. Berinert would still be covered on the medical side for treatment of acute attacks.	JJ
3/12/18	We updated the criteria, inserting "adverse effect" as a way to avoid taking androgens, adding the 2017 HAE (expert opinion) guidelines (ref 7), and better defining the diagnosis by requiring C4 antigen level below normal.	JJ/JK
3/16/21	I reformatted the criteria. Otherwise, no changes.	JJ

CONFIDENTIAL

Cabozantinib (Cometriq®, Cabometyx®)

EBRx PA Criteria

FDA-approvals:

Cabometyx 20mg, 40mg, and 60mg oral tablets

- Monotherapy for advanced renal cell carcinoma (RCC). EBRx covers second line use only (see criteria)
  - EBRx does not recommend coverage for first line use of cabozantinib as monotherapy. Cabozantinib was compared to sunitinib and was found to improve progression free survival (cabo 8.6 mo vs. placebo 5.3 mo)[1], response rate (33% vs. 12%) but not overall survival at 35 month follow up (26.6 mo vs. 21.2 mo; HR 0.8, 95% CI 0.53-1.21)[2]. Alternatives to cabozantinib for first line treatment of RCC include pazopanib and sunitinib for any risk category of RCC and ipilimumab+nivolumab for intermediate or poor risk RCC.
  - REFERENCES:

    1. Choueiri TK et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. J Clin Oncol. 2017 Feb 20;35(6):591-597.

    2. Choueiri TK et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. Eur J Cancer. 2018 May;94:115-125.
- In combination with nivolumab for first-line treatment of advanced renal cell carcinoma (see criteria)
- Hepatocellular carcinoma (HCC) previously treated with sorafenib NOT COVERED
  - In HCC patients (Child Pugh A only) previously treated with sorafenib, cabozantinib statistically improved overall survival compared to placebo (10.2 mo vs 8 mo) (Abou-Alfa GK et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018 Jul 5;379(1):54-63. PMID 29972759 [NCT01908426]). EBRx deemed this increase in overall survival not to be clinically significant and does not recommend coverage of this indication.

Cometriq 20 and 80 mg oral capsules

- Progressive, metastatic medullary thyroid cancer

Medullary Thyroid Cancer (COMETRIQ only) Criteria for new users
1. Diagnosis of progressive, metastatic, medullary thyroid cancer
2. Medullary thyroid cancer must have known RET M918T mutation
3. Patient must be ECOG performance status 0-2 at initial request.
If the answer to all 3 questions above are “yes,” approve for 1 year.
Notes: 1. Cabozantinib 140 mg daily (Cometric) was compared with placebo in patients with

metastatic medullary thyroid cancer that was progressing (on or off therapy). There was no limit on # of prior therapies allowed. PFS was improved in the cabozantinib group (11.2 mo vs 4 mo) as well as response rate (28% vs 0%). Overall survival was not statistically higher in the cabozantinib group at the 42 mo follow up (26.6 mo vs 21.1 mo).[1] However, subgroup analysis showed a larger treatment effect in pt with RET M918T mutated tumors (overall survival of cabo vs. placebo: 44.3 mo vs 19.8 mo)[2]. RET mutations should be checked in all tumors per NCCN guidelines, therefore, EBRx criteria limits coverage to patients with the RET M918T mutation.

2. Per NCCN, kinase inhibitors may not be appropriate for patients with stable or slowly progressive indolent disease[3]. Note: vandetanib has similar indication but overall survival data have not been published yet.

Dose:

140mg/day unless taking concurrent 3A4 inducer.

Note that dosing for Cometriq is different from Cabometyx. Cometriq (capsules) was the first formulation of cabozantinib available. Cabometyx (tablets) was released at a later date and is manufactured more efficiently than the capsule. Bioequivalence studies of the capsules and tablets narrowly failed to meet criteria to deem the two formulations bioequivalent[4].

REFERENCES:

1. Elisei R et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013 Oct 10;31(29):3639-46. NCT00704730 PMID 24002501
2. Schlumberger M et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol. 2017 Nov 1;28(11):2813-2819. NCT00704730 PMID 29045520
3. NCCN guidelines. Thyroid Carcinoma version 3.2018. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed 3/18/19.

Nguyen et al. Pharmacokinetics of cabozantinib tablet and capsule formulations in healthy adults. Anti-Cancer Drugs. 27(7):669-678. PMID 27139820

Renal Cell Carcinoma (CABOMETYX): in combination with nivolumab
1. Patient meets criteria as listed in nivolumab (Opdivo) criteria under FIRST LINE TREATMENT CRITERIA for use with CABOZANTINIB.

Renal Cell Carcinoma (CABOMETYX): monotherapy
1. Diagnosis of advanced or metastatic renal cell carcinoma with a clear cell component that progressed after receiving at least one prior treatment with a VEGF-targeting TKI (pazopanib, sunitinib, axitinib, lenvatinib)
2. Patient must be Karnofsky performance status ≥70% at the initial request.
If the answer to both questions above are “yes,” approve for 1 year. QL of 60mg/day (RCC

dose) unless taking concurrent 3A4 inducer, not to exceed 80mg daily.

Notes:

1. Cabozantinib (Cabometyx) was compared to everolimus in patients with advanced renal cell carcinoma (RCC) with a clear cell component on pathology. Cabozantinib improved overall survival (21.4 mo vs 16.5 mo), progression free survival and response rate.[1]

Dose:

60 mg daily (Cabometyx).

Note that dosing for Cometriq is different from Cabometyx. Cometriq (capsules) was the first formulation of cabozantinib available. Cabometyx (tablets) was released at a later date and is manufactured more efficiently than the capsule. Bioequivalence studies of the capsules and tablets narrowly failed to meet criteria to deem the two formulations bioequivalent[2].

REFERENCES:

1. Choueiri TK et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomized, open-label, phase 3 trial. Lancet Oncol 2016;17:917-27). NCT01865747 PMID 27279544
2. Nguyen et al. Pharmacokinetics of cabozantinib tablet and capsule formulations in healthy adults. Anti-Cancer Drugs. 27(7):669-678. PMID 27139820

VEGFR=vascular endothelial growth factor, TKI=tyrosine kinase inhibitor

Revision History:

Date	What changed	Pharmacist's initials
9/16/16	I wrote the criteria	J Johnson
3/18/19	Updated FDA indications and recommended coverage. Added new FDA approvals of HCC and first line use in RCC (both not covered). Updated notes, rationale, and references.	SK
9/23/19	All criteria reviewed: no changes	SK
3/10/2020	Criteria reviewed: no changes	Sk
4/2/21	Applied EBRx criteria to UAS Plan.	JJ
4/29/21	Added criteria for renal cell carincoma in combination with nivolumab (see nivolumab criteria)	SK

Calcium acetate oral solution (Phoslyra Solution®)

PA Criteria

1. Is the patient unable to swallow tablets or capsules?	( ) YES ( ) NO

The claim should be denied if other tablets/capsules are on the current profile.

If both questions are answered yes, PA is approved for one year.

Revision History

Date	Notes	Pharmacist's initials
5/10/12	JJ created the criteria prior to the IB's 10/11/11 mtg. 5/10/12 JJ added the revision history table.	JJ

CONFIDENTIAL

Cannabidiol (CBD) Extract (Epidiolex)

100mg/mL solution

EBRx PA Criteria

FDA-approved for: Treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years old and above.

Criteria for new users
1. Patient must have the diagnosis of seizures due to either Lennox-Gastaut Syndrome or from Dravet Syndrome as documented in the medical record.
2. Patient must be ≥2 years of age.
3. Patient must have had at least 2 drop seizures each week for the previous 28 days (clinical trial inclusion)
4. Prescriber must submit chart notes and documentation that the patient is refractory to antiepileptic drugs with documented failure on ≥2 anticonvulsant drugs.
If all criteria above are met, approve for 3 months.

Criteria for continuation
1. Patient must be adherent to the prescribed dose.
2. Patient must show positive improvement by a reduction from baseline in seizure frequency.
If continuation criteria are met after initial use, approve for 12 months.

Note: Dose is 2.5mg/kg BID, then increase as quickly as 2.5mg/kg every other day to a max dose of 10mg/kg BID.

Revision History:

Date	What changed	Pharmacist's initials
1/14/19	I wrote the criteria.	JJ
6/23/2020	I reviewed the criteria. No changes.	JJ

CONFIDENTIAL

Clinical Trials: **

Trial	N	Population	Endpoints	Results
Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome[2] DB, PC, 23 Centers, 24 wk	225	2 to 55 years old with LGS Mean 15.5y previously tried ASDs: mean 6 # of ASDs in regimen: 3 Groups similar at baseline	Percentage reduction from baseline in the frequency of drop seizures (average per 28 days) during the treatment period	20-mg cannabidiol group→41.9% (p=0.005) 10-mg cannabidiol group→37.2% (p=0.002) placebo group→17.2% Estimated mean difference in reduction: 20-mg vs placebo: 21.6%. 10-mg vs placebo: 19.2%
Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome[3] DB, PC, 30 Centers, 24 wk	120	Ages 2y to 18 w/DS; Mean 9.8y previously tried ASDs: mean 4.6 # of ASDs in regimen: 3 Groups similar at baseline	% change per 28 days from the 4-week baseline period in convulsive-seizure frequency during the 14-week treatment period among patients who received cannabidiol vs placebo	Median 12.4 seizures per month at baseline Tx group down →5.9 (p=0.01) Median 14.9 at baseline to Placebo group→14.1 Adjusted median difference in convulsive-seizure frequency was significant with a 22.8% reduction.

DB=double-blind, PC=placebo controlled, LGS-Lennox-Gastaut Syndrome, DS- Dravet Syndrome, ASD- Anti-seizure Drugs

References:

1. Devinsky, Orrin, M.D., et al. "Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome." NEJM 378.20 (2018): 1888-97. ProQuest. 6 Nov. 2018 .

2. Orrin, Devinsky, et al. "Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome." NEJM 376.21 (2017): 2011-20. ProQuest. 6 Nov. 2018 .

CONFIDENTIAL

Caplacizumab (Cablivi®)

Kit 11mg

EBRx PA Criteria

Medical PA if needed; SQ can be self-administered.

is FDA-approved for: for treatment of acquired thrombotic thrombocytopenic purpura (aTTP) in adults, in combination with plasma exchange and immunosuppressive drug therapy

Criteria for new users
1. Must have diagnosis of acquired thrombotic thrombocytopenic purpura
2. Must have a platelet count of < 150,000 currently
3. Must be receiving plasma exchange concurrently
4. Must be receiving concomitant immunosuppressive therapy (e.g. rituximab, high dose steroids)
5. Must present initially with severe features (neurologic findings such as seizures, focal weakness, aphasia, dysarthria, confusion, coma, encephalopathy, high serum troponin levels) to warrant this more aggressive initial therapy.
6. Prescriber must be a hematologist.
Note: Must discontinue if >2 aTTP recurrences occur during treatment.

Criteria for continuation
1. Must have failed the first 30 days of caplacizumab and still be suffering from aTTP.
2. Must be receiving concurrent plasma exchange, immunosuppressive therapy, and still have a platelet count <150,000.

Note: PI says it should be given for 30 days initially, with an additional course extended up to an additional maximum 28 days.

Quantity Limits: 58 days max.

References:

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1. UpToDate. Thrombotic thrombocytopenia purpura. Accessed 5/6/19.

2. Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. Lancet Haematol 2017 Apr;4(4):e157.

3. Peyvandi, Flora, et al. "Caplacizumab for acquired thrombotic thrombocytopenic purpura." *New England Journal of Medicine* 374.6 (2016): 511-522. TITAN

4. Scully, Marie, et al. "Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura." *New England Journal of Medicine* 380.4 (2019): 335-346. HERCULES

Revision History:

Date	What changed	Pharmacist's initials
5/20/19	I wrote the criteria.	JJ
1/26/2021	I added the criteria to require the prescriber to be a hematologist.	JJ

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Carfilzomib (Kyprolis®)

10 mg, 30 mg, 60 mg single dose vial

EBRx PA Criteria

FDA-approved for:

- relapsed or refractory multiple myeloma after one to three lines of therapy in combination with
  - lenalidomide and dexamethasone (SEE CRITERIA) **OR**
  - dexamethasone (SEE CRITERIA) **OR**
  - daratumumab and dexamethasone NOT COVERED
    - Daratumumab/carfilzomib/dexamethasone was compared to carfilzomib dexamethasone. Progression free survival benefit was demonstrated, but an overall survival or quality of life benefit has not been demonstrated to date
      - Reference: Dimopoulos, Meletios, et al. "Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study." The Lancet 396.10245 (2020): 186-197.
- relapsed/refractory multiple myeloma, as a single agent for the treatment of patients who have received one or more lines of therapy (NOT COVERED) Monotherapy with carfilzomib was no better than steroid alone in a heavily pretreated population.
  - Reference: Hájek R et al. A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). Leukemia. 2017 Jan;31(1):107-114. PMID 27416912 NCT01302392

Additional indication not included in package insert:

- in combination with isatuximab (Sarclisa) and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy
  - not covered: benefit is limited to progression free survival only compared to carfilzomib plus dexamethasone
    - Reference: Moreau P et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet. 2021 Jun 4:S0140-6736(21)00592-4. doi: 10.1016/S0140-6736(21)00592-4. Epub ahead of print. PMID: 34097854.

Criteria for new users
1. Must have a diagnosis of multiple myeloma that is relapsed or refractory
2. Must have received 1-3 prior lines of therapy
3. Must be planning to receive carfilzomib in combination with dexamethasone **OR** in

combination with dexamethasone and lenalidomide
4. Must be ECOG Performance status 0-2 upon initial request for carfilzomib.
If all above criteria met, approve for 6 months

Note:

- Therapy continues until progression or unacceptable toxicity.
- Monotherapy is not approved. Monotherapy with carfilzomib was no better than steroid alone in a heavily pretreated population.[1]
- Carfilzomib/lenalidomide/dexamethasone improved OS compared with lenalidomide/dexamethasone (median 48 mo vs 40 mo). 20% of subjects received previous lenalidomide.[2]
- Carfilzomib/dexamethasone improved OS compared to bortezomib/dexamethasone (median 48 mo vs 40 mo) with less grade 3/4 neuropathy (1% vs 6%), but overall grade 3/4 and serious adverse events were higher in carfilzomib group (81% vs 71% and 59% vs 40%, respectively).[3]

Regimen	Dose	Infusion time
Carfilzomib + dexamethasone	20/70 mg/m2 once weekly	30 minutes
Carfilzomib + dexamethasone, or monotherapy	20/56 mg/m2 twice weekly	30 minutes
Carfilzomib, Lenalidomide, and dexamethasone, or monotherapy	20/27 mg/m2 twice weekly	10 minutes

References:

1. Hájek R et al. A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). Leukemia. 2017 Jan;31(1):107-114. PMID 27416912 NCT01302392
2. Siegel DS et al. Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma. J Clin Oncol. 2018 Mar 10;36(8):728-734. PMID 29341834 NCT01080391
3. Dimopoulos MA et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol. 2017 Oct;18(10):1327-1337. PMID 28843768 NCT01568866

Revision History:

Date	What changed	Pharmacist's initials

3/28/2017	I wrote the criteria. Coverage for combination therapy was covered because of comparative data. Compared to LEN+DEX, CFZ+LEN+DEX significantly improved OS (HR for death was 0.79 (95%CI 0.63-0.99), p=0.04, PFS was 0.69, (95%CI 0.57-0.83), p=0.0001.	JJ
4/18/17	For EBD, the Insurance Board approved carfilzomib as a covered drug through the medical benefit with EBRx applying the PA criteria above.	JJ
5/20/19	Expand coverage to include Carfilzomib + dexamethasone as noted above.	SK
10/31/19	Criteria Reviewed. No changes.	SK
11/19/2020	Document new indication for treatment of relapsed multiple myeloma (daratumumab+carfilzomib+dexamethasone). This combination was compared to carfilzomib+dex and progression free survival is only benefit demonstrated to date (do not cover).	SK
1/20/2021	Criteria reviewed. No changes. Reformatted FDA indications to match package insert	SK
6/17/2021	Added new indication (with isatuximab+dex)—not covered	SK

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Cenegermin (Oxervate®)

Eye Drops

EBRx PA Criteria

FDA-approved for:

Treatment of neurotrophic keratitis.

Criteria for new users
1. The patient has the diagnosis of stage 2 or 3 neurotrophic keratitis.
2. The patient should have failed preservative-free artificial eye drops and/or lubricant ointments.
3. The patient should have tried therapeutic soft contact lenses (per the American Academy of Opthalmology's recommendations (below)).
If all 3 criteria are satisfied, the patient may have an 8 week therapy.

Note: Quantity Limits: 8 weeks of therapy for a lifetime is currently the maximum. There are no data for repeat treatment.

[1]Therapy depending on stage:

Stage 1: Goal is to improve the quality and transparency of epithelium and to avoid epithelial breakdown. Use frequent application of preservative-free artificial eye drops and lubricant ointments. Punctal occlusion may be beneficial. Autologous serum tears could be used if there is persistent keratopathy. Last, recombinant human nerve growth factor (rhNGF) drops and self-retaining cryopreserved amniotic membrane (Prokera) can be considered.
Stage 2: Goal is to promote persistent epithelial defects (PED) healing and prevent corneal ulcers. Treatment options: Unpreserved artificial tears, lubricant ointments, therapeutic soft contact lenses or patching, topical autologous serum application, amniotic membrane grafting either in-office or in-operating room using a self-retaining

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cryopreserved amniotic membrane (Prokera) Tarsorrhaphy or botulinum induced ptosis Topical rhNGF drops Antibiotic eye drops to prevent bacterial infections Topical corticosteroids to control inflammation; could induce stromal melting
Stage 3: Goal: ulcer healing and prevention of corneal perforation Treatment: In addition to therapy in stages 1 and 2, N-acetylcysteine, oral tetracycline, and medroxyprogesterone can be used in the case of stromal melting Vitamin C to prevent collagen degradation
If corneal perforation occurs, the treatment varies. Cyanoacrylate glue and soft bandage contact lens or amniotic membrane is performed. In case of a larger defect, a tectonic penetrating or lamellar keratoplasty can be performed
Surgical Management: Prognosis of patients affected by NK depends on disease stage, degree of anesthesia, and association with other ocular surface diseases. Corneal neurotization has become an increasingly explored topic in the management of neurotrophic keratitis. Neurotization of the cornea typically transfers the supraorbital or supratrochlear nerve to either directly or indirectly with a nerve graft (i.e. sural nerve) to the neurotrophic cornea. Neurotization and nerve reconstruction are well established for use in the reinnervation of peripheral nerve injuries.[31] Results thus far reveal neurotization leads to improvement in corneal sensation, improvement in visual acuity, and reduction of symptoms for months to years after surgery. It is worth noting that neurotization of the cornea is an extensive surgery that requires a high level of experience shared between Neurosurgery, Cornea, and Oculoplastics. The surgical outcome of keratoplasty in patients affected by NK is generally poor due to impairment in wound healing and risk of PED recurrence.

References:

1. American Academy of Ophthalmology. Allessandro. Rabiolo, Paolo Rama, Giulio Ferrari. Neurotrophic Keratitis, 12/10/2020. https://eyewiki.org/Neurotrophic_Keratitis#General_Management

2. Bonini, Stefano, et al. "Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis." *Ophthalmology* 125.9 (2018): 1332-1343. (enrolled only stage 2 or 3 patients; no patient-centered endpoints)

Revision History:

Date	What changed	Pharmacist's initials
1/12/21	I wrote the criteria.	JJ

Cladribine (Mavenclad®)

10mg tablets

EBRx PA Criteria

FDA-approved for:

- Multiple sclerosis, relapsing (oral tablet only): treatment of relapsing forms of MS, including relapsing remitting (RRMS) and active secondary progressive disease in adults who have had inadequate response or are intolerant to other therapies for MS. NOT recommended for patients with clinically isolated syndrome.
- The injection is FDA approved for treatment of hairy cell leukemia.

Criteria for new users
1. Diagnosis of relapsing remitting multiple sclerosis or active secondary progressive disease
2. Must have tried at least 1 other therapy for RRMS
3. Must have active disease.
4. Must be 18y or older.
If fulfill the above criteria, may have access for 1 cycle lasting 4-5 consecutive days during the first year.

Criteria for continuation
1. The above criteria must have been satisfied.
2. The patient must have successfully (defined: physician attestation that the patient demonstrated clinical benefit compared to baseline) received and tolerated the first cycle of cladribine during the previous 1 year.
3. This request is for **only the second** course of cladribine. (No further courses are allowed.)
If fulfill the continuation criteria, may receive the second cycle.

Note: **Dosing in RRMS:**

3.5mg/kg over 2-year treatment course, administered as 1.75 mg/kg in each year. Divide the 1.75 mg/kg dose over 2 cycles, each cycle lasting 4-5 consecutive days. Do not administer more than 20mg/day.

- 1st year: initiate the first cycle at any time; administer the second cycle 23 to 27 days after the last dose of the first cycle.
- 2nd year: initiate the first cycle ≥ 43 weeks after the last dose of the first year's second cycle. Administer the second cycle 23 to 27 days after the last dose of the second year's

first cycle. Following 2 years of treatment, do not administer oral cladribine during the next 2 years. Refer to manufacturer's labeling for additional dosing details, including dosing tables.

Quantity Limits: 2 cycles (see dosing above for the limits.)

Revision History:

Date	What changed	Pharmacist's initials
6/3/19	I wrote the criteria. Will revisit the coverage 5/2020	JJ
6/23/2020	I reviewed the criteria. No changes	JJ
12/10/2020	Changed criteria **from** glatiramer and 3 other therapies **to** 1 other therapy before use. Could not justify causing someone to fail a less effective therapy first.	JJ, LE
4/1/21	I added age 18y+ to be consistent with FDA-approved use. I clarified for continuation that "successful" may mean the prescriber's attestation that clinical benefit occurred over baseline for the first course. Also clarified that only 2 courses are allowed.	JJ

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Clobazam (Onfi©)

EBRx PA Criteria

1. Diagnosis of Lennox-Gastaut seizure disorder or Dravet Syndrome
2. Clobazam must be used in conjunction with at least one other antiseizure medication.
Approve for 1 year. Notes: 1. There is no consensus by any national neurology group as to practice guidelines to date (4/23/2015). 2. FDA approved for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older. 3. Onfi is a benzodiazepine, scheduled IV, abusable, and can lead to a withdrawal syndrome upon stopping.

Re-review, 3/13/15:

A 2013 Cochrane systematic review concluded:

"The optimum treatment for LGS remains uncertain and no study to date has shown any one drug to be highly efficacious; rufinamide, lamotrigine, topiramate and felbamate may be helpful as add-on therapy, clobazam may be helpful for drop seizures. Until further research has been undertaken, clinicians will need to continue to consider each patient individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects."

Other findings: High-dose clobazam works better than low dose in reducing the number of drop attacks.

Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD003277. DOI: 10.1002/14651858.CD003277.pub3.

A second Cochrane systematic review regarding the comparison of antiepileptic drugs in kids with benign epilepsy with centro temporal spikes concluded clobazam was not different than carbamazepine.

Tan HJ, Singh J, Gupta R, de Goede C. Comparison of antiepileptic drugs, no treatment, or placebo for children with benign epilepsy with centro temporal spikes. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD006779. DOI: 10.1002/14651858.CD006779.pub2.

A third study (funded by the manufacturer) was an indirect comparison of antiepileptic drugs (felbamate, lamotrigine, topiramate, rufinamide, and clobazam) in children with LGS. In

individual trials, each had been compared to placebo, but due to a lack of trials in pediatric patients generally, together with the low prevalence of LGS, HTH comparisons are not likely to occur. The findings showed high dose clobazam had the largest reduction (compared to placebo) in drop seizures (-56%) than the other drugs,(felbamate -36%, lamotrigine -25%, topiramate -20%, rufinamide -44%, low dose clobazam -29%,and medium dose clobazam -37%). The difference in total seizures rate vs placebo were: high dose clobazam -56%, med dose clobazam -36%, low dose clobazam -26%, felbamate -31%, lamotrigine -23%, topiramate (not significantly different), rufinamide -21%.

- The comparison of high dose clobazam vs lamotrigine was the only one that reached statistical significance for a ≥50% decrease in frequency of drop attacks.

Cramer JA, Sapin C, Francois C. Indirect comparison of clobazam and other therapies for Lennox-Gastaut syndrome. *Acta Neurol Scand* 2013: 128: 91–99 DOI: 10.1111/ane.12086

References

1. Onfi PI. http://www.lundbeck.com/upload/us/files/pdf/Products/Onfi_PI_US_EN.pdf Accessed 2/2/12.
2. Arzimanoglou A, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol. 2009;8:82-93.
3. Hancock EC, Cross HJ. Treatment of Lennox-Gastaut syndrome. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD003277. DOI: 10.1002/14651858.CD003277.pub2.
3. Van Rijckevorsel K. Treatment of Lennox-Gastaut syndrome: overview and recent findings. Neuropsychiatric Disease and Treatment 2008;4(6):1001–1019.
4. Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD003277. DOI: 10.1002/14651858.CD003277.pub3.
5. Tan HJ, Singh J, Gupta R, de Goede C. Comparison of antiepileptic drugs, no treatment, or placebo for children with benign epilepsy with centro temporal spikes. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD006779. DOI: 10.1002/14651858.CD006779.pub2.
6. Cramer JA, Sapin C, Francois C. Indirect comparison of clobazam and other therapies for Lennox-Gastaut syndrome. *Acta Neurol Scand* 2013: 128: 91–99 DOI: 10.1111/ane.12086

Revision History:

Date	What changed?	Pharmacist's initials
2/2/12	I wrote the criteria. The drug was discussed at DUEC but was excluded from coverage. In March 2015 the drug was	JJ

	requested on appeal and it was Clobazam revisit 2015at DUEC where they voted to PA the drug. I also added references 5-7.	
6/3/19	I added Dravet Syndrome as a qualifying diagnosis.	JJ
6/23/2020	I reviewed the criteria. No changes.	JJ
3/31/2021	No effective change from previous criteria	JJ

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Coagulation Factor X, Human (Coagadex®)

EBRx PA Criteria

is FDA-approved for: hereditary Factor X deficiency in age ≥12 as on-demand treatment and control of bleeding episodes; also perioperative management of bleeding in patients with mild hereditary Factor X deficiency.

Criteria for new users
1. Diagnosis of HEREDITARY Factor X deficiency, defined as factor activity level below 20% of normal.[1]
2. Planning to undergo surgery that is perceived by the prescriber to place the patient at risk for excess bleeding.

Note: The drug is not indicated for ACQUIRED factor X deficiency.

[1]**Factor X deficiency** – Bleeding can be treated with a factor concentrate (if available) or a 4 factor or 3 factor prothrombin complex concentrate (PCC) (table 5). Importantly, PCCs carry a prothrombotic risk, so they are not used for less severe bleeding. If a factor concentrate or PCC is not available, a plasma product such as FFP may be used. (See 'Factor X deficiency (F10D)' below and 'PCCs' below and 'Plasma products' below.)

References:

1. UpToDate. Rare inherited coagulation disorders. http://www.uptodate.com/contents/rare-inherited-coagulation-disorders?source=see_link Accessed 2/8/16.

Revision History:

Date	What changed	Pharmacist's initials
2/8/16	I wrote the criteria.	JJ

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Cobimetinib (Cotellic®)

20mg tablets

EBRx PA Criteria

FDA-approved for:

treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.

The following indication is not included in the cobimetinib package insert but is FDA approved per the atezolizumab (Tecentriq) package insert:

- **Melanoma**
  - in combination with atezolizumb and vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma NOT COVERED
    - Benefit of this combination is limited to progression free survival. Overall survival nor quality of life have been shown to be improved at this time.
    - Reference: Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;395(10240):1835-1844. doi:10.1016/S0140-6736(20)30934-X PMID 32534646

Criteria for new users
1. The patient must have the diagnosis of histologically confirmed unresectable or metastatic stage IIIC or stage IV melanoma.
2. The patient must have a BRAF V600 mutation detected with the use of a real-time polymerase-chain-reaction assay.
3. The patient must be ECOG 0-1 at first request.
4. Patients could have brain metastases if they have been clinically stable for at least 3 weeks.
5. Must receive vemurafenib 960mg BID concurrently with cobimetinib.
6. This combination therapy must be first line. No previous treatment for melanoma is allowed prior to access to cobimetinib/vemurafenib.
If the patient meets ALL criteria above, PA is good for 12 months.

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Criteria for continuation
1. ECOG score must still be 0-1; decline in ECOG would signal deterioration/progression and require stopping the drug.
2. Review of the patient's profile must verify they are receiving vemurafenib concurrently with cobimetinib.

Note: Cobimetinib's dose is 60mg daily days 1-21 out of each 28 day cycle until disease progression or unacceptable toxicity, concurrently with vemurafenib which is taken 960mg BID.

Quantity Limits: 63/28 (3-20mg tabs X 21 days)

References:

1. Larkin J, Ascerto P, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014;371(20):1867-76.

2. http://www.roche.com/media/store/releases/med-cor-2015-11-23.htm Accessed 12/16/15. Atkinson V. Larkin J, McArthur GA, et al. Improved OS with cobimetinib and vemurafenib in advanced BRAFV600-mutated melanoma and biomarker correlates of efficacy. Abstract presented at the 12th International Congress of the Society of Melanoma Research in San Francisco, CA, 21 Nov 2015.

3. http://www.cancernetwork.com/smr-2015/cobimetinib-vemurafenib-improves-survival-braf-mutated-melanoma Accessed 12/16/15.

Revision History:

Date	What changed	Pharmacist's initials
2/2/16	I wrote the criteria.	JJ
2/13/18	Added "or metastatic" to criteria #1 for clarity	Sk
10/2019	Criteria reviewed. No change	SK
8/7/2020	Added new indication for combination use with atezolizumab for melanoma (not covered)	SK
12/15/2020	Criteria reviewed. No change	SK

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Cysteamine Ophthalmic Drops 0.37% or 0.44% (Cystadrops®)

EBRx PA Criteria

FDA-approved for: Ocular cystinosis: treatment of corneal cystine crystal accumulation in patients with cystinosis.

Criteria for new users
1. The patient must have the diagnosis of ocular cystinosis with corneal cystine crystal accumulation

Note: The dose is 1 drop in each eye 4 times daily while awake.

Quantity Limits: 1 bottle per 30 ds.

References:

1. Liang, Hong, et al. "A new viscous cysteamine eye drops treatment for ophthalmic cystinosis: an open-label randomized comparative phase III pivotal study." *Investigative Ophthalmology & Visual Science* 58.4 (2017): 2275-2283.

2. Lexicomp. Cysteamine ophthalmic. Accessed 10/26/2020.

Revision History:

Date	What changed	Pharmacist's initials
3/5/21	I wrote the criteria.	JJ

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Dabrafenib (Tafinlar®)

50mg, 75mg capsules

EBRx PA Criteria

FDA approved for:

Monotherapy:

- treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. NOT COVERED
  - EBRx prefers combination therapy over monotherapy. First-line dabrafenib monotherapy improved PFS compared to chemotherapy. There was no statistical difference in overall survival, however, this result was likely confounded by crossover. Combination therapy shows superior overall survival compared with dabrafenib or vemurafenib monotherapy. Therefore, EBRx recommends that combination therapy be preferred over monotherapy.
  - References for monotherapy: Long et al. Ann Oncol. 2017;28(7): 1631-1639 (PMID 28475671); https://clinicaltrials.gov/ct2/show/NCT01227889

In combination with trametinib:

- treatment of patients with unresectable or **metastatic melanoma** with BRAF V600E or V600K mutations as detected by an FDA-approved test.
- **adjuvant treatment** of patients with **melanoma** with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.
- treatment of patients with metastatic **non-small cell lung cancer (NSCLC)** with BRAF V600E mutation as detected by an FDA-approved test. NOT COVERED: data limited to single arm trial only; no comparative data at this time (other option: platinum-based chemotherapy +/- pembrolizumab)

  References:

  a. Planchard D et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol. 2016 Jul;17(7):984-993. PMID 27283860 NCT01336634

  b. Planchard D et al. Dabrafenib plus trametinib in patients with previously untreated $BRAF^{V600E}$-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. 2017 Oct;18(10):1307-1316.
- treatment of patients with locally advanced or metastatic **anaplastic thyroid cancer (ATC)** with BRAF V600E mutation and with no satisfactory locoregional treatment options NOT COVERED: no comparative data at this time (other option: chemotherapy)

Reference: Subbiah V et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. J Clin Oncol. 2018 Jan 1;36(1):7-13. PMID 29072975 NCT02034110

Limitations of Use: dabrafenib is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF anaplastic thyroid cancer.

Metastatic melanoma criteria for new users
1. Patient must have histologically confirmed unresectable or metastatic cutaneous melanoma
2. Tumor must have BRAF V600E or BRAF V600K mutation
3. Patient must be ECOG 0 or 1.
4. The patient must not have received previous systemic therapy for advanced/metastatic melanoma.
5. Dabrafenib must be used in combination with trametinib (Mekinist)
If above criteria fulfilled, approve for 6 months. For subsequent requests, approve for 12 months.
Quantity limits: 75 mg and 50 mg capsules: #120/30 days
Note: Treatment continues until progression or unacceptable toxicity.
Starting doses: Dabrafenib 150 mg PO bid Trametinib 2 mg PO daily **Evidence:** Dabrafenib+trametinib was superior to dabrafenib monotherapy and vemurafenib monotherapy in the Combi-d and Combi-v studies, respectively. Overall survival for combination therapy was 25 mo versus 17-18 months in the monotherapy arms[1,2]. References: 1. Long GV et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol. 2017 Jul 1;28(7):1631-1639. PMID 28475671 NCT01584648 2. Robert C et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015 Jan 1;372(1):30-9. PMID 2539951 NCT01597908

Adjuvant treatment of melanoma criteria for new users
1. Patient must have resectable stage III cutaneous melanoma
2. Patient must have undergone complete resection of melanoma
3. Tumor must have BRAF V600E or BRAF V600K mutation
4. Patient must be ECOG 0 or 1.
5. Dabrafenib must be used in combination with trametinib [monotherapy has not been studied]
If above criteria fulfilled, approve for 6 months. Adjuvant therapy for melanoma should not exceed 12 months.
Quantity limits: 75 mg and 50 mg capsules: #120/30 days
Starting doses: Dabrafenib 150 mg PO bid Trametinib 2 mg PO daily **Evidence:** The combination of dabrafenib+trametinib improved relapse-free survival compared with placebo in patients with resected stage III melanoma. Four-year relapse free survival was 54% (dab/tram) vs 38% (placebo). An interim analysis of overall survival showed an improvement with combination therapy (3-year OS of 86% versus 77% in the placebo group (HR, 0.57; 95% CI, 0.42 to 0.79; *P* = .0006), but this improvement did not cross the prespecified interim analysis significance threshold of *P* = 0.000019. References: 2. Long GV et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. 2017;377(19):1813. PMID 28891408 NCT01682083 3. Hauschild A et al. Longer Follow-Up Confirms Relapse-Free Survival Benefit With Adjuvant Dabrafenib Plus Trametinib in Patients With Resected BRAF V600-Mutant Stage III Melanoma. J Clin Oncol. 2018 Oct 22:JCO1801219. [Epub ahead of print] PMID 30343620 NCT01682083

Revision history:

Date	Notes	Pharmacist's initials
9/17/13	Criteria written	JJ
1/15/15	I changed the criteria to include combination trametinib + dabrafenib since new OS data are published. Dabrafenib monotherapy is still not covered. This was discussed at DCWG	JJ
7/14/15	Re-review.	JJ
4/19/19	Criteria reviewed; added adjuvant treatment of melanoma as a covered indication. New FDA approved indications of NSCLC and anaplastic thyroid cancer not covered.	SK
4/23/19	I included references 3-5 on NSCLC and thyroid cancer to show what we considered in excluding the use.	JJ
9/30/19	Criteria reviewed. Did some slight rewording and reformatting, but no changes to criteria.	SK
6/18/2020	Extend subsequent approvals for metastatic indication to 12 months	SK
12/29/2020	Criteria reviewed. No change.	SK

CONFIDENTIAL

Dacomitinib (Vizimpro®)

15, 40, 45 mg tablets

EBRx PA Criteria

FDA-approved for: initial treatment of metastatic non-small cell lung cancer for patients with epidermal growth factor receptor exon 19 deletion or exon 21 L858R substitution mutations (by FDA- app. test)

Criteria for new users
1. Patient must have confirmed, stage IIIb/IV or recurrent non-small cell lung cancer with tumor tissue that tested positive for at least one EGFR activating mutation (exon 19 deletion or exon 21 L858R EGFR mutation)
2. Patient must have NOT had disease progression on a prior EGFR inhibitor (e.g. erlotinib, osimertinib, gefitinib, afatinib)
3. Patient must not have brain metastases.
4. Patient must be age ≥18.
5. ECOG status 0-1 at initiation of dacomitinib.
6. Dacomitinib will be used as single agent
If all criteria are met, approve x 1 year

Note: The dacomitinib dose is 45mg/day continuously; treat to progression.

Dacomitinib was compared to gefitinib in patients with untreated advanced/metastatic non-small cell lung cancer with the exon 19 deletion or exon 21 L858R EGFR mutation. Patients with brain metastasis were excluded. Dacomitinib improved overall survival compared to gefitinib (median 34 months vs 26.8 months). [1,2]

Dacomitinib has not been shown to be effective in patients who have received therapy with a prior EGFR inhibitor therapy. NCCN guidelines recommend that dacomitinib be used in the first line setting only.[3]

References:

1. Wu YL et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017 Nov;18(11):1454-1466. PMID 28958502 NCT01774721
2. Mok TS et al. Improvement in Overall Survival in a Randomized Study That Compared

Dacomitinib With Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. J Clin Oncol. 2018 Aug 1;36(22):2244-2250. PMID 29864379 NCT01774721

3. NCCN guidelines. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Quantity Limits (all strengths): 30 tabs/30 days

Revision History:

Date	What changed	Pharmacist's initials
1/9/19	I wrote the criteria.	JJ
6/17/19	Criteria reviewed. No significant change.	SK
3/30/20	Criteria reviewed, no change	SK
7/26/2021	Criteria reviewed. No change.	SK

CONFIDENTIAL

Daratumumab (Darzalex®, Darzalex Faspro®)

100mg/5mL and 400mg/20mL vials

Daratumumab and hyaluronidase (Darzalex Faspro)

1800 mg daratumumab and 30,000 units hyaluronidase per 15 ml vial

EBRx PA Criteria

Note: For simplicity, EBRx will consider Darzalex and Darzalex Faspro interchangeable despite slight differences in FDA indications.

Darzalex and Darzalex Faspro are FDA-approved for:

- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant (NOT COVERED) and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy (SEE RELAPSED/REFRACTORY CRITERIA)
  - The benefit of daratumumab/lenalidomide/dexamethasone is limited to progression free survival without evidence of overall survival, quality of life, or toxicity benefit.

    Reference: Facon T et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019 May 30;380(22):2104-2115. NCT02252172 PMID 31141632
- In combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (SEE NEWLY DIAGNOSED CRITERIA)

  References:
  - Mateos MV et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. NEJM. 2018;378(6):518-528. PMID 29231133 NCT02195479
  - Niesvizky R et al. Efficacy and safety of three bortezomib-based combinations in elderly, newly diagnosed multiple myeloma patients: results from all randomized patients in the community-based, phase 3b UPFRONT STUDY [abstract]. Blood 2011;118:Abstract 478. Available at: http://www.bloodjournal.org/content/118/21/478?sso-checked=true. (Accessed 4/17/19)
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed multiple myeloma patients who are eligible for autologous stem cell transplant (SEE NEWLY DIAGNOSED CRITERIA)
- In combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy (SEE RELAPSED/REFRACTORY CRITERIA)
- As monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI, bortezomib, carfilzomib, ixazomib) and an immunomodulatory agent (lenalidomide, thalidomide, pomalidomide) or who are double-refractory to a PI and an immunomodulatory agent (SEE RELAPSED/REFRACTORY CRITERIA)

Darzalex is also FDA-approved for:

- In combination with carfilzomib and dexamethasone in multiple myeloma patients who have received one to three prior lines of therapy NOT COVERED. Daratumumab/carfilzomib/dexamethasone was compared to carfilzomib

dexamethasone. Progression free survival benefit was demonstrated, but an overall survival or quality of life benefit has not been demonstrated to date

- Reference: Dimopoulos, Meletios, et al. "Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study." The Lancet 396.10245 (2020): 186-197.

- In combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (NOT COVERED)
    - Benefit is limited to progression free survival

References:

- Chari A et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood. 2017 Aug 24;130(8):974-981. PMID 28637662 NCT01998971 (EQUULEUS; MMY1001)
- Dimopoulos MA et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021 Jun;22(6):801-812. doi: 10.1016/S1470-2045(21)00128-5. PMID: 34087126. NCT03180736 (APOLLO)

Darzalex Faspro is also FDA-approved for:

- light chain (AL) amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone in newly diagnosed patients. (accelerated approval) NOT COVERED due to lack of overall survival data (NCT03201965)
- multiple myeloma in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor NOT COVERED due to lack of overall survival data (NCT03180736)

Criteria for new users (NEWLY DIAGNOSED)
1. Must have a diagnosis of multiple myeloma with no prior therapy
2. Must be ECOG performance status 0, 1, or 2 before initiation of daratumumab.
3. If the patient is eligible for high-dose therapy with autologous stem-cell transplantation, daratumumab will be used in combination with bortezomib, thalidomide, and dexamethasone (D-VTD).
4. If the patient is ineligible for high-dose therapy with autologous stem-cell transplantation, daratumumab will be used in combination with bortezomib, melphalan, and prednisone (D-VMP).
Approve x 8 months if criteria 1, 2, and 3 are met. This timeframe should allow for completion of entire treatment course barring any major complications. Renewals are not allowed. Approve x 12 months if criteria 1, 2, and 4 are met. Daratumumab is continued until disease progression. Renewals x 12 months may be approved as long as there is no disease progression.

Daratumumab dose: 16 mg/kg IV

Daratumumab schedule for D-VTD regimen (transplant eligible)		
Treatment phase	**Weeks**	**Schedule**
Induction	Weeks 1 to 8	Weekly (total of 8 doses)
	Weeks 9 to 16	Every two weeks (total of 4 doses)
Stop for high dose chemotherapy and autologous stem cell transplant (ASCT)		
Consolidation*	Weeks 1 to 8	Every two weeks (total of 4 doses)

*****Consolidation starts upon hematopoietic reconstitution after ASCT but no sooner than 30 days after transplant.

Daratumumab schedule for D-VMP regimen (transplant ineligible)		
Treatment phase	**Weeks**	**Schedule**
Cycle 1	Weeks 1 to 6	Weekly (total of 6 doses)
Cycles 2-9	Weeks 7-54	Every 3 weeks (total of 16 doses)
Cycle 10+	Weeks 55 and beyond (Until progression of disease)	Every 4 weeks

Note:

- In newly-diagnosed, transplant eligible patients, daratumumab/bortezomib/thalidomide/dexamethasone (D-VTD) improved overall survival at day 100 after stem cell transplant compared with bortezomib/thalidomide/dexamethasone alone although data are immature.[1]
- In newly-diagnosed, transplant ineligible patients, daratumumab/bortezomib/melphalan/prednisone (D-VMP) improved overall survival compared to VMP (HR 0.6 95% CI 0.46-0.8; p=0.0003).[2,3] At 36 months, the rate of overall survival was 78% in the daratumumab group and 67.9% in the control group. Median was not reached in either group.

References:

1. Moreau P et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019 Jul 6;394(10192):29-38. PMID 31171419 NCT02541383
2. Mateos MV et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet. 2020 Jan 11;395(10218):132-141. doi: 10.1016/S0140-6736(19)32956-3. Epub 2019 Dec 10. PMID 31836199
3. Mateos MV et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. NEJM. 2018;378(6):518-528. PMID 29231133 NCT02195479

Criteria for new users (RELAPSED/REFRACTORY)
1. Must have a diagnosis of multiple myeloma that is progressing
2. Must be ECOG performance status 0, 1, or 2 before initiation of daratumumab.
3. If daratumumab is to be used in combination with other agents, patient must have received at least 1 prior line of therapy AND be planning to take daratumumab with dexamethasone+lenalidomide OR dexamethasone+bortezomib
4. If daratumumab monotherapy is to be used, patient must have been treated with at least 3 prior therapies including a proteasome inhibitor (bortezomib, carfilzomib, ixazomib) AND an immunomodulatory agent (lenalidomide, thalidomide, pomalidomide) OR be double-refractory to a proteasome inhibitor and an immunomodulatory agent.
If 1 and 2 plus either 3 or 4 is met, approve for 12 months. May renew approval if no progression of disease.
Note: • Therapy continues until progression or unacceptable toxicity. • Daratumumab/bortezomib/dexamethasone improved progression free survival compared with bortezomib/dexamethasone alone. Overall survival was not significantly better but trended towards an improvement and post-trial use of daratumumab may have confounded overall survival analysis.[1] • Daratumumab/lenalidomide/dexamethasone improved progression free survival compared with lenalidomide/dexamethasone alone. Overall survival is trending towards improvement but still considered immature at last follow up.[2,3] • Daratumumab monotherapy was found have improved overall survival compared to pomalidomide/dexamethasone in a matched adjusted indirect comparison analysis.[4] References: 1. Spencer A et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018 Dec;103(12):2079-2087. PMID 30237264 NCT02136134 2. Dimopoulos MA et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Oct 6;375(14):1319-1331. PMID27705267 NCT02076009 3. Dimopoulos MA et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. Haematologica. 2018 Dec;103(12):2088-2096. PMID 30237262 NCT02076009 4. Van Sanden S et al. Comparative Efficacy of Daratumumab Monotherapy and Pomalidomide Plus Low-Dose Dexamethasone in the Treatment of Multiple Myeloma: A Matching Adjusted Indirect Comparison. Oncologist. 2018 Mar;23(3):279-287. PMID 29192016

Revision History:

Date	What changed	Pharmacist's initials
3/28/17	I wrote the criteria. The SIRIUS trial is the monotherapy trial in heavily pretreated MM patients and was not comparative; additionally they measured response rates. Need more evidence to show benefit over the alternative to cover monotherapy.	JJ
5/20/19	Criteria reviewed. Expand coverage to allow monotherapy.	SK

10/28/19	Criteria reviewed. Add coverage for daratumumab used with thalidomide, bortezomib, dex per CASSIOPEIA trial.	SK
4/27/2020	Criteria reviewed. Added coverage for D-VMP for newly diagnosed, transplant ineligible patients. Correct typo in relapsed/refractory criteria.	SK
11/19/2020	Document new indication for treatment of relapsed multiple myeloma (daratumumab+carfilzomib+dexamethasone). This combination was compared to carfilzomib+dex and progression free survival is only benefit demonstrated to date (do not cover).	SK
1/19/2021	Criteria review. No changes. Added several references with updated data.	SK
3/19/2021	Updated to include Darzalex Faspro per 3/2021 P&T meeting.	SK
7/26/2021	Added new indication for Faspro (relapsed/refractory myeloma in combination with pom/dex)—PFS data only. Do not cover.	SK
10/12/2021	Added new reference (APOLLO) trial for dara/pom/dex indication. No change in criteria.	SK

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Darolutamide (Nubeqa®)

300 mg tablets

EBRx PA Criteria

FDA-approved for:

Non-metastatic castration-resistant prostate cancer (nmCRPC)

Note: CRPC is defined as progression of disease (rising PSA or increase in tumor size on imaging) when testosterone level is <50 ng/dl.

Criteria for new users
1. Diagnosis of castration-resistant prostate cancer without evidence of metastatic disease
2. The patient has castrate level of testosterone (<50 ng/dl)
3. PSA doubling time is </= 10 months
4. Minimum of three rising PSA values at an interval of at least 1 week apart
5. At time of first request, PSA is 2 ng/ml or greater
If all of the above criteria are met, approve for 1 year
Notes: Darolutamide was compared to placebo in men with castration resistant prostate cancer WITHOUT metastasis (n=1509). Time to development of metastasis or death was longer with apalutamide (40.4 mo) compared with placebo (18.4 mo). This indication is also approved for enzalutamide and apalutamide. At the first interim overall survival analysis, overall survival appeared to be prolonged compared with placebo (HR 0.71, 95% CI 0.5-0.99) though authors cautioned that results are not mature.[1] A subsequent analysis showed improved overall survival in the darolutamide group (medians not reached; HR 0.69; p=0.003). Improvement seen despite crossover of 170 placebo patients to darolutamide.[2] Two meta-analyses indicate a possible improvement in overall survival compared to placebo when the results of apalutamide, enzalutamide, and darolutamide studies were pooled.[3,4] The darolutamide study allowed enrollment of patients with history of or predisposition to seizures. However, these patients were NOT allowed in enzalutamide and apalutamide studies. Darolutamide **may** be associated **less** with seizures, CNS effects, falls, fractures, and hypertension

compared with enzalutamide and apalutamide.

Criteria developed with guidance of study protocol located at https://www.nejm.org/doi/suppl/10.1056/NEJMoa1815671/suppl_file/nejmoa1815671_appendix.pdf.

Dose: 600 mg PO bid until progression of disease or unacceptable toxicity.

REFERENCE:

1. Fizazi K et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019 Mar 28;380(13):1235-1246. PMID 30763142 NCT02200614
2. Fizazi K et al. Overall Survival (OS) results of phase III ARAMIS study of darolutamide (DARO) added to androgen deprivation therapy (ADT) for nonmetastatic castration-resistant prostate cancer (nmCRPC). J Clin Oncol 38: 2020 (suppl; abstr 5514). https://meetinglibrary.asco.org/record/187482/abstract. Accessed 6/16/2020.
3. Di Nunno V et al. New Hormonal Agents in Patients With Nonmetastatic Castration-Resistant Prostate Cancer: Meta-Analysis of Efficacy and Safety Outcomes. Clin Genitourin Cancer. 2019 Jul 8. pii: S1558-7673(19)30207-1. doi: 10.1016/j.clgc.2019.07.001. [Epub ahead of print] PMID 31378578
4. Hird AE, Magee DE, Bhindi B, et al. A Systematic Review and Network Meta-analysis of Novel Androgen Receptor Inhibitors in Non-metastatic Castration-resistant Prostate Cancer [published online ahead of print, 2020 Mar 6]. Clin Genitourin Cancer. 2020;S1558-7673(20)30039-2. PMID 32278840

Revision History:

Date	What changed	Pharmacist's initials
9/23/19	Criteria written	sk
4/15/2020	Added reference for second meta analysis to show improvement in overall survival of antiandrogens (including darolutamide) vs placebo.	SK
6/16/2020	Added new reference showing improved OS data in darolutamide trial. No change in criteria.	SK
3/31/21	I clarified this is for castration-resistant prostate cancer (nonmetastatic).	JJ
5/25/2021	Added 4th reference. Criteria reviewed. No change	SK

Dasatinib (Sprycel®)

EBRx PA Criteria

FDA-approved for:

- Newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. EBRx does not cover dasatinib for first line treatment of CML unless imatinib cannot be used.
- Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.
- Pediatric patients 1 year of age and older with Ph+ CML in chronic phase.
- Pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy.

Criteria for new users
2. Philadelphia chromosome + (Ph+) acute lymphoblastic leukemia (ALL) resistant or intolerant to imatinib (note: Ph+ may also be denoted as t(9;22) or BCR/ABL)
3. Ph+ chronic myeloid leukemia (CML) in chronic phase, accelerated/advanced phase, or blast crisis with resistance*, intolerance, or contraindication to imatinib (note: Ph+ may also be denoted as t(9;22) or BCR/ABL)
*Resistance to CML therapy is generally defined as any of the following (see notes below): g. Inadequate response (defined as one of the following): i. After 3 months of therapy: Lack of complete hematologic response (Platelets <450 x10^9/L; leukocyte count <10 x 10^9/L) ii. After 3 months of therapy: Cytogenetic analysis shows >95% Ph+ metaphases iii. After 6 months of therapy: BCR-ABL1 (IS) >10% by quantitative PCR (qPCR) iv. After 6 months of therapy: Cytogenetic analysis shows >35% Ph+ metaphases v. After 12 months of therapy: BCR-ABL1 (IS) >1% by quantitative PCR (qPCR) vi. After 12 months of therapy: Cytogenetic analysis shows >0% Ph+ metaphases h. Progression of disease after a cytogenetic/hematologic response was achieved i. Documentation of mutation associated with drug resistance (typically checked after failure of first-line therapy—see below)
If criteria 1 or 2 is fulfilled, approve for 6 months
Criteria for continuation
Review of fill history indicates compliance with therapy
No progression of disease
No unacceptable toxicity
If continuation criteria fulfilled, approve for 1 year Quantity limits: 30 day supply max

Note about EBRx coverage: EBRx prefers imatinib for treatment of all phases of CML and ALL. Dasatinib may be covered if the patient experiences resistance or intolerance to imatinib. NCCN guidelines suggest using a non-imatinib agent for first line therapy for intermediate/high risk patients (risk determined by Sokal or Hasford methods) based on quicker time to response. Although quicker time to response has been associated with improved outcomes, non-imatinib agents have not been shown to improve overall survival compared to imatinib in the first line setting. Therefore, EBRx recommends that non-imatinib agents be denied access for first line use unless there is documentation of resistance or intolerance to a trial of imatinib.

Notes:

General CML information:

9. Cytogenetic monitoring: Chromosomes are examined directly for BCR-ABL chromosomal translocation. Number of cells in metaphase are examined. The number of metaphase cells that contain BCR-ABL are divided by total number of metaphase cells to get a percentage. Test requires bone marrow aspirate.
10. Molecular monitoring: Transcripts for BCR-ABL mRNA are quantified via real time PCR. "IS" denotes that the result is obtained via a standardized method. Test requires peripheral blood sample.
11. Cytogenetic and molecular monitoring are both valid. Since cytogenetic monitoring requires bone marrow biopsy, molecular monitoring may be preferred.
12. Analysis of BCR-ABL mutations is typically not done until failure of first-line therapy for CML. If a mutation is documented that predicts resistance to imatinib, an alternative agent should be used. NCCN has guide for treatment options according to which mutation is identified.

Treatment recommendations based on BCR-ABL1 mutation profile (NCCN CML version 2.2022)	
Contraindicated Mutations	Drugs
T315I/A, F317L/V/I/C, V299L	Dasatinib
T315I, Y253H, E255K/V, F359V/C/I	Nilotinib
T315I, V299L, G250E, F317L	Bosutinib
None	Asciminib, Ponatinib, Omacetaxine, stem cell transplant, clinical trial

Notes regarding EBRx criteria:

6. Above criteria for resistance/failure of CML treatment were obtained from NCCN guidelines Early Treatment Response Milestones page CML-3 in version 1.2019 and guideline published by European LeukemiaNet.[1] ELN proposes more restrictive

resistance/failure definitions for second line therapy, however, NCCN has no specific guidelines. Therefore, will leave resistance/failure definitions as listed above for simplicity.
7. Criteria for resistance/failure of therapy for ALL is not well defined
8. Dasatinib in the first line setting was shown to induce quicker responses as compared to imatinib. Though quicker responses have been associated with improved outcomes, no overall survival benefit has been demonstrated in the primary study.[2,3] Imatinib will be preferred until more data is available.
9. After failure of first line therapy, there are no randomized trials showing one TKI to be superior to another.

Adult dasatinib dosing:

CML chronic phase: 100 mg PO daily; may escalate to 140 mg daily if inadequate response

CML accelerated/blast phase: 140 mg daily; may escalate to 180 mg daily if inadequate response

ALL: 140 mg PO daily; may escalate to 180 mg PO daily if inadequate response

Pediatric dasatinib dosing:

10 to less than 20 kg: 40 mg daily

20 to less than 30 kg: 60 mg daily

30 to less than 45 kg: 70 mg daily

≥45 kg: 100 mg daily

REFERENCE:

7. Baccarani M et al. Blood. 2013 Aug 8;122(6):872-84. PMID 23803709
8. Kantarjian H et al. N Engl J Med. 2010 Jun 17;362(24):2260-70. (NCT00481247)
9. Cortes JE et al. J Clin Oncol. 2016 Jul 10;34(20):2333-40. (NCT00481247)

Revision History:

Date	What changed	Pharmacist's initials
8/10/12	I wrote the criteria.	JJ
3/4/19	Updated criteria to require imatinib before dasatinib for CML. Added general information about CML monitoring and rationale for criteria.	SK
8/7/19	Criteria reviewed. No change.	SK
6/18/2020	Added "(note: Ph+ may also be denoted as t(9;22) or BCR/ABL)"	SK
8/20/2020	Criteria reviewed. No change	SK

10/27/2021	Criteria reviewed. No change	SK
12/16/2021	Updated Table re: treatments recs based on mutation	SK

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Deferasirox (Exjade®)

125, 250, 500 mg tablets for oral suspension

EBRx PA Criteria

Note: Jadenu and Jadenu Sprinkle are not covered. Exjade is now available in a generic formulation.

FDA approved for

- Treatment of chronic iron overload due to blood transfusions in patients 2 y of age and older
- Treatment of chronic iron overload in patients 10 y of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes, and with a liver iron (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L.
  - This indication is based on achievement of an LIC less than 5 mg Fe/g dw. An improvement in survival or disease-related symptoms has not been established.
- Limitations of use:
  - Controlled clinical trials of Exjade in patients with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusion have not been performed.
  - The safety and efficacy of Exjade when administered with other iron chelation therapy have not been established

Chronic iron overload due to blood transfusion
1. Age is 2 years or older
2. Diagnosis of chronic iron overload due to blood transfusions (transfusional hemosiderosis)
3. At time of first request, serum ferritin ≥1000 mcg/L in the absence of infection or acute inflammation
4. Creatinine clearance is at least 40 ml/min
5. Platelet count is at least 50 x 10^9/L
6. Patient does NOT have diagnosis of high-risk myelodysplastic syndrome
7. Patient does NOT have advanced malignancy
8. Patient does NOT have history of known hypersensitivity to deferasirox or any component of formulation.

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9. The patient (or caregiver) has been provided the following information for proper timing and administration technique: o Take once daily on an empty stomach at least 30 minutes before food o Dose should be taken at the same time of day each day o Completely dissolve tablet in water, apple juice, or orange juice and drink immediately o Re-suspend and drink any residual drug with a small amount of additional liquid o Do not take at the same time as aluminum-containing antacid products.
If above criteria met, approve x 1 year QL: 30 day supply.
Notes: Dose: 20 mg/kg once daily. Round dose to the nearest whole tablet. Criteria 4-8 relate to contraindications listed in the package insert. Reference: Product Package Insert, Exjade (deferasirox). Novartis. May 2019. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/exjade.pdf

Chronic iron overload due to non-transfusion-dependent thalassemia (NTDT) syndromes
1. Age is 10 years or older
2. Diagnosis of chronic iron overload due to a non-transfusion-dependent thalassemia (NTDT) syndrome
3. Liver iron (Fe) concentration (LIC) is at least 5 mg Fe per gram of dry weight
4. Serum ferritin is greater than 300 mcg/L
5. Creatinine clearance is at least 40 ml/min
6. Platelet count is at least 50 x 10^9/L
7. Patient does NOT have diagnosis of high-risk myelodysplastic syndrome
8. Patient does NOT have advanced malignancy
9. Patient does NOT have history of known hypersensitivity to deferasirox or any component of

formulation.
10. The patient (or caregiver) has been provided the following information for proper timing and administration technique: o Take once daily on an empty stomach at least 30 minutes before food o Dose should be taken at the same time of day each day o Completely dissolve tablet in water, apple juice, or orange juice and drink immediately o Re-suspend and drink any residual drug with a small amount of additional liquid o Do not take at the same time as aluminum-containing antacid products.
If above criteria met, approve x 1 year QL: 30 day supply.
Notes: Dose: 10 mg/kg once daily. Round dose to the nearest whole tablet. Criteria 5-9 relate to contraindications listed in the package insert. Reference: Product Package Insert, Exjade (deferasirox). Novartis. May 2019. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/exjade.pdf

Revision History:

Date	Notes	Pharmacist's initials
3/5/08	Criteria created; S. Saccente was consulted.	JJ/SV
5/11/12	Revision history table inserted	JJ
6/25/15	I added Jadenu to this pa	JJ
6/17/19	Criteria reviewed. Added criteria for NTDT. EBRx will exclude Jadenu and Jadenu Sprinkle since Exjade is now generic and cheaper.	SK
6/15/2020	Criteria reviewed. No change	SK
8/31/2021	Criteria reviewed. No change	SK

Deferiprone (Ferriprox®)

EBRx PA Criteria

FDA-approved for: treatment of transfusional iron overload due to thalassemia syndromes with inadequate response to other chelation therapy.

Criteria for new users
1. The patient must have the diagnosis of transfusional iron overload due to thalassemia (safety & efficacy have not been established for the treatment of transfusional iron overload in patients with other chronic anemias).
2. the patient must have failure of monotherapy (must have unsatisfactory reduction in serum ferritin with deferoxamine monotherapy) OR be intolerant to deferoxamine.
3. A baseline serum ferritin should be obtained

Criteria for continuation
1. There must be evidence of regular adherence to deferiprone tablets. (at least 60% medication possession rate
2. There must be evidence of a reduction in serum ferritin after 6 months.

[1]A Cochrane systemic review concluded that deferiprone (Ferriprox) is indicated for the treatment of iron overload due to blood transfusions if deferoxamine (Desferal) is inadequate or contraindicated.

[2]"Approval of Ferriprox was based on an unpublished, prospective, pooled analysis (summarized in the package insert) of 12 trials in a total of 236 pts w/ transfusional iron overload w/ an inadequate response (serum ferritin concentrations remained above 2500 mcg/L) to, or were unable to tolerate, other iron chelation therapy. "

[4]A RCT comparing deferiprone (Ferriprox) to deferoxamine (Desferal) found a statistically significant difference in the primary outcome of myocardial T2 levels favoring deferiprone (Ferriprox). Participants were 18 years or older without HF and previously taking deferoxamine (Desferal). They were randomized to either a higher dose of Desferal or switching to Ferriprox. While it is stated that cardiac measurements were made in London by 2 reviewers who were blinded to treatment arms, it does not state whether pts and physicians were blinded. There was a statistically significant difference in baseline serum ferritin levels, with the deferiprone (Ferriprox) arm having a lower baseline level. Several of the authors have financial interest in Apotex, which produces deferiprone (Ferriprox).[4]

- No RCT comparing Exjade to Ferriprox.

[5] Cochrane Syst Rev stated deferasirox should be offered as an alternative to those not tolerating deferoxamine or with poor compliance to deferoxamine. Pt-important, long-term outcomes and AEs should be conducted prior to routine recommendation of deferasirox as 1st line therapy in thalassemia pts w/ iron overload.

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[6] No iron chelator has superior efficacy to date.

References:

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2. The Medical Letter. Deferiprone (Ferriprox) for iron overload. The Medical Letter, 2012, Issue 1384, Volume 54.
3. Ferriprox prescribing information. http://www.ferriprox.com/us/pdf/ferriprox_full_pi.pdf
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11. “Highlights of Prescribing Information: Ferriprox” FDA (2011). https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021825lbl.pdf
12. “Highlights of Prescribing Information: Exjade” FDA (2005). https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021882s006lbl.pdf
13. Maggio, Aurelio, et al. "Deferiprone versus deferoxamine in patients with thalassemia major: a randomized clinical trial." Blood Cells, Molecules, and Diseases 28.2 (2002): 196-208.
14. Pennell, Dudley J., et al. "Efficacy of deferasirox in reducing and preventing cardiac iron overload in β-thalassemia." Blood 115.12 (2010): 2364-2371.

Revision History:

Date	What changed	Pharmacist’s initials
10/18/19	I wrote the criteria.	JJ
06/23/2020	I reviewed the criteria. No changes	JJ
4/1/21	I reviewed the criteria. No changes	JJ

Delafloxacin (Baxdela®)

EBRx PA Criteria

is FDA-approved for:

- Community-acquired pneumonia caused by susceptible organisms (Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella, E Coli, Pseudomonas aeruginosa, H. flu, H parainfluenzae, Legionella, Mycoplasma, Chlamydophila
- Skin and Skin structure infection caused by MRSA, MSSA, Staph haemolyticus, Staph lugdunensis, Strep agalactiae, Strep anginosis, Strep pyogenes, Enterocuccus faecalis, E. coli, Enterobacter cloacae, K. pneumonia, and P. aeruginosa

Criteria for new users
1. The patient must have a diagnosis of bacterial skin and soft tissue infection or community-acquired pneumonia susceptible to delafloxacin AND
2. The bacteria must be resistant to all other generic alternative antibiotics.
3. The prescriber must be an infectious disease specialist.

Note: Dosing:

- 300 mg by **IV infusion** over 60 minutes q12h OR
- 450-mg **tablet PO** q12h

BOTH for 5 to 14 days total

Quantity Limits: #28 tablets for a 14 day supply.

Revision History:

Date	Notes	Pharmacist's initials
12/8/17	Criteria were written	JK
2/5/18	I reviewed the criteria.	JJ
6/23/2020	I reviewed the criteria. Added ID specialist. Added new indication (CAP). Added must be resistant to all other generic alternative antibiotics.	JJ
3/10/2021	I reviewed the criteria. Would not cover IV on the pharmacy benefit unless it is for a plan we are managing medically administered drugs.	JJ

Denosumab (Xgeva®, Prolia®)

Xgeva 120mg/1.7mL (1.7mL) for SC injection

Prolia 60mg/mL (1mL) for SC injection

XGEVA (denosumab 120 mg/1.7ml) is FDA-approved for:

- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy
- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe mortality

Xgeva 120mg/1.7mL (dose: 120 mg SQ every 4 weeks. Additional dose given on days 8 and 15 of first month for hypercalcemia and giant cell tumor of bone)
Diagnosis of hypercalcemia of malignancy refractory to bisphosphonate therapy and least 7 days have lapsed since last bisphosphonate dose to allow maximum effect.
Requested indication is prevention of skeletal-related events in patients with bone metastases from solid tumors
Requested indication is prevention of skeletal-related events in patients with multiple myeloma AND patient has a CrCl < 30 ml/min or previous intolerance of zoledronic acid
Treatment of giant cell tumor of the bone in adults and skeletally mature adolescents that is unresectable or where surgical resection is likely to result in severe morbidity AND bisphosphonate treatment has been attempted
If one of the above is fulfilled, approve for 6 months
Continuation criteria
Hypercalcemia of malignancy: Corrected calcium level has improved from baseline
Giant cell tumor of the bone: No disease progression
All indications: No unacceptable toxicity
If criteria fulfille, approve for 1 year

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Evidence (prevention of skeletal-related events in patients with bone metastases from solid tumors):

- In patients with bone mets due to breast CA, Denosumab delayed time to 1st on-study skeletal related event by 18% compared to AZ (HR, 0.82;95%CI, 0.71 to 0.95; p<0.001 noninferiority; p=0.01 superiority). Median time to 1st on study SRE was 26.4m for ZA and not yet reached with denosumab. Denosumab reduced the risk of developing multiple SREs by 23% compared to AZ (rate ratio, 0.77;95%CI, 0.66 to 0.89; p=0.001). Overall survival and disease progression were similar between groups. Overall and SAEs were similar between groups. (Stopeck AT, Lipton A, Body JJ, Steger GG, et al. Denosumab compared with ZA for treatment of bones metastases in patients w/ advanced breast cancer: a R, DB study. J Clin Oncol. 2010;28:5132-39.)
- Stopeck 2010 reported prolonged median time to develop moderate/severe pain for patients w/ no pain at baseline (denosumab vs ZA: HR 0.78;p=0.0024) and had a lower proportion of patients with no pain at baseline, and had moderate/severe pain at week 73 (denosumab 14.8% vs ZA 26.7%). Median time to pain improvement was similar b/w treatment arms (denosumab 82 days, vs ZA 85d: HR 1.02; p=0.72) (Wong MHF, Stockelr MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003474. DOI: 10.1002/14651858.CD003474.pub3.)
- Breast cancer with bone mets is not a cost-effectiveness use according to a study comparing denosumab vs ZA showed it is not cost effectiveness in this setting and provides a cost per QALY gained of $697,499. The incremental cost effectiveness ratio ranged from $192,472 to $1,340,901. (Snedecor SJ, Carter JA, et al. Cost-effectiveness of denosumab vs ZA in the management of skeletal metastases secondary to breast cancer. Clinical Therapeutics.2012;34(6):1334-1349.)

Denosumab will be approved for this indication due to superiority over zoledronic acid regarding skeletal related events. Additionally, denosumab showed superiority over ZA or pamidronate for SRE, time to SRE, and time to worsening pain. (Peddi P, et al. Denosumab in patients with cancer and skeletal metastases: a systematic review and meta-analysis. Cancer Treatment Reviews. 2013;39:97-104.)

Evidence (prevention of skeletal-related events in patients with multiple myeloma)

- Denosumab was compared to zoledronic acid in patients with multiple myeloma with primary endpoint of non-inferiority of denosumab to zoledronic acid for time to first skeletal-related event. Denosumab was shown to be non-inferior to zoledronic acid with similar rates of adverse effects.
- Because denosumab is not superior to zoledronic acid and zoledronic acid is less expensive, prefer zoledronic acid. The exception is for patients who have severe renal dysfunction (CrCl <30 ml/min) in whom zoledronic acid would be contraindicated or patients who are intolerant of zoledronic acid (infusion reaction, severe flu-like symptoms, renal failure). Note that osteonecrosis of the jaw and hypocalcemia may occur with both zoledronic acid and denosumab and is not a reason to prefer denosumab.

REFERENCE

- Raje N et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol. 2018 Mar;19(3):370-381. PMID 29429912

Evidence (giant cell tumor of the bone):

- Bisphosphonates (several ZA trials and 1 alendronate trial) showed to control disease progression in giant cell tumor of the bone. (Balke M, Campanacci L, Gebert C, Picci P, et al. Bisphosphonate treatment of aggressive primary, recurrent and metastatic giant cell tumour of bone. BMC Cancer. 2010;10:462.)
- Denosumab treatment in patients with GCTB significantly reduced or eliminated RANK Positive tumor giant cells. Clinical endpoints were not measured. Denosumab continues to be studied for potential treatment of GCTB. (Branstetter DG, Nelson SD, Manivel JC, et al Denosumab induces tumor reduction and bone formation in patients with GCTB. Clin Cancer Res; 18(16):4415-24.)
- Denosumab was compared to zoledronic acid in patients with surgically unsalvageable giant cell tumor of bone (n=250). There was no difference in response rate, clinical benefits, or overall survival. (Li S et al. Denosumab versus zoledronic acid in cases of surgically unsalvageable giant cell tumor of bone: a RCT. J Bone Oncol 2019; 15:100217. PMID 30740297)

Denosumab is a covered drug for GCTB ONLY when bisphosphonates have failed. Since there is a lack of comparative data in this setting and neither drug has measured clinical endpoints such as overall survival, it is not known whether either is superior in efficacy or safety over the other in this setting. Cost is more for denosumab.

Prolia (denosumab 60 mg/1 ml) is FDA-approved for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture NOT COVERED (SEE BELOW)
- Treatment of glucocorticoid-induced osteoporosis in men at high risk for fracture NOT COVERED (SEE BELOW)
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor for breast cancer

Other information of interest (from uptodate.com): Fracture risk after discontinuation of denosumab — Emerging data have raised concern about increased fracture risk after discontinuation of denosumab. In a case series, vertebral fractures occurred in postmenopausal women after denosumab withdrawal [21-23]. Fractures were often multiple and occurred 8 to 16 months after the last dose, raising concerns about a rebound in fracture risk when denosumab

wears off. In a post hoc analysis of 1471 patients in the FREEDOM trial and its extension (patients who received at least two doses of denosumab or placebo, discontinued treatment, and remained in the study for at least seven months after discontinuation), there was a rapid rise in vertebral fracture rate upon discontinuation of denosumab (from 1.2 to 7.1 per 100 participant-years), similar to those who received and then discontinued placebo [24]. However, patients who discontinued denosumab had a higher rate of multiple vertebral fractures than the placebo group (60.7 versus 38.7 percent [4.2 versus 3.2 per 100 patient-years]). Patients with a prior vertebral fracture were at greatest risk for multiple fractures upon discontinuation.

CRITERIA for: Prolia 60mg/1mL (dose: 60 mg SQ every 6 months)
1. Request is for treatment of postmenopausal woman with osteoporosis at high risk for fracture AND the patient has contraindication, failure, or intolerance of IV and oral bisphosphonates*.
2. Request is for treatment of bone loss in men receiving androgen-deprivation therapy for non-metastatic prostate cancer
3. Request is for treatment of bone loss in women receiving an aromatase inhibitor (anastrozole, letrozole, or exemestane) therapy for breast cancer
*failure: fracture or decrease in bone mineral density (BMD) while compliant on bisphosphonate therapy *contraindications to IV bisphosphonates: CrCl <35 ml/min (zoledronic acid) *intolerances seen with IV bisphosphonates: severe flu-like symptoms, bone/joint/muscle pain, anaphylaxis, urticarial, renal failure. Note: osteonecrosis of the jaw and hypocalcemia may occur with denosumab therapy as well as zoledronic acid. *contraindications to oral bisphosphonates: achalasia, esophageal stricture, Barrett's esophagus, esophageal varices, inability to stay upright for at least 30-60 minutes; CrCl <35 ml/min (alendronate), CrCl <30 ml/min (risedronate). *intolerances seen with oral bisphosphonates: reflux, esophagitis, esophageal ulcers
If 1, 2, or 3 is fulfilled, approve for 1 year
Continuation criteria
No unacceptable toxicity
If criteria fulfilled, approve for 1 year.
POSTMENOPAUSAL WOMEN AT HIGH RISK FOR FRACTURE: • Over 36 months, denosumab reduced the rate of new radiographic vertebral fracture vs placebo, rates were 2.3% vs 7.2% (HR 0.32, 95%CI 0.26-0.41, p<0.001). Denosumab also reduced hip fracture, cumulative incidence was 0.7% vs 1.2% (HR 0.60;95%CI, 0.37-0.97;p=0.04). Denosumab reduced nonvertrebral fracture, cumulative incidence 6.5% with denosumab vs 8% placebo (HR, 0.80;95%CI, 0.67 to 0.95;p=0.01). Pts were 60-90, Tscore <-2.5 but not less than -

4.0 at lumbar spine or total hip.(Cummings SR, Martin Js, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756-65.)

- Bisphosphonates reduce new vertebral fractures and hip fractures. (Freemantle N, et al. Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis. Osteoporos Int. 2013;24:209-217)
- A large randomized study found that in patients receiving oral bisphosphonates with BMD t score <-2.5 who were randomized to either denosumab or annual IV zoledronic acid, there was an increase in t score in both groups and a greater increase in the denosumab group. Study was not designed to evaluate fracture risk. Change in BMD is a surrogate endpoint and need fracture data to establish superiority for denosumab over zoledronic acid (Miller et al. J Clin Endocrinol Metab. 2016 Aug;101(8):3163-70). According to AACE/ACE guidelines for tx of postmenopausal osteoporosis, lack of increase in BMD change is not necessarily correlated with change in fracture risk, and the goal of BMD monitoring is to identify patients who have substantial bone loss. Stable or increasing BMD indicates a satisfactory response to treatment (Comach et al. Endocr Pract. 2016 Sep 2;22(Suppl 4):1-42. PMID 27662240).
- Guideline: ACOG Osteoporosis Practice Bulletin recommends bisphosphonates first line for most women Hauk L et al. Am Fam Physician 2013 Aug 15;88(4):269-75. PMID 23944732

Summary: Since bisphosphonates have fracture data and are cheaper, denosumab will be covered ONLY if the patient has a contraindication or intolerance to oral and IV bisphosphonates.

MEN RECEIVING ANDROGEN DEPRIVATION THERAPY FOR NONMETASTATIC PROSTATE CANCER:

- N=1468 pts with nonmetastatic prostate cancer receiving androgen-deprivation therapy to denosumab 60mg SC q6m or placebo. 1`endpt was change in BMD at lumbar spine at 24m. 2` endpts were %change in BMD at femoral neck and total hip at 24m and all 3 sites at 36m, and new vertebral fractures. Results: at 24m, BMD lumbar increased 5.6%D vs -1%plac (p<0.001). D showed significant increased in BMD at total hip, fem neck, and distal 1/3 of the radius at all time points. Denosumab decreased new vertebral fxs at 36m (1.5% vs 3.9%plac)(RR 0.38; 95%CI 0.19 to 0.78; p=0.006). Rates of AEs similar. Smith MR, Egerdie B, et al. Denosumab in men receiving ADT for prostate CA. N Engl J Med. 2009;361:745-55.
- The trial with zoledronic acid was underpowered to show a reduction in fracture risk in pts with NON-metastatic prostate CA. Denham JW, Nowitz M, et al. Impact of androgen suppression and ZA on BMD and fractures in the Trans-Tasman Radiation Oncology Group (TROG) 03.04 randomized androgen deprivation and radiotherapy (RADAR) RCT for locally advanced prostate cancer. BJU Int. 2014;114(3):344-53.

There are no data comparing ZA to denosumab in this population looking at the endpoint fracture reduction. (2/1/19 sk)

Summary: Denosumab has been shown to reduce fractures for this indication, but bisphosphonates have not. Therefore, denosumab will be covered.

WOMEN RECEIVING AROMATASE INHIBITORS:

- From the PI: The efficacy of Prolia in the treatment of bone loss was evaluated in 252 women

treated with aromatase inhibitor therapy due to breast CA. The trial was 2 y, was DB, placebo-controlled. 1` endpoint was % change in lunbar spine BMD from baseline to month 12. The treatment difference was 5.5% (it decreased -0.8% in placebo and increased +4.8% with Prolia; 95%CI: 4.8, 6.3;p<0.0001). Fracture rate was not measured. There was not a bisphosphonate control arm.

- Bisphosphonates also increase lumbar spine vs placebo in women with breast CA on AIs. The % change in weighted mean difference was 5.42% at the lumbar spine and 3.03% (95%Ci, 4.37-6.48) at the total hip. Su G, Xiang Y, He G, Jiang C, et al. Bisphosphonates may protect against bone loss in postmenopausal women with early breast cancer receiving adjuvant aromatase inhibitor therapy: results from a meta-analysis. Arch Med Res. 2014. Oct;45(7):570-9.
- I could not find that bisphosphonates reduce fractures in AI breast cancer patients. (JJ 7/6/15)
- Denosumab reduced the risk of clinical fractures in postmenopausal women with HER2+ breast cancer, nonmetastatic, ER+ or progesterone+, postmenopausal women, receiving AIs. They were given 60mg 2x/year SC or placebo. N=3420. HR 0.50 (95%CI 0.39-0.65) for time to 1st fracture. Also received 500mg elemental Ca and at least 400IU vit D daily. Excluded if on SERMs or received bisphosphonates. 99% were white. At 36m, 5% (95%CI 3.8-6.2) of denosumab and 9.6%(95%CI,8.0-11.2) of placebo had experienced a fracture. At 84m, 11.1% (95%CI 8.1-14.1) denosumab group and 26.2%(15.6-36.8) in the placebo group. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicenter, R, DB, PC trial.

Guideline: ACOG Osteoporosis Practice Bulletin recommends bisphosphonates first line for most women Hauk L et al. Am Fam Physician 2013 Aug 15;88(4):269-75. PMID 23944732

Summary: Denosumab has been shown to reduce fractures for this indication, but bisphosphonates have not. Therefore, denosumab will be covered.

NOT COVERED: MEN AT HIGH RISK FOR FRACTURE

- From PI: Men in 1y, R, DB, PC trial with baseline BMD t-score -2 to -3.5 at lumbar spine or femoral neck OR T-score -1 to -3.5 and a hx of prior fragility fracture. N=242 age 31-84 (mean 65), received 60mgSC q6m or placebo. Effect was an increase in BMD from baseline of 4.8% over placebo at LS, 2% at hip, 2.2% at femoral neck. No fracture rates were measured.
- No further comparative or fracture data available as of 2/1/19

Denosumab does not have fracture data for this indication, and bisphosphonates do have fracture data. Denosumab will NOT be a covered drug for this use at this time due to no data either comparing it with bisphosphonates for any endpoint, or comparing denosumab with placebo with fractures as an endpoint.

NOT COVERED GLUCOCORTICOID-INDUCED OSTEOPOROSIS

-Double blind, RCT non-inferiority study of denosumab vs risedronate in patients receiving >7.5 mg prednisone daily. Denosumab was noninferior AND superior to risedronate for improvement in lumbar spine BMD. No fracture data available.[1]

-Guideline: For pt >40 y/o at moderate/high risk for fracture, the 2017 American College of Rheumatology Guideline for Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

recommends oral bisphosphonates (BP) OVER IV BP, denosumab, teriparatide, or raloxifene. If oral BP not an option, recommend the following in order of preference: IV BP, teriparatide, denosumab, raloxifene.[2]

Summary: Prefer bisphosphonates because they have fracture data for this indication. Denosumab does not have fracture data and will not be covered.

1. Saag KG et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. Lancet Diabetes Endocrinol. 2018 Jun;6(6):445-454. NCT01575873, PMID 29631782

2. Buckley et al. 2017 American College of Rheumatology Guideline for Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis & Rheumatology. 2017 Aug;69(8):1521-1537. PMID 28585373

Revision History

Date	What changed	Pharmacist's initials
7/7/15	I revised the criteria.	JJ
2/25/2016	I added information covering males with NON metastatic prostate cancer receiving androgen deprivation therapy. No comparative trials of denosumab vs ZA have been powered to evaluate fracture risk. The population with bone mets is a different population entirely.	JJ
3/7/19	1. For treatment of bone loss in women receiving aromatase inhibitor (anastrozole or exemestane) therapy for breast cancer: removed requirement for HER2+ breast cancer. Patients in referenced study were allowed to be HER2 negative. Also added that letrozole is another aromatase inhibitor on the market. 2. New indication: glucocorticoid induced osteoporosis: not covered due to lack of fracture data 3. Allow use for post-menopausal women at high risk for fracture if intolerant/ contraindication to oral AND IV BP. 4. Added new Xgeva indication for prevention of skeletal related events in patients with multiple myeloma which will only be covered if patient has contraindication to zoledronic acid.	sk
5/25/2021	Criteria reviewed. Change approval period for Xgeva to 12 months. Updated some evidence statements. No other changes	SK
9/01/2021	Criteria reviewed.	JJ

Dexcom G6 Continuous Glucose Monitor

EBRx PA Criteria

FDA-approved for: continuous glucose monitoring in patients 2 years and older with diabetes.

Criteria for new users
Pediatric/Adolescent Use (ages 2-18):
Must have Type 1 Diabetes documented by an Endocrinologist or PCP **AND**
Must meet **ALL** criteria 1a, 1b, 1c, & 1d: 1a. Multiple daily insulin injections (3+) **OR** insulin pump therapy with frequent dosage adjustments **OR** recurring (>3 per month) episodes of severe hypoglycemia (54 mg/dL or below); **AND** 1b. Documented average frequency of glucose testing 4 or more times per day during the previous two months; **AND** 1c. Must share Dexcom data with at least one caregiver, one provider and Plan's Diabetes Management Program; **AND** 1d. Alerts must be turned on at all times, subject to verification by healthcare provider or Plan's Diabetes Management Program provider
OR Hospitalization and/or emergency department visit for severe hypoglycemia in the past 3 months
Adult Use (18 and older):
Must have Type 1 Diabetes documented by an Endocrinologist or PCP **AND**
Must meet **ALL** criteria 3a, 3b, 3c, 3d, & 3e, 3a. 3 or more injections daily for at least 6 months OR pump with frequent dosage adjustments for at least 6 months; **AND** 3b. Documented average frequency of glucose testing 4 or more times per day during the previous 2 months; AND 3c. Must share Dexcom data with at least one healthcare provider and Plan's Diabetes Management Program 3d. Alerts must be turned on at all times, subject to verification by healthcare provider or

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Plan's Diabetes Management Program provider 3e. Participation in Plan's Diabetes Management Program
OR Hospitalization and/or emergency department visit for severe hypoglycemia (54 mg/dL or below) in past 3 months

Criteria for continuation
1. Fulfillment of requirements from the previous year: a. Pediatric/Adolescent : Requirements 1c & 1d. b. Adult : Requirements 3c, 3d, & 3e.
2. Sensor adherence (timely fills)
3. Patient that has been confirmed to have access to the CGM monitor/mobile app

Quantity Limits (per year): 1 Monitor & 39 sensors (based on 1 sensor/10 days & 3 sensors/pack)

Revision History:

Date	Notes	Pharmacist's initials
6 /22/2020	Criteria written.	OD

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Dextromethorphan/quinidine (Nuedexta®)

20-10mg capsules

EBRx PA Criteria

FDA-approved for: treatment of pseudobulbar affect (PBA)

Criteria for new users
1. The patient must have a diagnosis of clinically significant pseudobulbar affect (a baseline score of >13 on the Center for Neurologic Studies Lability Scales (CNS-LS).
If yes, approve for 1 year.

The center for neurologic study lability scale (CNS-LS)	
Circle the number that best define your feelings.	
I find that even when I try to control my laughter I am often unable to do so	1 2 3 4 5
I find that I am easily overcome by laughter	1 2 3 4 5
There are times when I won't be thinking of anything happy or funny at all, but then I'll suddenly be overcome by funny or happy thoughts	1 2 3 4 5
Others have told me that I seem to become amused very easily or that I seem to become amused about things that really aren't funny	1 2 3 4 5
I find myself crying very easily	1 2 3 4 5
There are times when I feel fine one minute, and then I'll become tearful the next over something small or for no reason at all	1 2 3 4 5
I find that even when I try to control my crying I am often unable to do so	1 2 3 4 5

Resource:
Moore S.R., Gresham L, Bromberg M.B., Kasarkis E., Smith R.A. (1997). A self report measure of affective lability. *J. Neurol. Neurosurg. Psychiatry* 1997;63;89-93 Retrieved on February 22, 2007 from jnnp.bmj.com.

Note: This drug is covered at T3 with PA. It is not effective for heroin detox. The quinidine increases dextromethorphan's bioavailability by 20-fold. The dextromethorphan is what treats the disease.

Quantity Limits:

References:

1. Pioro EP, Brooks BR, et al. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. ANN NEUROL 2010;68:693–702.

2. CNS-LS Questionnaire. http://hablemosdeem.com/desdemibalcon/wp-content/uploads/2010/03/CNS.pdf

Revision History:

Date	Notes	Pharmacist's initials
1/11	JJ created criteria	JJ
5/11/12	JJ added references and revision history table.	JJ
6/23/2020	I reviewed the criteria. I removed the diagnoses amyotrophic lateral sclerosis (ALS) and multiple sclerosis.	JJ
4/7/2021	I reviewed the criteria. No changes were made. No current users.	JJ

CONFIDENTIAL

Dihydroergotamine intranasal (brand Migranal and generic)

EBRx PA Criteria

is FDA-approved for: Acute treatment of moderate to severe migraine w or w/o aura (nasal spray; injection)

Criteria for new users
1. Patient must have the diagnosis of moderate to severe migraine
2. Patient must have intolerance/nonresponse/contraindication to at least 2 triptans.
3. Patient must have intolerance/nonresponse/contraindication to Rimegepant (Nurtec ODT), used for treatment of migraine.

Note: The dose is 0.5mg per spray. One spray in each nostril; repeat after 15 minutes for a total of 4 sprays (2mg). Safety of >6 sprays (3mg) in 24h or 8 sprays (4mg) in a week have not been established.

Also given as an acceptable dose: 0.725mg/spray in each nostril (total of 2 sprays per dose), may repeat as needed after >1h (total of 4 sprays in 2 doses). Max is 4 sprays (2 doses) /24h; 6 sprays (3 doses) in 7 days.

Quantity Limits: 8 sprays per claim

Revision History:

Date	What changed	Pharmacist's initials
11/3/21	I wrote the criteria.	JJ

CONFIDENTIAL

Dimethyl fumarate (Tecfidera®)

EBRx PA Criteria

is FDA-approved for: relapsing-remitting multiple sclerosis (RRMS)

Criteria for new users
1. The patient must have the diagnosis of a relapsing form of multiple sclerosis.
2. The patient must not be receiving concurrent diroximel fumarate.

Quantity Limits: QL of #14 for the 120mg dosage form. Dose is 120mg twice daily for 7 days, then the PI states to increase to 240mg BID after that.
QL of #62 for each fill. NO more than a 31 days supply with each fill.

References:

1. Tecfidera PI. www.tecfidera.com. Accessed 5/28/13.

2. Expanded Disability Status Scale.
http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3582b1px.pdf

3. Filippini G, Del Giovane C, Vacchi L, D'Amico R, Di Pietrantonj C, Beecher D, Salanti G. Immunomodulators and

immunosuppressants for multiple sclerosis: a network meta-analysis. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD008933. DOI: 10.1002/14651858.CD008933.pub2.

4. AAN. Practice Guideline: Disease-modifying Therapies for Adults with multiple sclerosis. American Academy of Neurology 4/24/2018.
https://www.aan.com/Guidelines/Home/GetGuidelineContent/900

Revision History:

Date	Notes	Pharmacist's initials
5/28/13	JJ created the criteria.	JJ
5/20/2014	JJ added the requirement of failing interferon (Rebif or Betaseron) per the Cochrane Sys Review that states Avonex is inferior to those. Rebif showed decreased exacerbations and a delay in progression. Betaseron was not statistically different from Rebif. Avonex was. Reference #3 was added.	JJ
9/19/19	I changed the criteria and removed requirement for failure of	JJ

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	interferon first. Added reference 4.	
06/23/2020	I reviewed the criteria. No changes.	JJ
7/6/2020	I added criteria #2 to disallow concurrent use with diroximel fumarate.	JJ
12/8/2020	Reviewed. Added no concurrent monomethyl fumarate either (not covered by the plan, but to be complete)	JJ

CONFIDENTIAL

Dolutegravir/rilpivirine (Juluca®)

50-25 mg tablet

EBRx PA Criteria

FDA-approved: as a complete regimen for the treatment of HIV-1 infection in adults in select patients (described below)

Criteria for new users

1. The patient **must have** a diagnosis of HIV-1 infection and meet all of the following criteria.
   - Virologically suppressed (HIV-1 RNA < 50 copies/mL) AND
   - On the same, stable antiretroviral regimen for at least 6 months AND
   - No history of treatment failure with other HIV regimens AND
   - No known resistance to dolutegravir OR rilpivirine (the resistance panel must be done right before or after the initiation of their current HIV regimen).
2. The request for Juluca must decrease the number of tablets the patient takes daily. (ie. Juluca will not be approved for patients switching from once daily Genvoya to once daily Juluca).

If all of criteria 1 and criteria 2 are met, approve Juluca 50-25 mg once daily for 1 year.

- **If the patient is on concomitant rifabutin – the patient must take an additional 25 mg tablet of rilpivirine with Juluca once daily for the duration of the rifabutin coadministration.**

Dosing: one tablet PO once daily with a meal.

Revision History:

Date	What changed	Pharmacist's initials
1/19/18	I wrote the criteria. Current approval is only for pediatric population described above.	JK
2/6/18	I reviewed the criteria.	JJ

Ref:

1. Juluca package insert accessed 1/19/18

CONFIDENTIAL

Dornase alfa (Pulmozyme®)

Solution for nebulization (single-use ampules): Pulmozyme 2.5 mg/mL

EBRx PA Criteria

Pulmozyme is a mucolytic agent used in the treatment of cystic fibrosis (labeled) and complicated parapneumonic effusion (unlabeled).

1. Does the patient have a diagnosis of cystic fibrosis?	☐ yes ☐ no
2. Does the patient have FVC ≥40%?†	☐ yes ☐ no
IF YES TO BOTH QUESTIONS, APPROVE	
3. Does the patient have parapneumonic effusion?	☐ yes ☐ no
4. Will dornase alfa be used as an adjunct therapy to alteplase?‡	☐ yes ☐ no
IF YES TO BOTH QUESTIONS, APPROVE PA for 1 year.	
†Note: Dornase alfa has been shown to improve FEV_1, decrease bacterial exacerbations, and decrease antibiotic use in patients ≥3 months old if they had FVC≥40% at baseline. **‡Note:** Alteplase may be given for parapneumonic effusion and should be administered at a dose of 10mg in 30 mL NS BID given intrapleurally with 1 hour dwell time for a total of 3 days, with each dose of dornase alfa >2 hours after alteplase administration. Current medical practice favors a stepwise approach for treating parapneumonic effusion, starting with less invasive measures and stepping up to fibrinolytic therapy only in refractory cases to medical management.	

DOSING:

Adult: **Cystic Fibrosis mucolytic** (labeled) – 2.5 mg once daily through nebulizer
Complicated parapneumonic effusion (unlabeled) - 5 mg diluted in 30 mL sterile water given intrapleurally twice daily >2 hours after intrapleural alteplase administration

Pediatric (≥3 months): **Cystic Fibrosis mucolytic** – 2.5 mg once daily through nebulizer

** Limited experience with administration to patients younger than 5 years of age. Its use should be considered only for those patients in whom there is a potential for benefit in pulmonary function or in risk of respiratory tract infection.

NOTES:

Pulmozyme is derived from genetically engineered Chinese hamster ovary cells. Hypersensitivity to such components is contraindicated to its use. Safety and efficacy of daily administration have not been demonstrated in patients for longer than twelve months. Voice

alterations and rash appear to be the only side effects reported with consistency in randomized trials.

While inhaled N-acetylcysteine has been used as a mucolytic drug in cystic fibrosis for decades, it has no proven benefit and carries risk for epithelial damage if administered via aerosol. Dornase alfa has been shown to reduce pulmonary exacerbations and improve lung function and is currently the only mucolytic agent with proven efficacy in CF.

There is now growing interest in the potential for long-term benefits of dornase alfa in young patients having mild lung dysfunction. In the Robinson trial, children 6-10 years of age with FEV1 ≥85% were evaluated in a placebo-controlled trial comparing PFT's and respiratory tract exacerbations (RTE) associated with use of dornase alfa and placebo. Results showed improvement in PFT's with dornase alfa starting at week 4, as well as decreased RTE's in the dornase alfa group. In these patients with mild lung disease, greater improvements were seen in peripheral flow (FEF25–75 and MEF) than lung volumes (FVC or FEV1), supporting early and aggressive therapy in cystic fibrosis patients.

- A trial performed evaluating exacerbation of pulmonary symptoms in treated patients versus those untreated revealed an exacerbation frequency of 0.25, with a 95% confidence interval. This was equivalent to a reduction of 25 exacerbations per 100 treated patients per year. The confidence intervals did not overlap zero. This difference was found for both males and females.
- A separate trial was later performed which compared only patients aged 6-10 years and found similar results regarding pulmonary exacerbations in cystic fibrosis patients.[5,6]

Fig. 3. Results from dornase alfa v. placebo in relation to predicted values at baseline in 96 week trial of patients ages 6-10 years

Characteristic	**Dornase alfa (n = 206)**	**Placebo (n = 204)**
FEV_1	0.04% ± 0.8% predicted	-3.2% ± 0.8% predicted
Benefit	3.2% ± 1.2% predicted (*P* = .006)	
FEF_{25-75}	3.8% ± 1.6%	-4.1% ± 1.7%
Benefit	7.9% ± 2.3% predicted (*P* = .0008)	
FVC	–2.2% ± 0.7%	–2.9% ± 0.7% predicted
Benefit	Not statistically significant	
Respiratory Tract Exacerbations	**N=474, unsure if they used ITT for results.** **-34% (relative risk 0.66, 95% CI 0.44-1.00, *P* = .048)****	

	Dornase 40 pts had 62 exacerbations over 96 w (28 early, 34 late); 0.65 exac/week	**Placebo 56 pts had 92 exacerbations over 96 w (47 early, 45 late); 0.96 exac/week**
	Dornase rash 5.9%	**Plac rash 1.3%**
****A time-to-first-event analysis demonstrated that patients receiving dornase alfa had a lower risk of exacerbations versus placebo throughout the study.		

REFERENCES:

1. Henke MO, Ratjen F. Mucolytics in Cystic Fibrosis. Pediatric Respiratory Reviews. 8(1):24-9, 2007 Mar.
2. Johnson, Charles A., Steven M. Butler, Michael W. Konstan et al. Estimating effectiveness in an observational study: A case study of dornase alfa in cystic fibrosis. The Journal of Pediatrics. 1999;134(6):734-39.
3. Lexi-Comp Online , Lexi-Drugs Online , Hudson, Ohio: Lexi-Comp, Inc.; Accessed October 8, 2012.
4. Pulmozyme prescribing information. Genentech. Accessed October 7, 2012.
5. Robinson, Phillip J. Dornase Alfa in Early Cystic Fibrosis Lung Disease. Pediatric Pulmonology 34:237–241 (2002).
6. Joanne M. Quan, MD, Harm A. W. M. Tiddens, MD, et al. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. Journal of Pediatrics. 139(6):813-20, 2001 Dec.
7. Naomi B. Bishop, Steven Pon, H. Michael Ushay, et al. Alteplase in the Treatment of Complicated Parapneumonic Effusion: A Case Report. Pediatrics 2003;111;e188
8. Konstan MW, Wagener JS, Pasta DJ, Mmillar SJ, et al. Clinical use of dornase alfa is associated with a slower rate of FEV1 decline in CF. Pediatr Pulmonol. 2011; 46:545–553.

REVISION HISTORY:

Date	Changes	Pharmacist
10/18/2012	Document Created	JJ /CC

CONFIDENTIAL

Dulaglutide (Trulicity®)

EBRx PA Criteria

FDA-approved for:

- treatment of type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control in adults
- as risk reduction of major CV events (CV death, NFMI, NF stroke in patients with T2DM with established CV disease or multiple CV risk factors.

Criteria for new users
1. The patient must have the diagnosis of type 2 diabetes mellitus.
2. The patient have a documented HbA1C in the previous 3 months of 7.0%-9.5%.
3. Patient must be receiving metformin at 1000mg twice daily for the past 4-5 months. Pharmacist should look back to be sure this occurred. OR The patient must have a contraindication to metformin that must be documented by the pharmacist.
4. No duplication of therapy with exenatide or other GLP-1 agonists (liraglutide, exenatide, albiglutide, semaglutide) or SGLT2 inhibitors.
Criteria for continuation
1. The patient should have dulaglutide on the profile as having filled for 10 of the 12 previous months.
2. The patient should have metformin on the profile as having filled for 10 of the 12 previous months.

Note: Metformin must be titrated slowly upward. Metformin 500mg BID is the initial dose.

References:

1. Gerstein, Hertzel C., et al. "Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial." *The Lancet* (2019).

2. Palmer, Suetonia C., et al. "Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials." *bmj* 372 (2021).

Revision History:

Date	What changed	Pharmacist's initials
10/28/19	I wrote the criteria.	JJ

3/29/2021	I reviewed the criteria. Omitted the statement about exenatide. Added the indication to reduce CV risk.	JJ
4/22/21	Removed these criteria per the rebate contract: 5a. Patient must be age 50+ with vascular disease (previous MI, ischemic stroke, revascularization, hospital admission for unstable angina, or imaging evidence of myocardial ischemia. OR 5b. Patient must be aged 55y+ and myocardial ischemia, coronary/carotid/or lower extremity artery stenosis exceeding 50%, left ventricular hypertrophy, or albuminuria. OR 5c. Patient must be age 60+ with at least 2 of tobacco use, dyslipidemia, hypertension, or abdominal obesity.	JJ
4/26/21	Per EBRx P&T meeting 4/22, we removed criteria all together on SGLT2 inhibitors, but left criteria on GLP1a. We also decided to disallow concurrent SGLT2i and GLP1a therapy due to uncertain benefit with the combination. I added reference 2.	JJ
4/28/21	I added no concurrent therapy with SGLT2i due to uncertainty of combination therapy.	JJ

CONFIDENTIAL

Dupilimab (Dupixent®)

300mg SC injection

EBRx PA Criteria

FDA-approved for:

- treatment of adult moderate-severe atopic dermatitis
- add-on maintenance treatment of moderate to severe asthma in adults and pediatric patients ≥12 y of age with an eosinophilic phenotype or with corticosteroid dependent asthma.
- Rhinosinusitis, chronic, with nasal polyposis, as add-on maintenance treatment in adults with inadequately controlled chronic rhinosinusitis with nasal polyposis

MODERATE TO SEVERE ATOPIC DERMATITIS
Criteria for new users
1. Patient must be ≥6 years old
2. Patient must have tried 1 month of a high potency topical steroid and 1 month of a topical calcineurin inhibitor, unless area is on face (in which case only a topical calcineurin inhibitor should be tried for 1 month).
3. Patient must have the diagnosis: **MODERATE TO SEVERE** as measured by dermatologist, allergist, or immunologist.
4. Prescriber must be a dermatologist, allergist, or immunologist
Note: The first dose is 600mg (2-300mg syringes followed by 1-300mg dose every 2 weeks. PA is good for 16 weeks; assessment of efficacy should occur then.
Criteria for continuation
1. Patient must be adherent to the q2w dosing
2. Patient must have experienced an improvement in symptoms. The physician must have documented this improvement.
Note: if both are satisfied, approve PA for 1 year.

Quantity Limits: 1 SC injection every 2 weeks (except for the 600mg [2-300mg syringes] first dose).

References:

1. Simpson, Eric L., et al. "Two phase 3 trials of Dupilumab versus placebo in atopic dermatitis." *NEJM* 375.24 (2016): 2335-2348.

MODERATE TO SEVERE ASTHMA, AS ADD-ON MAINTENANCE TREATMENT
Criteria for new users

1. Patient must be ≥12 years old
2. Patient must currently have on their profile: • an inhaled corticosteroid (medium-high-dose, fluticasone propionate at a total daily dose of ≥500ug or equipotent equivalent, for at least 3 months and with a stable dose for at least 1 month prior to first request of dupilumab), • a long-acting beta agonist, • and an inhaled long acting muscarinic agonist (LAMA) for the previous 4 months. May have montelukast in place of LAMA. OR The patient must be dependent on chronic oral corticosteroids (defined as being on oral steroids ≥50% of the year)
3. The patient must have a blood eosinophil count of >150 cells/mm3 at baseline.
4. Prior to the first dupilumab request, the patient MUST have experienced, within 1 year prior to first request, any of the following: • treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once • Hospitalization or emergency medical care visit for worsening asthma
5. Patient must have the diagnosis: **Moderate to SEVERE** asthma with an eosinophilic phenotype and still be symptomatic.
6. Prescriber must be an allergist, immunologist, or pulmonologist.
7. The patient must be a non-smoker.
8. The patient must have an FEV1 <80% of predicted (or <90% of predicted for adolescents).
9. The patient is not currently being treated with omalizumab, mepolizumab, reslizumab, or benralizumab.
Note: The first dose is up to 600mg (2-300mg syringes followed by up to 1-300mg dose every other week. PA is good for 16 weeks; assessment of efficacy should occur then.
Criteria for continuation
1. Patient must be adherent to the q2w dosing.
2. Patient must have experienced an improvement in symptoms. The physician must have documented this improvement in the medical record. A reduction in oral corticosteroid dose would be considered an improvement.
Note: if both are satisfied, approve PA for 1 year.

Quantity Limits: 1 SC injection every 2 weeks (except for the 600mg [2-300mg syringes] first dose).

References:

1. ICER Asthma. 2018. Final Evidence Report.

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2. Rabe, Klaus F., et al. "Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma." *NEJM* (2018).

3. Castro, Mario, et al. "Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma." *NEJM* (2018).

4. 2021 GINA Asthma Guidelines. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS, AS ADD-ON MAINTENANCE TREATMENT
Criteria for new users
1. Patient must be ≥18 years old
2. Patient must have the diagnosis of bilateral nasal polyposis and chronic symptoms of sinusitis despite intranasal coritosteroid treatment for at least 2 months. (attestation of the physician will have to suffice since intranasal steroids are OTC.).
3. Prescriber must be an allergist, immunologist, or pulmonologist.
4. The patient is not currently being treated with omalizumab, mepolizumab, reslizumab, or benralizumab.
Note: The first dose is up to 600mg (2-300mg syringes followed by up to 1-300mg dose every other week. PA is good for 16 weeks; assessment of efficacy should occur then.
Criteria for continuation
1. Patient must be adherent to the qw dosing.
2. Patient must have experienced an improvement in symptoms. The physician must have documented this improvement in the medical record.
Note: if both are satisfied, approve PA for 1 year.
DOSE is 600mg LD followed by 300mg every other week; the patient should be receiving concurrent intranasal steroids.

Reference:

1. Bachert, Claus, et al. "Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *Jama* 315.5 (2016): 469-479.

Revision History:

Date	What changed	Pharmacist
5/31/17	I wrote the criteria	JJ
6/15/17	I updated the criteria after speaking with Brent Flaherty.	JJ
12/19/18	I updated the criteria to include severe eosinophilic asthma. Moderate	JJ

	asthma was not included despite the FDA approval due to the evidence not showing as big an advantage.	
3/13/19	I changed the age down to age 12. FDA approval reduced the age today.	JJ
10/30/19	I updated the criteria, added the indication of rhinosinusitis w/ nasal polyps, and reference.	JJ
2/23/2020	I reviewed the criteria. No changes	JJ
6/22/2020	Dupixent received FDA approval for ages 6y+ for atopic dermatitis only. I revised the criteria.	JJ
12/8/2020	For asthma: I added requirement for new users to have sputum eosinophil counts of >300 cells/uL, per ICER comparative effectiveness review.	JJ
12/10/2020	For asthma: The box/whisker plot on figure 1 for ref 3 (Castro, et al) showed no benefit in exacerbations for eosinophil count <150 for either dose. ICER used >300 for dupilumab. I added the definition for med-high dose ICS and the length of trial of ICS before access to dupilumab. I also added the requirement that prior to the first dupilumab request, the patient MUST have experienced, within 1 year prior to first request, any of the following: • treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once • Hospitalization or emergency medical care visit for worsening asthma	JJ
7/23/2021	I changed the eosinophil count to >150 for Mod-sev asthma per Castro, et al. Also added the 2021 GINA Asthma update.	JJ

CONFIDENTIAL

Durvalumab (Imfinzi®)

120mg/2.4mL, 500mg/10mL IV solution

EBRx PA Criteria

FDA-approved for:

- Unresectable, stage III non-small cell lung cancer (NSCLC), whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy
- In combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)

Non-Small Cell Lung Cancer
1. Diagnosis of stage III, unresectable non-small cell lung cancer (NSCLC)
2. Patient must have received at least two cycles of platinum-based chemotherapy (containing either cisplatin or carboplatin along with etoposide, vinblastine, vinorelbine, paclitaxel, docetaxel, or pemetrexed).
3. Must NOT have had progression after platinum-based, concurrent chemoradiotherapy (verified with imaging such as CT or MRI done after completion of radiation)
4. Last chemoradiation session must have been no more than 42 days ago, from first request of durvalumab.
If all criteria are met, approved x 1 year. Maximum duration of therapy for this indication is 1 year. No renewals allowed.
Notes: Dose: 10mg/kg q2w for a maximum of 1 year **[1]PACIFIC Trial: Phase III, RCT, durvalumab IV 10mg/kg or placebo q2w for 12 m. 1` endpts were PFS and OS; 2` endpts time to death or distant mets, time to second progression, safety. N=713 (709 received the assigned interventions: 473 durvalumab, 236 placebo). Median f/u 25.2m. 24m OS was 66.3% (95%CI,61.7 to 70.4m) vs 55.6% (95%CI 48.9 to 61.8m, p=0.0005). HR for death 0.68; 99.73%CI 0.47 to 0.997; p=0.00025)**

	Median OS	12 m OS rate (95%CI)	24m OS rate (95%CI)	Harms Grade 3/4 AEs	Harms: DC 2` AEs	Harms: SAEs
Durvalumab	**NR (34.7-NR)**	**83.1% (79.4-86.2)**	**66.3 (61.7-70.4)**	**30.5%**	**15.4%**	**29.1%**
Placebo	**28.7 (22.9-NR)**	**75.3 (69.2-80.4)**	**55.6 (48.9-61.8)**	**26.1%**	**9.8%**	**23.1%**

	HR for death 0.68 (99.73%CI, 0.47-0.997; P=0.0025)					

References:

1. Antonia, Scott J., et al. "Overall survival with Durvalumab after Chemoradiotherapy in stage III NSCLC." *New England Journal of Medicine*(2018).

Small Cell Lung Cancer
1. Diagnosis of extensive stage small cell lung cancer (SCLC)
2. The patient has received no prior therapy for small cell lung cancer
3. Durvalumab will be used in combination with cisplatin or carboplatin AND etoposide
If criteria met, approve for 1 year
Notes: Dose: 1500 mg every 4 weeks until disease progression or unacceptable toxicity. Outcomes (durvalumab+chemo vs chemo): Median overall survival: 13 months versus 10.3 months (HR 0.73, 95% CI 0.59-0.91; p=0.0047) -12-month overall survival: 54% versus 40% -18-month overall survival: 34% versus 25% Reference: Paz-Ares L et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019 Nov 23;394(10212):1929-1939. doi: 10.1016/S0140-6736(19)32222-6. Epub 2019 Oct 4. PMID 31590988 NCT03043872

Revision History:

Date	What changed	Pharmacist's initials
12/13/18	I wrote the criteria based on the PACIFIC trial inclusion/exclusion criteria. Most likely, this would be a medical benefit.	JJ
7/18/19	Criteria reviewed, no significant changes made	SK
1/29/2020	Criteria review. Added that CT or MRI must be done to verify no disease progression before proceeding with durvalumab therapy.	SK
4/27/2020	Added new indication for treatment of SCLC and criteria for coverage.	SK

2/22/2021	Removed urothelial carcinoma indication from FDA indications. Indication withdrawn. Was not covered by EBRx.	SK
7/26/2021	Criteria reviewed. No change	SK

CONFIDENTIAL

Eculizumab (Soliris®)

300mg/30mL for intravenous use

EBRx PA Criteria

Please go to the table with the black headline that is relevant to your patient's diagnosis.

NMOSD not a covered use. NOTE: Because a network meta-analysis showed neither rituximab nor satralizumab was different from eculizumab and is much less costly, eculizumab is no longer covered by EBRx's plans for neuromyelitis optica spectrum disorder (NMOSD). Xue, Tao, et al. "Efficacy and Safety of Monoclonal Antibody Therapy in Neuromyelitis Optica Spectrum Disorders: Evidence from Randomized Controlled Trials." *Multiple Sclerosis and Related Disorders* (August 2020): 102166.

Paroxysmal Nocturnal Hemoglobinuria (PNH)
Although FDA-approved for this indication, ravulizumab is EBRx's preferred drug. Please see the PA for Ultomiris.

Note: Both eculizumab and ravulizumab increase the risk for Neisseria meningitidis meningitis. Vaccines are recommended before either of these drugs.

References:

1. Greenbaum, Larry A., et al. "Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome." Kidney international 89.3 (2016): 701-711.

2. Lee, Jong Wook, et al. "Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study." *Blood* 133.6 (2019): 530-539.

3. Kulasekararaj, Austin G., et al. "Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor–experienced adult patients with PNH: the 302 study." *Blood* 133.6 (2019): 540-549.

Atypical hemolytic uremic syndrome (aHUS) • Atypical HUS cases are cases due to complement dysregulation (complement gene mutations or with antibodies to complement factor H (CFH) • aHUS is NOT due to infection, drug toxicity, or related to pregnancy or SLE.
1. Has the patient been diagnosed with atypical hemolytic uremic syndrome?
2. Is the patient 2 years old or older?
3. Is the adult patient immunized against *Neisseria meningitidis* serotypes A, C, Y and W135 and subtype B, 2 weeks before eculizumab will be initiated? OR will the adult patient receive prophylactic antibiotics upon eculizumab initiation until at least 2 weeks after *Neisseria meningitidis* vaccination?

For approval, all of the 3 criteria above must be 'yes'.

References:

1. Hillmen P, et al. the complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006;355:1233-43.

2. Eculizumab in Lexicomp. Accessed 5/15/17.

3. Azoulay, Elie, et al. "Expert statements on the standard of care in critically ill adult patients with atypical haemolytic uraemic syndrome." Chest (2017).

Refractory generalized myasthenia gravis
1. The patient must have a confirmed diagnosis of refractory, generalized myasthenia gravis.
2. The patient must have a serological test for anti-acetylcholine receptor antibodies and be the test must be positive for the antibodies.
1. The patient must have either failed therapy with rituximab or else not be a candidate for it.
3. The patient must have impaired activities of daily living.
4. The patient must have received treatment with at least 2 immunosuppressive therapies OR at least one immunosuppressive therapy with IVIG or plasma exchange at least four times per year for 12 months without symptom control.
5. The prescriber must be a neurologist.

For approval, all of the 3 criteria above must be 'yes'.

References:

1. Howard Jr, James F., et al. "Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study." *The Lancet Neurology* 16.12 (2017): 976-986.

2. Andersen, Henning, et al. "Eculizumab improves fatigue in refractory generalized myasthenia gravis." *Quality of Life Research* (2019): 1-8.

3. UpToDate. Chronic immunosuppressive therapy for myasthenia gravis. Accessed 8/10/2020.

Date	What changed?	Pharmacist's initials
7/31/07	Criteria written	JJ
10/16/07	IB approval	JJ
5/15/17	I changed age to 2 or older per dosing guidelines in Lexicomp. Added references 2-3. In the setting of aHUS, early treatment with eculizumab appears to reduce and reverse the number of patients receiving hemodialysis.	JJ

2/25/19	I removed the FDA indication for PNH from eculizumab. Ravulizumab is noninferior and less costly. I added references 2 & 3 under PNH above.	JJ
10/24/19	I updated the PA to include the diagnosis neuromyelitis optica; also added the reference. I also added myasthenia gravis and relevant references. The Lancet Neurology missed its primary endpoint, but the reference 2 showed reduced perceived fatigue (greater improvement in Neuro-QOL Fatigue vs placebo).	JJ
8/10/2020	I reviewed the criteria. I added the need to fail or not be a candidate for rituximab in patients with refractory generalized myasthenia gravis. I concur that ravizulimab is still the EBRx-preferred therapy for PNH, and I provided in black in bulleted format the added information for neuromyelitis optica spectrum disorder treatment sequence.	JJ
10/28/2020	I updated the PA to show EBRX would not cover eculizumab for NMOSD since it is very costly while satralizumab (and possibly rituximab) are less costly alternatives and with similar annual relapse rates.	JJ
12/8/2020	Reviewed. No effective changes.	JJ
3/10/2021	Reviewed. No changes.	JJ

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Edaravone (Radicava®)

30mg/100mL IV infusion

EBRx PA Criteria

FDA-approved for: treatment of amyotrophic lateral sclerosis (ALS)

Criteria for new users
1. Patient must have diagnosis of ALS
2. The patient must have recent (from the previous 3 months) pulmonary function tests showing an FVC of at least 80% predicted
3. The patient must NOT have any history of spinal symptoms
If all 3 criteria above are fulfilled, approve the PA for 6 months.

Criteria for continuation
1. The patient must have recent (from the previous 3 months) pulmonary function tests showing an FVC of at least 80% predicted
2. The patient must maintain adherence to the 10 days out of 14 days IV infusions.
If both of the continuation criteria are fulfilled, approve this PA for 3 months.

Note: The dose is 60mg QD IV infusion X14days, followed by a 14 day drug-free period. Subsequent cycles are 60mg IV infusion daily X10 days out of every 14 days, followed by a 14 day drug-free period.

Quantity Limits: Edaravone is supplied in 2-30mg IV infusion bags.

The QL is 2 bags QD; 28 bags/28 days initially.

The QL is 20 bags/28 days after the initial 28 days.

Revision History:

Date	What changed	Pharmacist's initials
8/24/17	I wrote the criteria.	JJ

References:

1. Abe K, Itoyama Y, Sobue G, et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2014;15:610-617.

2. The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled trial. Lancet Neurol 2017;16:505-12.

CONFIDENTIAL

Elagolix/estradiol/norethindrone (Oriahnn®)

300-1-0.5mg capsules

EBRx PA Criteria

is FDA-approved for: Management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

Limitation: Use should be limited to 24 months due to risk of continued bone loss, which may not be reversible.

Criteria for new users
1. Diagnosis of heavy menstrual bleeding (HMB) due to fibroids,
2. Premenopausal woman,
3. Hb ≤10.5g/dL at baseline,
4. Failed trial of 3 months (arbitrary) of estrogen-progestin oral contraceptives or hormone-releasing IUD.
5. No history of thrombosis (this drug contains estradiol).
6. Not a candidate for fibroid resection (1st line therapy).
If the above are satisified, PA is good for 3 months.

Criteria for continuation
1. Hb improved by at least 2g/dL since baseline. (arbitrary)

Note: Limitation: Use should be limited to 24 months due to risk of continued bone loss, which may not be reversible.

Quantity Limits: 60/30

Revision History:

Date	What changed	Pharmacist's initials
7/27/2020	I wrote the criteria.	JJ

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Elapegademase-lvlr (Revcovi©)

IM for self-injection

EBRx PA Criteria

is FDA-approved for: Adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatrics and adults

Criteria for new users
1. The patient must have the diagnosis of ADA-SCID.
2. The patient must be awaiting HSCT or else not be able to undergo HSCT.

Note: HSCT is curative.

Dose: *normal maintenance=20units/kg/wk ¥based on initial dosing since maintenance is based on levels (unsure what an estimate would be)

Elapegademase dose is 0.2mg/kg (ideal body weight) twice weekly for a minimum of 12-24 weeks; may increase dose by 0.033mg/kg once weekly based on ADA trough levels.

References:

1. Hershfield, Michael S. "PEG-ADA replacement therapy for adenosine deaminase deficiency: an update after 8.5 years." *Clinical immunology and immunopathology* 76.3 (1995): S228-S232.
2. LexiComp: elapegademase. Accessed 12/10/2018.
3. LexiComp: pegademase bovine. Accessed 12/10/2018.
4. UpToDate: adenosine deaminase deficiency. Accessed 12/10/2018.

Revision History:

Date	What changed	Pharmacist's initials
7/29/21	I wrote the criteria.	JJ

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Elexacaftor Tezacaftor-ivacaftor (Trikafta®)

ELEX100mg/IVA75mg/TEZ50mg) tablets plus an additional IVA 150mg

EBRx PA Criteria

Initial approval criteria:

1. **The patient must be age ≥6 years old.**

2. **The patient must have the diagnosis of cystic fibrosis and have at least one F508del mutation,**

   OR

   The patient must have no F508 deletions (must have at least one mutation in the CFTR gene that is responsive based on in vitro data. If the genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least 1 F508del mutation or a mutation that is responsive based on in vitro data. Here are the current (as of 4/7/21) "responsive" CFTR mutations:

Table 4: List of *CFTR* Gene Mutations that are Responsive to TRIKAFTA

3141del9	*E822K*	*G1069R*	*L967S*	*R117L*	*S912L*
546insCTA	*F191V*	*G1244E*	*L997F*	*R117P*	*S945L*
A46D	*F311del*	*G1249R*	*L1077P*	*R170H*	*S977F*
A120T	*F311L*	*G1349D*	*L1324P*	*R258G*	*S1159F*
A234D	*F508C*	*H139R*	*L1335P*	*R334L*	*S1159P*
A349V	*F508C;S1251N*†	*H199Y*	*L1480P*	*R334Q*	*S1251N*
A455E	*F508del**	*H939R*	*M152V*	*R347H*	*S1255P*
A554E	*F575Y*	*H1054D*	*M265R*	*R347L*	*T338I*
A1006E	*F1016S*	*H1085P*	*M952I*	*R347P*	*T1036N*
A1067T	*F1052V*	*H1085R*	*M952T*	*R352Q*	*T1053I*
D110E	*F1074L*	*H1375P*	*M1101K*	*R352W*	*V201M*
D110H	*F1099L*	*I148T*	*P5L*	*R553Q*	*V232D*
D192G	*G27R*	*I175V*	*P67L*	*R668C*	*V456A*
D443Y	*G85E*	*I336K*	*P205S*	*R751L*	*V456F*
D443Y;G576A;R668C†	*G126D*	*I502T*	*P574H*	*R792G*	*V562I*
D579G	*G178E*	*I601F*	*Q98R*	*R933G*	*V754M*
D614G	*G178R*	*I618T*	*Q237E*	*R1066H*	*V1153E*
D836Y	*G194R*	*I807M*	*Q237H*	*R1070Q*	*V1240G*
D924N	*G194V*	*I980K*	*Q359R*	*R1070W*	*V1293G*
D979V	*G314E*	*I1027T*	*Q1291R*	*R1162L*	*W361R*
D1152H	*G463V*	*I1139V*	*R31L*	*R1283M*	*W1098C*
D1270N	*G480C*	*I1269N*	*R74Q*	*R1283S*	*W1282R*
E56K	*G551D*	*I1366N*	*R74W*	*S13F*	*Y109N*
E60K	*G551S*	*K1060T*	*R74W;D1270N*†	*S341P*	*Y161D*
E92K	*G576A*	*L15P*	*R74W;V201M*†	*S364P*	*Y161S*
E116K	*G576A;R668C*†	*L165S*	*R74W;V201M;D1270N*†	*S492F*	*Y563N*
E193K	*G622D*	*L206W*	*R75Q*	*S549N*	*Y1014C*
E403D	*G628R*	*L320V*	*R117C*	*S549R*	*Y1032C*
E474K	*G970D*	*L346P*	*R117G*	*S589N*	
E588V	*G1061R*	*L453S*	*R117H*	*S737F*	

* *F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data *[see Clinical Studies (14)]*.
† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

3. **The patient must be currently demonstrating adherence with the evidence-based standard of care for inhaled therapies for cystic fibrosis.[1] (Or else the patient must have documented experience of intolerance to dornase alfa &/OR bronchospasm or**

	irritability with inhaled hypertonic saline and therefore cannot use it.—This must be documented in the medical record and represented to the call pharmacists.)
4.	**The patient must be a nonsmoker.**

Continuation criteria:	
1.	**The patient must be currently demonstrating adherence with the evidence-based standard of care for inhaled therapies for cystic fibrosis.[1] (or the patient must have experienced intolerance to dornase alfa &/OR bronchospasm or irritability with inhaled hypertonic saline and therefore cannot use it).**
2.	**The patient must have had transaminases (ALT and AST) drawn in the past 6 months and they were lower than 5 times the ULN**
3.	**The patient must be a nonsmoker.**
4.	**The patient must demonstrate a clinical benefit with Trikafta as shown by lung function (FEV1), weight gain, or reduction in CF exacerbations or CF hospitalizations.**
5.	**The patient must be adherent (1 fill/1 month) with therapy as determined by refill history or reported by physician.**

References:

1. *HIGHLIGHTS OF PRESCRIBING INFORMATION*. Trikafta. (n.d.). Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212273s000lbl.pdf
2. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *New England Journal of Medicine*. 2015;373(3):220-231. doi:10.1056/nejmoa1409547
3. ORKAMBI® (lumacaftor/ivacaftor) | Clinical Studies and Results. Orkambi.com. https://www.orkambi.com/results-with-orkambi. Published 2018. Accessed November 16, 2019.
4. Walker S, Flume P, McNamara J, et al. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis. *Journal of Cystic Fibrosis*. 2019;18(5):708-713. doi:10.1016/j.jcf.2019.06.009
5. Clinical Studies | SYMDEKO® (tezacaftor/ivacaftor and ivacaftor). Symdeko.com. https://www.symdeko.com/clinical-studies?gclid=Cj0KCQiAiNnuBRD3ARIsAM8KmlvxR-Mjlz0a-7Zv1F6Bj1kruejlbRimlOeB4DKk8v-6Ib3tVMq1WLUaAkg6EALw_wcB&gclsrc=aw.ds. Published 2019. Accessed November 16, 2019.
6. *HIGHLIGHTS OF PRESCRIBING INFORMATION*. https://pi.vrtx.com/files/uspi_ivacaftor.pdf. Accessed November 19, 2019.
7. CFTR Modulator Types. Cff.org. https://www.cff.org/Research/Developing-New-Treatments/CFTR-Modulator-Types/. Published 2019. Accessed November 19, 2019.
8. Studies: ARRIVAL & KIWI | KALYDECO® (ivacaftor) | Healthcare Professionals. Kalydecohcp.com. https://www.kalydecohcp.com/trials-8-6. Published 2019. Accessed November 18, 2019.
9. Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *New England Journal of Medicine*. 2019;381(19):1809-1819. doi:10.1056/nejmoa1908639
10. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet*. October 2019. doi:10.1016/s0140-6736(19)32597-8

11. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *New England Journal of Medicine*. 2015;373(3):220-231. doi:10.1056/nejmoa1409547
12. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *New England Journal of Medicine*. 2017;377(21):2013-2023. doi:10.1056/nejmoa1709846
13. LexiComp: Orkambi. Accessed 11/15/2019.
14. LexiComp: Symdeko. Accessed 10/15/2019.
15. LexiComp: Kalydeco. Accessed 10/18/2019.
16. UpToDate: Cystic Fibrosis: Treatment with CFTR Modulators. Accessed 11/22/19.
17. Trikafta PI. Accessed 2/1/21. And 4/7/2021.

Revision History:

Date	What changed?	Pharmacist
12/17/19	I updated the format and limited Symdeko coverage to only ages 6-12y because Trikafta is recommended and superior in homozygotes older than 12.	JJ
1/6/2020	I changed the criteria to allow for CF with at least one F508deletion to have access to the drug per the data.	JJ
8/10/2020	Reviewed. No changes	JJ
1/8/2021	I reviewed the new FDA approval for Trikafta. Their 12/2020 package insert states "The in vitro CFTR chloride transport response threshold was designated as a net increase of at least 10% of normal over baseline because it is predictive or ***reasonably expected to predict clinical benefit***. **For individual mutations, the magnitude of the net change over baseline in CFTR-mediated chloride transport in vitro is not correlated with the magnitude of clinical response."** Without known clinical benefit for the non-F508 mutations, we will continue to require at least one F508 deletion.	JJ
2/1/21	After P&T discussion, we voted to include coverage for patients with a mutation in the CFTR gene that is responsive based on in vitro data. (without any F508del mutation) It was determined the change would be cost-neutral.	JJ
4/7/21	I clarified responsive mutations and inserted the table from the PI.	JJ
9/21/21	I changed the age requirement from age 12y to age 6y now that it has received FDA approval down to that age. ICER projected the age would need to be lowered once the label was expanded to this younger population.	JJ

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Eliglustat (Cerdelga®)

84 mg capsules

EBRx PA Criteria

FDA-approved as: long-term treatment of adult patients with Gaucher disease type 1.

Criteria for new users
5. Patient must have a diagnosis of Gaucher's disease Type 1. (NOT INDICATED FOR TYPES 2-4).
6. The patient must be age 18+
7. The patient must have an FDA-cleared test determining their CYP2D6 metabolism status. Dosing for extensive (EM), intermediate (IM), and poor metabolizers (PM) below. CERDELGA NOT INDICATED FOR ULTRA RAPID METABOLIZERS.
8. The patient must NOT be receiving concurrent enzyme replacement therapy (no data for combination use).
If criteria 1-4 fulfilled, approve eliglustat (depending on CYP2D6 metabolism status) for 1 year.

Dosing: **Based off CYP2D6 metabolism. Must have metabolism determined from FDA-cleared test for approval.**

- CYP2D6 IM or EM – 84 mg BID
- CYP2D6 PM – 84 mg daily
- CYP2D6 ULTRA RAPID METABOLIZERS – not indicated (won't achieve adequate concentrations)

Revision History:

Date	What changed	Pharmacist's initials
1/19/18	I wrote the criteria	JK
2/6/18	I reviewed the criteria written by JKing.	JJ
6/20/18	I added the criterium to not allow combination enzyme replacement therapy (ERT)[taliglucerase, velaglucerase, imiglucerase] WITH enzyme substrate reduction therapy [eliglustat or miglustat].	JJ
7/16/2020	Reviewed. No changes.	JJ
4/12/21	Reviewed. No changes.	JJ

Ref:

1. Cerdelga package insert accessed 1/19/18
2. Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study Blood. 2011 May 19;117(20):5551. PMID: 20713962.
3. The 52-week EDGE trial (NCT01074944)
4. Long-term skeletal response- Trial 4 EXOSKEL

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Elotuzumab (Empliciti®)

300 and 400 mg vials

EBRx PA Criteria

FDA-approved for:

- treatment of adult patients with multiple myeloma in combination with lenalidomide and dexamethasone in patients who have received 1-3 prior therapies.
- treatment of adult patients with multiple myeloma in combination with pomalidomide and dexamethasone after at least two prior therapies including lenalidomide and a proteasome inhibitor (NOT COVERED) This combination improved progression free survival compared to pomalidomide/dexamethasone (10.3 mo vs 4.7 mo). Overall survival not mature at first analysis and no significant QOL improvement. Estimated study completion date: 4/22/19 so will follow data.

References: Dimopoulos MA et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. N Engl J Med. 2018 Nov 8;379(19):1811-1822. PMID 30403938 NCT02654132; Weisel et al. Quality-of-Life Outcomes in Patients with Relapsed/Refractory Multiple Myeloma Treated with Elotuzumab Plus Pomalidomide and Dexamethasone: Results from the Phase 2 Randomized Eloquent-3 Study. Blood (2018) 132 (Supplement 1): 2288. https://doi.org/10.1182/blood-2018-99-112080

Criteria for new users
1. Diagnosis of multiple myeloma
2. Must have been treated with at least 1 prior therapy (prior lenalidomide therapy may count as a prior therapy)
3. Must have documented progression after most recent therapy
4. Must be ECOG performance status 0-2 upon first request
If above criteria met, approved for 6 months
Evidence: • Elotuzumab/lenalidomide/dexamethasone improved progression free survival and overall survival compared with lenalidomide/dexamethasone in previously treated multiple myeloma. Of all patients, 5% had received prior lenalidomide before enrolling in study.[1,2,3] No quality of life benefit was reported.[4] References: Dimopoulos MA et al. Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma:Extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. Cancer. 2018 Oct 15; 124(20):4032-4043. PMID 30204239 NCT01239797

Lonial S et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2015 Aug 13;373(7):621-31. PMID 26035255 NCT01239797

Dimopoulos MA, Lonial S, White D, et al. Elotuzumab, lenalidomide, and dexamethasone in RRMM: final overall survival results from the phase 3 randomized ELOQUENT-2 study. Blood Cancer J. 2020;10(9):91. Published 2020 Sep 4. doi:10.1038/s41408-020-00357-4 PMID 32887873

Cella D et al. Impact of elotuzumab treatment on pain and health-related quality of life in patients with relapsed or refractory multiple myeloma: results from the ELOQUENT-2 study. Ann Hematol. 2018 Dec;97(12):2455-2463. PMID 30178193

Revision History:

Date	What changed	Pharmacist's initials
1/29/2016	I wrote the criteria.	JJ
5/20/19	Criteria reviewed. Added new indication for Elotuzumab/pomalidomide/dexamethasone which is not covered.	Sk
10/31/19	Criteria reviewed. No changes	Sk
12/29/2020	Criteria reviewed. Added reference for OS benefit for elo/len/dex. Added reference showing lack of QOL benefit for elo/pom/dex.	SK

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Eltrombopag (Promacta®)

12.5mg, 25mg, 50mg, 75mg tablets

12.5mg, 25mg packets for oral suspension

EBRx PA criteria

FDA approved indications:

A. Chronic immune (idiopathic) thrombocytopenia (ITP): treatment of thrombocytopenia in adult and pediatric patients ≥ 1y of age with chronic ITP who have had insufficient response to corticosteroids, immune globulin, or splenectomy.
B. Aplastic anemia, severe: treatment of severe aplastic anemia in patients who have had an insufficient response to immunosuppressive therapy.
C. Aplastic anemia, severe: in combination with immunosuppressive therapy for the first line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia
D. Chronic hepatitis C infection-associated thrombocytopenia: treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.

Other indication:

Pre-procedure use in chronic liver disease is an FDA-approved use for avatrombopag; there are data to support eltrombopag's use. There are alternatives to these drugs which have not been compared; thus, platelet transfusion is the alternative covered by the plans on the medical benefit

*Not indicated for treatment of myelodysplastic syndromes.

*Do not use solely to normalize platelet counts

A. Chronic immune(idiopathic) thrombocytopenia (ITP)
1. The patient must have a diagnosis of chronic ITP
2. The patient must ≥ 1y of age
3. The patient must have a degree of thrombocytopenia and clinical condition severe enough to increase risk of bleeding (Plts < 30,000/mm^3) or had a clinically important bleeding event recently (Call Center PharmD use judgement)
4. The patient must have tried and had an insufficient response to one of the following: i. Dexamethasone 40mg x 4 days ii. Prednisone 1mg/kg for 21d plus taper iii. IVIg iv. Anti-D (rho D immune globulin) v. Splenectomy *insufficient response= platelet count fails to increase to a level that avoids clinically important bleeding after 4 weeks
5. If eltrombopag PACKETS for oral suspension are to be used AND dose is greater than 25

mg daily, patient must be unable to swallow tablets (see pricing info below).
PROPER DOSAGE *use lowest dosage needed to achieve and maintain plts ≥ 50,000/mm^3 to reduce risk of bleeding Initial: 50 mg once daily (25mg if East-Asian ethnicity such as Chinese, Japanese, Korean, Taiwanese) dose should be titrated based on plt response [MAX=75mg/d] Based on plt response: •Plt <50,000/mm^3 (≥ 2 wks after initiation or increase): increase dose by 25m (unless taking 12.5mg then only increase to 25mg/ d) [MAX=75mg/d] •Plt ≥200,000/mm^3 to ≤ 400,000/mm^3 (at any time): Reduce daily dose by 25mg and if taking 25mg/d decrease to 12.5mg/d •Plt > 400,000/mm^3: withhold dose and assess plt count twice weekly and can resume the daily dose reduced by 25mg •Plt >400,000/mm^3 after 2 weeks at lowest dose: discontinue treatment
If above criteria met, approve for 3 months; exceptions to 3mo can be granted by the medical director
Continuation criteria
1. Platelet count has increased to a level that avoids clinically important bleeding, at least to 50,000/uL.
2. The patient should gain access only to the dose aligned with the platelet count.
If yes to both, approve for 12 months
B. Aplastic Anemia after prior therapy with immunosuppression
1. The patient must have a diagnosis of SEVERE aplastic anemia [1] (defined as follows) a. Marrow cellularity <25% (or 25-50% with <30% residual hematopoietic cells) + at least TWO of the following: i. Neutrophils <500/mm^3 ii. Plts < 20/mm^3 iii. Reticulocyte count <20/mm^3
2. The patient must have had an inadequate response to the immunosuppressant regimen: cyclosporine + antithymocyte globulin (Equine) (most current guideline recommended therapy-2016[1])
3. If eltrombopag PACKETS for oral suspension are to be used AND dose is greater than 25 mg daily, patient is unable to swallow tablets. (see pricing info below)
Note: The initial dose must be 50mg once daily. If the patient is of East-Asian ethnicity, the initial dose must be 25mg daily.
If all criteria met, approve for 3 months
Continuation criteria
If the patient has had a platelet count >400 x 10^9/L =400,000/m^3 for ≥ 2 weeks; deny. Otherwise, approve for 3 months.

C. Aplastic Anemia (no prior therapy)
1. The patient has a diagnosis of severe aplastic anemia[1] (defined as follows) a. Marrow cellularity <25% (or 25-50% with <30% residual hematopoietic cells) + at least TWO of the following: i. Neutrophils <500/mm^3 ii. Plts < 20/mm^3 iii. Reticulocyte count <20/mm^3
2. The patient has not received prior therapy for severe aplastic anemia
3. Eltrombopag will be given with antithymocyte globulin and cyclosporine
4. Eltrombopag will be started on the same day at antithymocyte globulin and cyclosporine
5. If eltrombopag PACKETS for oral suspension are to be used AND dose is greater than 25 mg daily, patient is unable to swallow tablets. (see pricing info below)
If all criteria are met, approve for 3 months
Continuation criteria
1. Platelets have improved to a level that avoids clinically important bleeding
If continuation criteria met, approve for 3 more months. Please note that maximum duration of treatment for this indication is 6 months.
Note: Response rates with this regimen were higher compared with historical cohort (94% versus 66%). Achievement of a response has been correlated with improved overall survival. NCT02099747 is being conducted to confirm benefit (no results available as of 5/20/2020.
D. Chronic hepatitis C-associated thrombocytopenia
1. The patient must have a diagnosis of chronic hepatitis C
2. The patient must be in the process of being initiated on or is currently receiving interferon-based therapy.
3. The degree of thrombocytopenia prevents the initiation of or continuation of the interferon-based therapy *defined as platelet count < 30,000/mm^3
4. If eltrombopag PACKETS for oral suspension are to be used AND dose is greater than 25 mg daily, patient is unable to swallow tablets. (see pricing info below)
If all criteria are met, approve for 3 months
Continuation criteria
1. The patient must have platelets that are <25,000/mm^3 or be at risk for platelets to drop to

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this level.
2. The patient must still be prescribed an interferon therapy.
If both criteria are met, approve for 3 months
E. Pre-procedure use in patients with chronic liver disease
1. The patient must be scheduled to undergo a procedure within the next 14 days
2. The patient must be at significant risk for bleeding during the procedure (platelet count <50K)
3. The patient must have diagnosis of chronic liver disease
4. If eltrombopag PACKETS for oral suspension are to be used AND dose is greater than 25 mg daily, patient is unable to swallow tablets. (see pricing info below)
Dosing: 75mg QD starting 14 days before the procedure; must have procedure no more than 5 days after the final dose.
Approve for one 14 day supply
Notes for pre-procedural use of eltrombopag • [2,5] Eltrombopag is not FDA approved in chronic liver disease, but evidence supports its use. • [2]Although there is not an FDA approval, there is literature citing the use of eltrombopag pre-procedure in patients with chronic liver disease (which avotrombopag just came out with an indication for) o Patients received either eltrombopag at a dose of 75 mg once daily for 14 days o N=292, Plts <50,000/mm^3, Patients needed fewer platelet transfusions when they used this drug before procedures

Differences in AWP based on formulation (as of 5/20/2020, LexiComp)			
Dose	**Packets** (cost per 30d)	**Tablets** (cost per 30d)	**Difference**
12.5 mg daily	$6,325.50	$6,325.50	0
25 mg daily	$6,325.50	$6,325.50	0
50 mg daily	$12,651	$11,447.4	$1,203.60
75 mg daily	$18,976.50	$17,170.8	$1,805.70

References

1. Killick, Sally B., et al. "Guidelines for the diagnosis and management of adult aplastic anaemia." *British journal of haematology* 172.2 (2016): 187-207.
2. Afdhal, Nezam H., et al. "Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia." *New England Journal of Medicine* 367.8 (2012): 716-724.
3. Lexicomp accessed 7/26/18.
4. Package insert accessed 7/26/18.

5. Taylor, Alice, et al. "Thrombopoetin receptor agonist therapy in thrombocytopenia: ITP and beyond." *British journal of haematology* 177.3 (2017): 475-480.
6. Neunert, Cindy, et al. "The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia." *Blood*(2011): blood-2010.
7. Townsley DM et al. Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia. N Engl J Med. 2017 Apr 20;376(16):1540-1550. PMID 28423296 NCT01623167
8. Assi R et al. Addition of eltrombopag to immunosuppressive therapy in patients with newly diagnosed aplastic anemia. Cancer. 2018 Nov 1;124(21):4192-4201. doi: 10.1002/cncr.31658. PMID 30307606.

Revision History:

Date	What changed	Pharmacist's initials
7/26/18	I wrote the criteria.	ALM
7/18/19	Criteria reviewed: -added criteria for first-line treatment of severe aplastic anemia -added requirement for diagnosis of chronic liver disease to indication "D." – - Adjusted continuation criteria slightly (originally said pt still had to have low platelet count, but for continuation, there should be evidence of response to therapy)	SK
5/27/20	Criteria reviewed. Added new dosage form information and costs. Packets are 10% more expensive if dose is >25 mg daily—use only if pt unable to swallow when dose is >25 mg daily.	SK
3/19/21	No effective difference other than these criteria also allow for use in liver patients about to undergo a procedure within 14 days, per evidence.	JJ

CONFIDENTIAL

Emicizumab-kxwh (Hemlibra®)

30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, 150 mg/mL

EBRx PA Criteria

FDA-approved for: Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors [[NOT A COVERED INDICATION]].

Criteria for new users WITH INHIBITORS
1. The patient must have diagnosis of hemophilia A.
2. The patient must have a history of high factor VIII inhibitor titer (≥ 5 Bethesda units/mL).
3. The patient must have a history of ≥ 6 bleeds if on **episodic treatment with bypassing agents** (Feiba - activated prothrombin complex concentrate (aPCC), or NovoSeven - recombinant activated factor VII (factor VIIa)) within the last 24 weeks OR ≥ 2 bleeds if on **prophylactic treatment with bypassing agents** (Feiba, NovoSeven) within the last 24 weeks.
4. The patient must NOT be receiving concurrent prophylactic treatment with bypassing agents (Feiba, NovoSeven) or have ongoing/plan to receive immune tolerance induction therapy while concurrently taking emicizumab.
○ If criteria 1-4 are fulfilled, approve PA for 1 year. ○ The patient **CAN** receive episodic treatment with bypassing agents (Feiba, NovoSeven) prn for breakthrough bleeding episodes.

Dosing:

-SubQ: Initial: 3 mg/kg once weekly for 4 weeks, then 1.5 mg/kg once weekly **OR** 3 mg/kg every 2 weeks **OR** 6 mg/kg every 4 weeks thereafter. Round dose to nearest vial size.

-FDA approved for self-injection

Revision History:

Date	What changed	Pharmacist's initials
2/6/18	JK and I wrote the criteria.	JJ
8/26/19	Criteria reviewed. Added indication for patients WITH inhibitors per newer FDA approval.	SK
10/28/19	EBRx P&T reconsidered Hemlibra and determined for hemophilia A patients without inhibitors, it is reasonable to	JJ

	expect patients to use Factor VIII as prophylaxis and for episodic bleeding and to allow use of Hemlibra for patients with inhibitors.	
07/16/2020	Reviewed. No changes	JJ
3/9/21	RE-reviewed. ICER Hemophilia A 11/2020 shows Hemlibra to range from “highly cost saving to not at all cost effective ($10,393,000/QALY), depending on factor VIII use. Uncertainties exist. Need real world factor VIII use and the cost associated with it. Added ref 14. ICER.	JJ

Ref:

1. Oldenburg, Johannes, et al. "Emicizumab prophylaxis in hemophilia A with inhibitors." *New England Journal of Medicine* 377.9 (2017): 809-818. PMID 28691557 NCT02622321
2. Oldenburg et al 2017 Supplement https://www.nejm.org/doi/suppl/10.1056/NEJMoa1703068/suppl_file/nejmoa1703068_appendix.pdf Accessed 7/24/19.
3. ICER Draft Report, Emicizumab for Hemophilia A. 1/26/18. https://icer-review.org/wp-content/uploads/2017/08/ICER_Hemophilia_A_Draft_Report_012618.pdf
4. Mahlangu J et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018 Aug 30;379(9):811-822. doi: 10.1056/NEJMoa1803550. PMID 30157389 NCT02847637
5. Oldenburg, Johannes, et al. "Emicizumab prophylaxis in hemophilia A with inhibitors." *New England Journal of Medicine* 377.9 (2017): 809-818.
6. Emicizumab package insert and Lexicomp accessed 12/12/17.
7. Wyrwich KW, Krishnan S, Poon JL, et al. Interpreting important health-related quality of life change using the Haem-AQoL. Haemophilia 2015;21:578-84
8. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res 2005;14:1523-32.
9. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:70
10. Hay, J. W., and Z. Y. Zhou. "Economical comparison of APCC vs. rFVIIa for mild- to- moderate bleeding episodes in haemophilia patients with inhibitors." *Haemophilia* 17.5 (2011).
11. MINNO, MND DI, et al. "Cost of care of haemophilia with inhibitors." *Haemophilia* 16.1 (2010).
12. Chen, Sheh-Li. "Economic Costs of Hemophilia and the Impact of Prophylactic Treatment on Patient Management." *The American journal of managed care* 22.5 Suppl (2016): s126-33.
13. Guh, S., et al. "Healthcare expenditures for males with haemophilia and employer- sponsored insurance in the United States, 2008." *Haemophilia* 18.2 (2012): 268-275.
14. ICER. Hemophilia A 11/2020. https://icer.org/wp-content/uploads/2020/10/ICER_Hemophilia-A_Final-Report_112020.pdf

Encorafenib (Braftovi®)

75 mg capsules

EBRx PA Criteria

FDA-approved for:

- Treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation (in combination with binimetinib)
- Treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy in combination with cetuximab

Criteria for melanoma
1. Patient must have histologically confirmed, unresectable or metastatic cutaneous melanoma or unknown primary melanoma.
2. Tumor must be BRAF V600E or BRAF V600k mutation positive
3. Patient must be ECOG 0 or 1.
4. Encorafenib will be used in combination with binimetinib.
5. No prior BRAF or MEK inhibitor
If all criteria met, approve for 12 months QL: 6 caps/day
Note: Treatment is until progression or unacceptable toxicity.
Dose -encorafenib 450mg po once daily (in combination with binimetinib) **Evidence:** Encorafenib + Binimetinib improved overall survival compared to vemurafenib (34 mo versus 17 mo, HR 0.61 95% CI 0.47-0.79) in patients with advanced/metastatic melanoma who were either treatment naïve or had progressed on or after immunotherapy. References: 1. Dummer R et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018 May;19(5):603-615. NCT01909453 PMID 29573941 2. Dummer R et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre,

open-label, randomised, phase 3 trial. Lancet Oncol. 2018 Oct;19(10):1315-1327. NCT01909453 PMID 30219628

Criteria for colorectal cancer
1. Patient must have histologically confirmed, unresectable or metastatic colon or rectal adenocarcinoma.
2. Progression of disease on or after at least one regimen given for unresectable or metastatic disease OR relapse of disease within 6 months following adjuvant chemotherapy for localized disease
3. No prior treatment with a BRAF inhibitor, MEK inhibitor, cetuximab, panitumumab, or other EGFR inhibitors
4. Tumor must be BRAF V600E mutation positive
5. Patient must have ECOG performance status of 0 or 1.
6. Encorafenib will be used in combination with cetuximab (Erbitux).
If all criteria met, approve for 12 months QL: 4 caps/day
Note: Treatment is until progression or unacceptable toxicity.
Dose -encorafenib 300 mg QD (in combination with cetuximab) **Evidence:** Patients (n=665) meeting the above criteria were randomized to either encorafenib/binimetinib/cetuximab (triplet), encorafenib/cetuximab (doublet), or standard chemotherapy. Both the triplet and doublet regimens improved overall survival compared to standard chemo with median overall survivals of 9 mo, 8.4, mo and 5.4 mo. Incidence of grade ¾ toxicity was also less in the doublet group compared to control (50% vs 61%). There was no significant difference in overall survival between the doublet and triplet groups. [1] The doublet and triplet regimens also led to a statistically significant reduction of risk for deterioration of quality of life (measured by EORTC QLQ C30 and FACT C assessments) compared to chemotherapy per ASCO meeting abstract.[2] Reference: 1. Kopetz, Scott et al. “Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated

Colorectal Cancer." The New England journal of medicine vol. 381,17 (2019): 1632-1643. doi:10.1056/NEJMoa1908075]PMID 31566309, NCT02928224]

2. Kopetz S et al. Encorafenib plus cetuximab with or without binimetinib for BRAF V600E-mutant metastatic colorectal cancer: Quality-of-life results from a randomized, three-arm, phase III study versus the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC). J Clin Oncol 38, 2020 (suppl 4; abstr 8). https://meetinglibrary.asco.org/record/181898/abstract. NCT02928224 Accessed 4/20/2020

Revision History:

Date	What changed	Pharmacist's initials
9/25/18	I wrote criteria.	JJohnson
4/18/19	Reviewed criteria (no major change) and added references and evidence summary	SK
9/30/19	Reviewed criteria. No change in criteria. Added quantity limits. Omitted 50 mg cap from Braftovi strengths as it is no longer available as of 3/2019 per First Databank Drug and current PI.	SK
4/27/2020	Split encorafenib and binimetinib into two separate documents due to new indication for encorafenib. Added criteria for new indication for encorafenib for treatment of BRAF-mutated colorectal cancer.	SK
7/26/2021	Criteria reviewed. Clarified wording of criterion #5 for melanoma. No changes to critera.	SK

CONFIDENTIAL

Enzalutamide (Xtandi®)

40mg capsules

EBRx PA Criteria

FDA-approved for:

- Treatment of castration-resistant prostate cancer (CRPC) [COVERED, BUT MUST HAVE BEEN TREATED PREVIOUSLY WITH ABIRATERONE]
- Treatment of metastatic castration-sensitive prostate cancer [NOT COVERED, PREFER ABIRATERONE]
  -Enzalutamide improves overall survival compared to a 1st generation antiandrogen in patients with metastatic castration-SENSITIVE prostate cancer. EBRx prefers abiraterone in this setting due to cost and additional data showing improvement in symptoms. (Davis ID et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019 Jul 11;381(2):121-131. PMID 31157964 NCT02446405)

Notes:

1. CRPC is defined as progression of disease (rising PSA or increase in tumor size on imaging) when testosterone level is <50 ng/dl (due to LHRH antagonist/agonist or orchiectomy).
2. The two major populations within the CRPC FDA approved indication are patients with non-metastatic disease and patients with metastatic disease.

NON-METASTATIC CRPC
Diagnosis of prostate cancer without evidence of metastatic disease
The patient has castrate level of testosterone (<50 ng/dl)
PSA doubling time is </= 10 months
Minimum of three rising PSA values at an interval of at least 1 week apart
At time of first request, PSA is 2 ng/ml or greater
If all of the above criteria are met, approve for 1 year
Note: Enzalutamide was compared to placebo in men with castration resistant prostate cancer WITHOUT metastasis. Time to development of metastasis or death was longer with enzalutamide (37 mo) compared with placebo (15 mo). Apalutamide and darolutamide are also approved for this indication.[1] Two meta-analyses indicate a possible improvement in overall survival compared to placebo when the results of apalutamide, enzalutamide, and darolutamide studies were pooled.[2,3]

Another meta-analysis found that the three drugs had similar overall survival to each other. Darolutamide may have a more favorable toxicity profile.[4]

Although it is not an absolute contraindication, patients with history of or predisposition to seizures were NOT allowed in study. These patients WERE allowed in the darolutamide study.

Dose: 160 mg PO once daily until progression of disease or unacceptable toxicity.

REFERENCE:

1. Hussain M et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. NEJM 2018 June 28;378(26):2465-2474. [NCT02003924, PMID 29949494]

2. Di Nunno V et al. New Hormonal Agents in Patients With Nonmetastatic Castration-Resistant Prostate Cancer: Meta-Analysis of Efficacy and Safety Outcomes. Clin Genitourin Cancer. 2019 Jul 8. pii: S1558-7673(19)30207-1. doi: 10.1016/j.clgc.2019.07.001. [Epub ahead of print] PMID 31378578

3. Hird AE, Magee DE, Bhindi B, et al. A Systematic Review and Network Meta-analysis of Novel Androgen Receptor Inhibitors in Non-metastatic Castration-resistant Prostate Cancer [published online ahead of print, 2020 Mar 6]. Clin Genitourin Cancer. 2020;S1558-7673(20)30039-2. PMID 32278840

4. Mori, Keiichiro, et al. "Apalutamide, enzalutamide, and darolutamide for non-metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis." International journal of clinical oncology (2020): 1-9.

METASTATIC CRPC
Diagnosis of metastatic prostate cancer
The patient has castrate level of testosterone (<50 ng/dl)
At the start of therapy with this drug, the patient's ECOG performance level is 0-2
The patient does NOT have history of progression of disease (rising PSA or radiographic progression) on apalutamide, darolutamide, or enzalutamide.
The patient has had progression of disease on abiraterone (Zytiga/generic).
If all of the above criteria are met, approve for 1 year
Note: 1. Enzalutamide AFTER chemo: Enzalutamide was compared to placebo in men with metastatic castration resistant prostate cancer (mCRPC) who received prior chemotherapy. Overall survival was improved with enzalutamide (18.4 mo) versus placebo (13.6 mo).[1] 2. Enzalutamide BEFORE chemo: Enzalutamide was compared to placebo in men with

mCRPC who had not received prior chemotherapy. Progression free survival was improved with enzalutamide (20 mo) versus placebo (5.4 mo). Median overall survival was statistically improved with enzalutamide (35.3 mo) versus placebo (31.3 mo). This is a small change but placebo patients were allowed to crossover to enzalutamide which may confound OS results.[2,3]

3. Enzalutamide has not been studied in patients whose tumor progressed ON second-generation anti-androgens (apalutamide, darolutamide, or enzalutamide).
4. Abiraterone is generic and much cheaper (~$700/mo for abiraterone; ~$11,000/mo for enzalutamide as of 5/25/2021)

Dose: 160 mg PO once daily until progression of disease or unacceptable toxicity.

REFERENCE:

1. Scher HI et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012.
2. Beer JM et al. Enzalutamide in metastatic prostate cancer before chemotherapy. NEJM. 2014:371:424-33.
3. Beer T et al. Eur Urol. Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. 2017 Feb;71(2):151-154. PMID 27477525

Revision History:

Date		Pharmacist's initials
12/11/12	JJ wrote the PA criteria	JJ
5/14/14	JJ added "castration-resistant" in the needed diagnosis	JJ
11/5/15	I deleted the criterium requiring prior therapy with docetaxel. A NEJM article using enzalutamide before requiring traditional chemotherapy. The OS was 32.4m vs 30.2m placebo (p<0.001), only a 2.2m difference, however, together with the difference in time patients sought traditional chemotherapy of a median 28m Enzal vs 10.8m in placebo, first line enzalutamide warrants this change. Prior abiraterone users are not yet known to receive benefit. NCT02125357 in clinicaltrials.org is recruiting now.	JJ
3/18/19	Added non metastatic indication per 3-2019 P&T. Updated references and rationale. Enza will now be covered regardless of prior abiraterone use.	sk
9/23/19	Criteria/indications reviewed. Added that patient should not have progressed on prior apalutamide/darolutamide as	sk

	treatment with enzalutamide has not been studied in this setting. Based on mechanism of action, enzalutamide would not be expected to be effective.	
10/28/19	Added information about new data in castration-sensitive metastatic prostate cancer (see note above)	SK
12/17/19	Added new indication for metastatic castration sensitive prostate cancer. This indication was already reviewed in 10/2019 P&T meeting and will no be covered (abiraterone preferred).	SK
3/17/2020	For metastatic CRPC, added requirement of failure of abiraterone to drive use toward cheaper generic. Abiraterone is generic and much cheaper (~$3,300/mo for abiraterone; ~$11,200/mo for enzalutamide as of 3/2020)	SK
4/15/2020	Added reference for second meta analysis to show improvement in overall survival of antiandrogens (including enzaluatmide) vs placebo in non-metastatic prostate cancer	SK
5/25/21	Criteria reviewed. Added another meta-analysis looking at non-metastatic indication.	SK

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Erenumab (Aimovig®)
Galcanezumab (Emgality®)

EBRx PA Criteria

Criteria for access:	
9.	Patient must be 18 years old or older.
10.	Patient must have received the diagnosis of migraine onset before age 50.
11.	Patient must have tried and had an inadequate response to a trial of TWO preventative therapies: a. beta blocker- propranolol 80-240mg/day b. divalproex 500-1000mg/day, topiramate 100-200mg/day c. botulinum toxin A. A trial consists of 2 or more months of claims per drug.
12.	Patient must have had a trial of at least 2 different triptan fills on the profile within the previous year (or else be intolerant to triptans).
13.	The prescriber must be a neurologist or headache specialist or be working with one regarding the prescribing for this patient.
14.	If criteria are fulfilled. Approve erenumab 70 mg once monthly.
In order for 140 mg/month approval, pt must have had inadequate response to 3 months of claims for the 70 mg/mo dose.	
• If the above criteria are satisfied, the PA is good for 3 months. • It will be imperative for the call pharmacist to record the number of stated migraine days per month in order to assess response and subsequent access to the drug.	
Continuation Criteria for Migraine Users:	
1. To continue access to erenumab, the patient must have filled at least 2-30 day fills in the last 90 days and less rescue medication.	
If both of the continuation criteria were achieved, allow access for 6 months. After 6 months, the patient must have shown at least 5 erenumab fills in the previous 6 months (since it is prophylactic) and less consumption of rescue medication as evidenced by fewer triptan fills than before erenumab was accessed by the patient.	

Dosing: 70 mg once a month, up to 140 mg once monthly.

Revision History:

Date	What changed	Pharmacist's initials
6/25/18	I wrote the criteria.	JK
8/21/18	I added the age requirement, the neurologist-prescriber requirement.	JJ
8/30/18	I did not include SSRIs or SNRIs for prophylactic migraine prevention because neither showed to be more effective	JJ

	than placebo. Banzi, Rita, et al. "Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of migraine in adults." *Cochrane Database of Systematic Reviews* 2015.4 (2015): 1-56.	
8.30/18	For episodic migraine, I included valproate as a must fail prior to gaining access to erenumab. Valproate reduced HA days by 4 headaches per 28 days. Linde, Mattias, et al. "Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults." *Cochrane Database Syst Rev* 6.6 (2013).	JJ
8/30/18	For episodic migraine, I included topiramate, valproate, gabapentin as preventive therapies. I did not include levetiracetam because in one study there was a small but significant advantage with topiramate over levetiracetam for HA frequency. Linde, Mattias, et al. "Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults." *Cochrane Database Syst Rev* 6 (2013): CD010608.	JJ
8/30/18	For episodic migraine, I did NOT include gabapentin or pregabalin for preventive therapies because gabapentin was shown to not be efficacious and there is no published evidence from controlled trials with pregabalin. Linde, Mattias, et al. "Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults." *Cochrane Database Syst Rev* 6.6 (2013): CD010609.	JJ
9/4/18	I added that the call pharmacists will need to record the number of baseline headache days each patient states he/she has in order to determine whether there has been a reduction by 2 HA days/month for continued access to the drug.	JJ
07/16/2020	Reviewed. No change.	JJ
4/7/21	Reviewed. No change.	JJ
10/12/21	I reviewed the criteria, omitted a minimum # of HAs/month, added step therapy with 2 preventive therapies and 2 triptan fills in the history. ICER determined for preventive tx w/ CGRAi, that triptan therapy for acute relief can be effective for many patients, thereby limiting any potential added	JJ

	benefit of preventive therapy and avoiding uncertain long term SEs as well as CGRPi costs. ICER determined it is reasonable to require 2 or 3 prior preventive treatments PLUS a reasonable trial of triptans prior to covering CGRPi therapy.	

Ref:
7. Erenumab package insert. Accessed 6/25/18
8. Katsarava, Zaza, et al. "Defining the differences between episodic migraine and chronic migraine." *Current pain and headache reports* 16.1 (2012): 86-92.
9. Goadsby, Peter J., et al. "A controlled trial of erenumab for episodic migraine." *New England Journal of Medicine* 377.22 (2017): 2123-2132.
10. Tepper, Stewart, et al. "Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial." *The Lancet Neurology*16.6 (2017): 425-434.
11. ICER evidence report accessed 6/12/18.

CONFIDENTIAL

Eribulin (Halaven®)

1 mg/2ml vial

EBRx PA Criteria

FDA-approved for:

- Metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. *Covered if prior anthracycline, taxane, and capecitabine (see criteria)*
- Unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen *(see criteria)*

Metastatic Breast Cancer
1. Diagnosis of metastatic or unresectable breast cancer
2. Previously treated with at least 2 chemotherapeutic regimens for treatment of metastatic or unresectable breast cancer
3. Prior treatment for metastatic or unresectable disease included an anthracycline, a taxane, and capecitabine, unless contraindicated
If above criteria are fulfilled, approve x 1 year
Note: Eribulin was compared to physician's choice chemotherapy in patients who had received at least two prior chemotherapy regimens that included anthracycline- and taxane-containing regimens. 70% of subjects had also received prior capecitabine. Median overall survival was improved in the eribulin group (13.1 mo vs 11.8 mo; HR 0.81, 95% CI 0.66-0.99).[1] Eribulin was also compared directly to capecitabine in patients who had received 0-3 prior chemotherapy regimens that included anthracycline- and taxane-based regimens. Median overall survival was not statistically improved in the eribulin arm (15.9 mo vs 14.5 mo; HR 0.88, 95% CI 0.77-1.00; p=0.056). Quality of life scores were similar between groups.[2,3] Pooled analysis of the above two studies found an improvement in median overall survival in the eribulin group (15.2 mo vs 12.8 mo; HR 0.85, 95% CI 0.76-0.94).[4] A separate analysis including only patients who had received at least 1 prior therapy found an improvement in median overall survival in the eribulin group (15.2 mo vs 12.8 mo; HR 0.85, 95% CI 0.77-0.95).[5] Dose: 1.4 mg/m^2 IV over 2-5 minutes on days 1 and 8 of a 21-day treatment cycle

Approximate cost per cycle of therapy (will vary based on BSA): $5,800 (average sales price, 12/6/19)

REFERENCES:

1. 1. Cortes J et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (**EMBRACE**): a phase 3 open-label randomised study. Lancet. 2011 Mar 12;377(9769):914-23. doi: 10.1016/S0140-6736(11)60070-6. Epub 2011 Mar 2. PMID 21376385 NCT00388726

2. Kaufman PA et al. Phase III open-label randomized study of eribulin mesylate versus **capecitabine** in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015 Feb 20;33(6):594-601. doi: 10.1200/JCO.2013.52.4892. Epub 2015 Jan 20. PMID 25605862 NCT00337103

3. Cortes J et al. Health-related **quality of life** in patients with locally advanced or metastatic breast cancer treated with eribulin mesylate or capecitabine in an open-label randomized phase 3 trial. Breast Cancer Res Treat. 2015 Dec;154(3):509-20. doi: 10.1007/s10549-015-3633-7. Epub 2015 Nov 14. PMID 26567010

4. Twelves C et al. Efficacy of eribulin in women with metastatic breast cancer: a **pooled analysis** of two phase 3 studies. Breast Cancer Res Treat. 2014 Dec;148(3):553-61. doi: 10.1007/s10549-014-3144-y. Epub 2014 Nov 8. PMID 25381136

5. Pivot X et al. **Pooled analyses** of eribulin in metastatic breast cancer patients with at least one prior chemotherapy. Ann Oncol. 2016 Aug;27(8):1525-31. doi: 10.1093/annonc/mdw203. Epub 2016 May 13. PMID 27177860

Liposarcoma
1. Diagnosis of metastatic or unresectable liposarcoma
2. Prior treatment of metastatic or unresectable disease with an anthracycline-containing regimen (such as epirubicin or doxorubicin)
If above criteria are fulfilled, approve x 1 year
Evidence: Eribulin was compared to dacarbazine in patients with advanced liposarcoma or leiomyosarcoma. No overall survival difference was observed in leiomyosarcoma subgroup. In the liposarcoma subgroup, median overall survival was improved in the eribulin group (15.6 mo vs 8.4 mo, HR 0.51, 95% CI 0.35-0.75).

Reference:

1. Schöffski P et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet. 2016 Apr 16;387(10028):1629-37. doi: 10.1016/S0140-6736(15)01283-0. Epub 2016 Feb 10. PMID 26874885 NCT01327885

Revision History:

Date	Notes	Pharmacist's initials
12/6/19	Reviewed at DCWG, criteria written	SK
3/29/2021	Criteria reviewed. No change.	SK

CONFIDENTIAL

Erlotinib (Tarceva®)

25, 100, 150 mg tablets

EBRx PA Criteria

FDA approved for:

- The treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen.
- First-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine. NOT COVERED
    - Erlotinib+gemcitabine was compared to erlotinib+placebo and although OS (6.24 mo vs 5.91 mo) and PFS (3.75 mo vs 3.55 mo)[7] were statistically better in the erlotinib group, neither outcome met the Journal of Clinical Oncology's (JCO) threshold of a minimal clinically meaningful improvement. JCO states for pancreatic cancer in gemcitabine eligible patients, OS improvement would need to be 3-5 months better and PFS would need to be 3-5 months better.
- Limitations of Use:
    - Safety and efficacy of erlotinib have not been established in patients with NSCLC whose tumors have other EGFR mutations.
    - Erlotinib is not recommended for use in combination with platinum-based chemotherapy

The following indication for erlotinib is included in ramucirumab (Cyramza) package insert:

- Ramucirumab, in combination with erlotinib, is indicated for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations
    - NOT COVERED: ramucirumab + erlotinib was compared to placebo + erlotinib. Benefit is limited to progression free survival at this time. [Alternative: osimertinib or erlotinib monotherapy]
    - Note: ramucirumab (Cyramza) is excluded from coverage
    - Reference: Nakagawa K, Garon EB, Seto T, et al. Lancet Oncol. 2019;20(12):1655- 1669. doi:10.1016/S1470-2045(19)30634-5 [NCT02411448, PMID 31591063]

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Criteria for new users
1. Patient must have diagnosis of advanced/metastatic non-small cell lung cancer that tested positive for an EGFR activating mutation (exon 19 deletion or exon 21 L858R EGFR mutation)
2. Patient has NOT received a prior EGFR inhibitor (e.g. erlotinib, osimertinib, gefitinib, afatinib)
3. ECOG status 0-2 at initiation of erlotinib.
4. Erlotinib will be used as single agent
If all criteria are met, approve x 1 year

Notes:

Dose is 150 mg once daily

Erlotinib was compared with chemotherapy in untreated patients with metastatic non-small cell lung cancer with EGFR mutation. Progression free survival and response rate were improved and there were fewer adverse effects in the erlotinib group. 76% of chemotherapy patients crossed over to erlotinib, which confounds the overall survival analysis.

Erlotinib is not effective/minimally effective if in patients unselected for EGFR mutation (see data summary below).

Erlotinib has not been shown to be effective in patients who have received therapy with a prior EGFR inhibitor therapy. NCCN guidelines recommend that erlotinib be used in the first line setting only.[2]

References:

1. Rosell R et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012 Mar;13(3):239-46. PMID 22285168 NCT00446225.
2. NCCN guidelines. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 6/17/19.

Quantity Limits (all strengths): 30 tabs/30 days

Historical notes (erlotinib is not effective or minimally effective without EGFR mutation):

- Erlotinib is not effective in second-line treatment (after chemo) in patients with metastatic NSCLC without EGFR mutation. The TITAN trial[1] in n=424 patients (35-38% had squamous; only 3-4% had EGFR mutation though 43% had missing mutation status) with locally advanced, recurrent or metastatic NSCLC were treated with up to 4 cycles of 1st line platinum-based chemotherapy, after which patients with disease progression were randomized to either erlotinib 150mg/d or standard CTX (either docetaxel or pemetrexed). OS, the primary endpoint was not different. Rate of treatment related AE also did not differ.

Overall Survival (erlot)	E 5.3m (4.0-6.0m) vs STD chemotherapy 5.6m (4.4-7.1m)	HR 0.96 (95% CI, 0.78-1.19)

- Erlotinib was minimally effective in metastatic NSCLC patients previously treated with 1-2 chemotherapy regimens. 24% of patients were positive for EGFR mutation and 57% had unknown EGFR mutation status.[2] There was only a 2 month OS benefit of erlotinib over placebo; 2 m of prolonged OS does not meet the ASCO goal of a meaningful difference with a treatment (a minimum of >2.5m), nor does it meet the minimal PFS benefit of >3m. PFS was 0.4m with erlotinib vs placebo. [3]

- Erlotinib was minimally effective for the maintenance treatment of locally-advanced or metastatic NSCLC which had not progressed after 4 cycles of 1st line platinum-based chemotherapy (EGFR mutation was not required in this study and was present in only 14 patients). Neither the PFS or the OS reached a clinically significant improvement over placebo as judged by the American Society of Clinical Oncology. They suggest a minimal clinically meaningful improvement of 2.5-4 months in OS and an improvement of 3-4 months in PFS. Therefore, erlotinib is not covered as a maintenance therapy in NSCLC.
    - **Pérol, et al[4]:** Patients (n=464) with stage IIIB/IV NSCLC without tumor progression post-four cycles of cisplatin-gemcitabine were randomly assigned to gemcitabine, erlotinib (150 mg/day), or observation. Upon disease progression, pemetrexed was given in all three arms. Primary endpoint was PFS.

PFS gem	*G 3.8m vs Obs 1.9m*	*HR 0.56 (95% CI, 0.44-0.72)*
PFS erlot	*E 2.9m vs Obs 1.9m*	*HR 0.69 (95% CI, 0.54-0.88)*
OS gem	G 12.1m vs Obs 10.8m	HR 0.89 (95% CI, 0.69-1.15)
OS erlot	E 11.4 mg vs Obs 10.8m	HR 0.87 (95% CI, 0.68-1.13)

    - **SATURN[5]:** Patients (n=889) with advanced (stage IIIb/IV) NSCLC who had received 4 cycles of platinum-based doublet chemotherapy and were without progressive disease were randomly assigned to erlotinib (150 mg/day) or placebo. Data were assessed based on whether the patient was a complete/partial responder (CR/PR) or had stable disease (SD) following first-line chemo. Primary endpoint was PFS.

PFS CR/PR	*E 2.9m vs Plac 2.6m*	*HR 0.74 (95% CI, 0.60-0.92)*
PFS SD	*E 2.8m vs Plac 2.6m*	*HR 0.68 (95% CI, 0.56-0.83)*
OS CR/PR	12.5m vs 12.0m	HR 0.94 (95% CI, 0.74-1.20)
OS SD	*E 11.9m vs plac 9.6m (2.3month benefit)*	*HR 0.72 (95% CI, 0.59-0.89)*

- [6]Although erlotinib is FDA-approved for treatment of locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen, the DELTA trial was published 6/20/14 which included N=151 and randomized a nonselected group of NSCLC patients with stage IIIB or IV NSCLC including EGRF "-" (wild type). Erlotinib failed to show an improvement in PFS or OS compared with docetaxel in this EGFR-unselected population. In addition, the subgroup analysis of the patients with EGFR wild-type tumors showed the PFS was better (statistically) with docetaxel than with erlotinib, 2.9m vs 1.3m, p=0.01, respectively. OS was 10.1m vs 9.0m, p=0.91, respectively.

Pancreatic cancer data summary:

- Although erlotinib is FDA-approved for 1st-line treatment of locally-advanced, unresectable or metastatic pancreatic cancer in combination with gemcitabine, neither the PFS nor the OS met the Journal of Clinical Oncology's threshold of a minimal clinically meaningful improvement. The JCO states for pancreatic cancer in gemcitabine eligible patients, OS improvement would need to be 3-5 months better and PFS would need to be 3-5 months better.
- **Moore et al. (NCIC CTG)[7]:** Patients (n=569) with locally advanced or metastatic adenocarcinoma of the pancreas and without prior chemotherapy were randomly and blindly assigned to either gemcitabine plus erlotinib (100 mg/day) or gemcitabine plus placebo. Primary endpoint was OS. Female sex was significantly associated with prolonged survival (p=0.03).

PFS	*3.75m vs 3.55*	*HR 0.77 (95% CI, 0.64-0.92)*
OS	*6.24m vs 5.91m (10 days)*	*HR 0.82 (95% CI, 0.69-0.99)*

- **NCIC CTG PA.3 (mutation analysis)[8]:** Patients (n=569) with locally advanced or metastatic adenocarcinoma of the pancreas and without prior chemotherapy were randomly and blindly assigned to either gemcitabine plus erlotinib (100 mg/day) or gemcitabine plus placebo.

Primary endpoint was OS. Results were analyzed based on *KRAS* & *EGFR* FISH mutations. Data are presented below. Mutation status does not affect efficacy of erlotinib in pancreatic cancer.

OS KRAS Wild type	E 6.1m vs plac 4.5m	HR 0.66 (95% CI, 0.28-1.57)
OS KRAS Mutant	E 6.0m vs plac 7.4m	HR 1.07 (95% CI, 0.68-1.66)
OS EGFR FISH (+)	E 5.29m vs plac 5.32m	HR 0.90 (95% CI, 0.49-1.65)
OS EGFR FISH (-)	E 8.4m vs plac 6.7m	HR 0.6 (95% CI, 0.34-1.07)

References:

1. Ciuleanu T, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol. 2012;13(3):300-8. PMID 22277837 NCT00556322
2. Shepherd FA, Pereira JR, et al. Erlotinib in previously treated NSCLC. N Engl J Med. 2005;353:123-32. PMID 16014882
3. Ellis LM, Bernstein DS, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. Published online ahead of print at www.jco.org on March 17, 2014. 10.1200/JCO.2013.53.8009
4. Pérol M, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2012;30(28):3516-24. PMID 22949150
5. Coudert B, et al. Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. Ann Oncol. 2012;23(2):388-94. PMID 21610154
6. Kawaguchi T, Ando M, Asami K, Okano Y, et al. Randomized phase III trial of erlotinib vs docetaxel as second- or third-line therapy in patients with advanced NSCLC: docetaxel and erlotinib lung cáncer trial (DELTA). J Clin Oncol. 2014;32:1902-08.
7. Moore MJ, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25(15):1960-6
8. da Cunha Santos G, et al. Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: National Cancer Institute of Canada Clinical Trials Group Study PA.3. Cancer. 2010;116(24):5599-607.

Change Log

Date	Notes	Pharmacist's initials
6/9/14	JJ created PA criteria	JJ

2/10/15	I added reference 9 after answering the question that erlotinib is not covered for EGFR negative NSCLC at this time. It failed to show a benefit over docetaxel in a nonselected population (one including EGFR – patients) and when analyzed as a subgroup, the EGFR negative patients had improved PFS with docetaxel and no OS improvement over docetaxel. This was based on the DELTA trial that was published mid-2014.	JJ
6/23/15	I added reference 10.	JJ
3/7/2016	The ESMO document on cancer drugs places erlotinib on the ESMO Magnitude of Clinical Benefit Scale of 4 for first-line use in IIIb or IV nonsquamous and with EGFR mutation. It places erlotinib at 1 for stage IIIb or IV maintenance therapy after at least 4 cycles of platinum cTX. This evaluation confirms our original assessment of the data including the SATURN trial	JJ
6/17/19	Criteria reviewed with general updates but no significant change to criteria	SK
7/26/2021	Criteria reviewed. No change.	SK

ECOG Performance Status

Grade

0 Fully active, able to carry on all pre-disease performance without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours

3 Capable of only limited selfcare, confined to bed or chair for more than 50% of waking hours

4 Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 Dead

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Erythropoiesis-stimulating Agents (ESAs)
darbepoetin alfa (Aranesp®)
epoetin alfa (Epogen®, Procrit®)
epoetin alfa-epbx (Retacrit®) [biosimilar of Epogen/Procrit]
methoxy polyethylene glycol-epoetin beta (Mircera®)

EBRx PA Criteria

FDA approved for:

- Darbepoetin (Aranesp) is indicated for treatment of anemia due to:
  - Chronic Kidney Disease (CKD) in patients on dialysis and patients not on dialysis
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy

- Epoetin alfa (Procrit, Epogen) and epoetin alfa-epbx (Retacrit) are indicated for treatment of anemia due to:
  - Chronic Kidney Disease (CKD) in patients on dialysis and patients not on dialysis
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy
  - Zidovudine in patients with HIV-infection
  - Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery

- Methoxy polyethylene glycol-epoetin beta (Mircera) is indicated for treatment of anemia due to:
  - Chronic kidney disease (CKD) in adult patients on dialysis and adult patients not on dialysis
  - Chronic kidney disease (CKD) in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA

- **CRITERIA FOR ALL INDICATIONS.** These criteria must be met before proceeding to diagnosis-specific criteria for EVERY request for ESAs. If these criteria are met, proceed to criteria for individual indications below.

1. If patient has diagnosis of hypertension, blood pressure is currently under control. (Confirm by at least 1 antihypertensive agent on the patient's profile in the past 30 days.)	☐ Yes ☐ No
2. The patient has no documented or suspected serious allergy to epoetin.	☐ Yes ☐ No
3. The patient's hemoglobin level is less than 10 g/dL at first request	☐ Yes ☐ No

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The answers to the above criteria must be YES; if so, proceed to **diagnosis-specific criteria**. If NO to one or more criteria, stop and deny coverage.

References:

1. Epoetin alfa (Procrit) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103234s5369lbl.pdf (Accessed 8/15/19)
2. Epoetin alfa (Epogen) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103234s5369lbl.pdf (Accessed 8/15/19)
3. Darbepoetin alfa (Aranesp). https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103951s5378lbl.pdf (Accessed 8/15/19)
4. Epoetin alfa-epbx (Retacrit). https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125545s003lbl.pdf (Accessed 8/15/19)

- **Diagnosis-specific criteria.** Choose the indication seeking prior approval:
  1. Anemia due to chronic kidney disease (CKD)
  2. Anemia due to cancer chemotherapy
  3. Anemia due to zidovudine therapy
  4. Preoperative reduction of allogeneic blood transfusion
  5. Anemia due to myelodysplastic syndrome
  6. Anemia associated with ribavirin therapy (off-label)

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BOX 1: Anemia due to CKD	
1. The clinician has performed appropriate studies to rule out other possible causes of anemia (e.g. iron studies, folate and B_{12} levels, etc).	☐ Yes ☐ No
2. The patients has diagnosis of chronic kidney disease	☐ Yes ☐ No
If YES was answered to all of the above, approve. PA is good for 12 months. **The PA is to allow access to erythropoietic agents for the purpose of reducing blood transfusions in patients with anemia due to CKD.**	

BOX 2: Anemia due to Cancer Chemotherapy	
1. The patient is currently undergoing myelosuppresive chemotherapy AND there is a minimum of 2 additional months of planned chemotherapy	☐ Yes ☐ No
2. The clinician has performed the appropriate studies‡ to rule out anemia due to other causes.	☐ Yes ☐ No
3. The patient does **NOT** have a diagnosis of malignancy that is potentially curable (examples of cancers with curative intent therapy: early-stage breast cancer, Hodgkin lymphoma, non-Hodgkin's lymphomas, testicular cancer, early-stage non-small cell lung cancer, small cell lung cancer)	☐ Yes ☐ No
4. Request is for Epogen, Procrit, Retacrit, or Aranesp [not Mircera].	☐ Yes ☐ No
If YES was answered to all of the above, approve. PA is good for 12 months. **The PA is to allow access to erythropoietic agents for the purpose of reducing blood transfusions in patients with anemia due to myelosuppressive chemotherapeutic regimens.**	

Notes:

‡Such studies, at a minimum, include:

- Thorough drug exposure history
- Review of peripheral-blood smear/bone marrow examination
- Analyses for iron, folate or B_{12} deficiencies
- Assessments of reticulocyte count, occult blood smear, and renal insufficiency

References:

1. American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guidelines Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. *Journal of Clinical Oncology*. 2010;28(33):4996-5010
2. Bohlius J, et al. Erythropoietin or Darbepoetin for patients with cancer—meta-analysis based on individual patient data (Review). *The Cochrane Review Library.* 2010;11:1-239
3. Song X, et al. The Impact of Methodological Approach on Cost Findings in Comparison of Epoetin Alfa with Darbepoetin Alfa. *The Annals of Pharmacotherapy.* 2009;43:1203-10
4. NCCN guidelines for Hematopoietic Growth Factors (Version 2.2019). https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed 9/25/19.
5. Bohlius J et al. Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update. J Clin Oncol. 2019;37(15):1336. Epub 2019 Apr 10. PMID 30969847

BOX 3: Anemia due to zidovudine therapy	
1. The patient receives a weekly dose of zidovudine of 4200 mg or less**.**	☐ Yes ☐ No
2. The patient has a confirmed diagnosis of human immunodeficiency virus.	☐ Yes ☐ No
3. The patient's endogenous serum erythropoietin levels are **≤500 mUnits/mL or the patient is transfusion-dependent at baseline**.	☐ Yes ☐ No
4. The clinician has determined the cause of the anemia to be attributable to zidovudine therapy and has performed the appropriate studies to rule out other possible causes of anemia (e.g. iron studies, folate and B_{12} levels, etc).	☐ Yes ☐ No
5. The patient has a hematocrit of 30% or less OR has had a decline of 15% or more in hematocrit since initiation of zidovudine therapy.	☐ Yes ☐ No

If YES was answered to all of the above, approve. PA is good for 12 months. **The PA is to allow access to erythropoietic agents for the purpose of preventing blood transfusions in HIV-infected patients with anemia due to myelosuppressive zidovudine therapy.**

References:

1. Amgen, Inc. (2012). Epoetin alfa (Epogen®/Procrit®) for Injection. Thousand Oaks, CA: Author
2. Henry DH, et al. Epoetin Alfa for Treatment of Anemia in HIV-Infected Patients. *J Acquir Immune Defic Syndr*. 2004;37(2):1221-27. (Review)
3. Henry DH, et al. Recombinant Human Erythropoietin in the Treatment of Anemia Associated with Human Immunodeficiency Virus (HIV) Infection and Zidovudine Therapy. Overview of Four Clinical Trials. *Annals of Internal Medicine.* 1992;117:739-48.

7/10/12

Rationale for ESA coverage in anemia in HIV-infected patients due to zidovudine therapy:

In the clinical trials above (Ref 3), patients with baseline EPO level of 500 or less OR were transfusion-dependent were the only ones who experienced decreased transfusion requirement of ~2 in 12 weeks. Patients falling within the stratifications listed in the criteria above experienced the most benefit from ESA therapy. The surrogate marker for anemia in these trials was hematocrit ≤ 30% or a drop of ≥ 15% after start of zidovudine therapy. While not reflected in the PA criteria above, the trials were heavily weighted towards white males: in the treatment group 141/144 were male, 3/144 were female; and 129/144 were white race, 15/144 were any other race in the treatment arm. However, it does not logically follow that ESA therapy in non-white females is not beneficial, but merely a reflection of the disease state in the early '90s. Therefore, it would not be prudent to exclude ESA therapy from said population.

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BOX 4: Preoperative reduction of allogeneic blood transfusions	
1. The patient has been scheduled for <u>elective</u> orthopedic hip or knee surgery at <u>least 10 days in the future</u>.	☐ Yes ☐ No
2. The patient is either unable or unwilling to participate in autologous blood donation.	☐ Yes ☐ No
3. The patient is receiving oral iron supplementation.	☐ Yes ☐ No
4. Perisurgical deep vein thrombosis prophylaxis will be employed AND postsurgical anticoagulation **(VTE prophylaxis)** is planned**.**	☐ Yes ☐ No
If YES was answered to all of the above, approve. PA is good for 1 month. **The PA is to allow access to erythropoietic agents for the purpose of preventing allogeneic blood transfusions in patients undergoing planned, elective orthopedic hip or knee surgery and to whom autologous blood transfusion is unavailable.**	

References:

1. Amgen, Inc. (2012). Epoetin alfa (Epogen®/Procrit®) for Injection. Thousand Oaks, CA: Author
2. Epoetin alfa. Clin-eguide: Facts & Comparisons® eAnswers (Accessed 7/10/12)
3. Earnshaw, P. Blood conservation in orthopaedic surgery: the role of epoetin alfa. *International Orthopaedics.* 2001;25:273-78

7/10/12

Rationale for ESA coverage in preoperative reduction of allogeneic blood transfusions:

No data are available that compare autologous blood donation to ESA therapy; thus, access to ESA has been limited to those patients who cannot or will not receive blood autologously. The clinical trials that won FDA-approval utilized ESA 10 days prior to surgery, during surgery, and 4 days after surgery. All surgeries were elective orthopedic hip or knee procedures. Other types of surgeries did not demonstrate effectiveness where ESA therapy was concerned; ***<u>in some surgeries (such as CABG), ESA therapy was associated with increased mortality</u>****. In all trials, patients on ESA therapy were supplemented with oral iron and were anticoagulated after surgery. DVT prophylaxis is recommended during ESA therapy.*

BOX 5: Anemia due to Myelodysplastic Syndrome (MDS)	
1. The patient has been diagnosed with myelodysplastic syndrome.	☐ Yes ☐ No

2. The clinician has performed the appropriate studies‡ to rule out anemia due to other causes.	☐ Yes ☐ No
3. Serum erythropoietin level is ≤500 units/L	☐ Yes ☐ No
4. Request is for Epogen, Procrit, Retacrit, or Aranesp [not Mircera].	☐ Yes ☐ No
If YES was answered to all of the above, approve. PA is good for 12 months. **The PA is to allow access to erythropoietic agents for the purpose of reducing blood transfusions in patients with myelodysplastic syndrome.**	

Reference:

NCCN guidelines for Myelodysplastic Syndrome (version 1.2020). https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed 9/25/19.

BOX 6: Anemia due to ribavirin therapy (OFF-LABEL)	
1. The patient has a confirmed diagnosis of chronic hepatitis C virus (HCV) infection genotype 1¥.	☐ Yes ☐ No
2. The patient is currently receiving anti-HCV therapy, in accordance with current practice guidelines**.**	☐ Yes ☐ No
3. The patient is at least 18 years of age.	☐ Yes ☐ No
If YES was answered to all of the above, approve. PA is good for 12 months. **The PA is to allow access to erythropoietic agents for the purpose of improving tolerance to ribavirin therapy, thereby improving compliance to anti-HCV therapy and achieving SVR.**	

¥Studied patients were diagnosed with chronic HCV genotype 1b.

References:

1. Epoetin alfa. Clin-eguide: Facts & Comparisons® eAnswers (Accessed 7/10/12)
2. Gaetano B, et al. Epoetin alpha improves the response to antiviral treatment in HCV-related chronic hepatitis. Eur J Clin Pharmacol. 2010;66:1055-1063.
3. Ghany MG, Nelson Dr, Strader DB, Thomas DL, et al. An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases: AASLD PRACTICE GUIDELINE HEPATOLOGY. 2011; Vol. 54, No. 4:1433-1444.

7/10/12

Rational for ESA coverage in HCV-infected patients with chronic hepatitis treated with ribavirin:

The study (Ref 2 above) was very limiting on the inclusion of its participants; thus, the PA criteria have been designed to reflect that. In the study, patients were not given ESA therapy until after the 12th week of HCV therapy, and patients deemed as nonresponders were excluded from the study at that point. The patients also had to demonstrate signs and symptoms of chronic hepatitis. Only epoetin alfa has been studied in this population.

History:

Date	Changes	Pharmacist
7/10/12	Created criteria	JLB
7/31/12	Made changes the committee voted on.	JJ
7/25/18	Added Retacrit to drug list (epoetin alfa), biosimilar to Epogen, Procrit	ALM
9/23/19	Criteria reviewed: -Omitted Omontys (peginesatide) as it was withdrawn by the FDA at the manufacturer's request due to severe/fatal anaphylactic reactions -for core criteria, change required baseline hgb to <10 per current FDA guidance (see package inserts) -simplified CKD criteria to require diagnosis only -for MDS, require serum EPO level <500 -remove coverage for anemia due to heart failure (not recommended by American College of Physicians and no benefit per systematic review). 1. Qaseem A et al. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2013 Dec 3;159(11):770-779. PMID 24297193 2. Kansagara D et al. Treatment of anemia in patients with heart disease: a systematic review. Ann Intern Med. 2013 Dec 3;159(11):746-757. PMID 24297191 -Add Mircera as product that falls under these criteria -Split criteria for MDS and chemo-induced anemia (formerly included in same box).	SK
12/29/2020	Criteria reviewed, no change	SK
1/28/2021	After discussion at EBRx P&T, change duration of approval to 12 mo for all indications except Preoperative reduction of allogeneic blood transfusion	SK

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Esketamine (Spravato®)

EBRx PA Criteria

Medical Benefit PA

FDA-approved for: treatment resistant depression in adults in conjunction with PO antidepressants

Criteria for new users
1. Patient must be between ages 18 and 75 years old.
2. Patient must have the diagnosis of treatment-resistant depression.
3. Patient must show treatment-resistance in the following ways: a. have on their profile, in the past 2 years, at least 3 different antidepressant strategies(2 previous and 1 concomitant) nonconcurrent antidepressant therapies. i. either 3 from different classes (SSRIs, or SNRIs, or bupropion monotherapies). ii. 2 monotherapies plus one augmentation strategy iii. 1 monotherapy, 1 augmentation strategy, ECT/Repetitive transcranial magnetic stimulation (rTMS) i.v. other combination of the above
4. The profile must show *a fill history of at least 6* weeks EACH* for the nonconcurrent monotherapies, at the maximum or maximally tolerated dose, before esketamine.
5. Patient must have *current fill* of at least 2 30-day fills of SSRI, SNRI, or bupropion at the maximum or maximally tolerated dose.
6. The prescriber must be a psychiatrist.
7. The prescriber must have checked the AR PMP to rule out substance abuse.
8. The prescriber must, in good conscience, attest to the patient NOT being a current, active substance abuser.
The initial PA is good for 4 weeks. QL is 84mg TWICE weekly.

Criteria for continuation
1. The patient must be currently adherent with receiving esketamine nasal.
2. The patient must be receiving a concurrent antidepressant therapy (SSRI, SNRI, bupropion or other drug or procedure) as evident by the fill history of paid claims or medical claims.

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###The continuation PA will be good for 12 months. QL will be 84mg ONCE weekly.###

Note: Dosing is:

- Induction: 56mg twice wkly up to 84mg twice wkly for 4 weeks total
- Maintenance: At week 5 dose from induction phase move to QW, then after 9wks can possibly move to q 2wks
- After 4wks evaluate for evidence of therapeutic benefit to determine need for continued treatment

Quantity Limits: Twice weekly if in the initial 4 weeks of therapy. Once weekly after the first 4 weeks.

References:

1. Canuso, Carla M., et al. "Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study." *American journal of psychiatry* 175.7 (2018): 620-630.
2. Duru, Gérard, and Bruno Fantino. "The clinical relevance of changes in the Montgomery–Asberg Depression Rating Scale using the minimum clinically important difference approach." *Current medical research and opinion* 24.5 (2008): 1329-1335.
3. Aripiprazole (Abilify): Depression, Major Depressive Disorder (MDD) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Nov. Table 18, Validity and Minimal Clinically Important Difference of Outcome Measures.
4. UpToDate: Treatment resistant depression
5. LexiComp: esketamine. Accessed 3/26/19.
6. Daly, Ella J., et al. "Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial." *JAMA psychiatry* 75.2 (2018): 139-148.
7. ICER Draft Evidence Report. Esketamine for the Treatment of TreatmentResistant Depression: Effectiveness and Value. 3/21/2019.

Revision History:

Date	What changed	Pharmacist's initials
5/6/19	I wrote the criteria. *The 6 weeks of therapy with each trial of an SSRI or SNRI or bupropion before failure can be determined and the patient be diagnosed as "treatment resistant". Six weeks was the minimum in the trials per the ICER report. Our criteria are relatively generous because the trials reported therapy might require dose adjustments and 6-12 weeks to assess response. ICER also reported that the TRANSFORM trials required failure of at least 2 monotherapies FOR EACH DEPRESSIVE EPISODE before esketamine was allowed.	JJ
5/25/19	I adjusted the PA criteria after the ICER Midwest CEPAC meeting on esketamine.	JJ

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Everolimus (Afinitor®)

2.5, 5, 7.5, 10mg tablets

EBRx PA Criteria

FDA approved for:

- Postmenopausal women with advanced hormone receptor-positive, HER2- negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole. NOT COVERED
  - Benefit is limited to progression free survival, and no overall survival or quality of life benefit has been demonstrated. Scroll to bottom of this document for further details.
- Adults with progressive neuroendocrine tumors of pancreatic origin (PNET) and adults with progressive, well-differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic.
  - Limitation of Use: Everolimus is not indicated for the treatment of patients with functional carcinoid tumors.
- Adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.
- Adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.
- Treatment of adult and pediatric patients aged 1 year and older with TSC who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

Pancreatic Neuroendocrine Tumor (PNET)
1. The patient has a diagnosis of advanced pancreatic neuroendocrine tumor PNET.
2. Tumor is low or intermediate grade
3. Tumor is progressing at time of request
4. If radiolabeled somatostatin analog diagnostic imaging (e.g. OctreoScan or Ga-68 dotatate) is positive, patient has been treated previously with a long-acting somatostatin analogue (lanreotide or octreotide)
If both criteria met, approve for 12 months.
Notes: Everolimus improved progression free survival compared to placebo. A high crossover rate (73%) confounds overall survival analysis.[1] An indirect comparison of everolimus and placebo showed improved overall survival.[2]

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In study, ~50% of patients received prior somatostatin analogue therapy. Therefore, will require this as a prior therapy to drive use toward a less expensive therapy first.

References:

1. Yao JC et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011 Feb 10;364(6):514-23. NCT00510068 PMID 21306238
2. Signorovitch J et al. Everolimus and sunitinib for advanced pancreatic neuroendocrine tumors: a matching-adjusted indirect comparison. Exp Hematol Oncol. 2013 Dec 6;2(1):32. PMID 24314093

Renal Cell Carcinoma
1. The patient has a diagnosis of advanced renal cell carcinoma.
2. The patient is being treated with everolimus **in combination with** lenvatinib (and has an approved lenvatinib PA on file).*
If both criteria met, approve for 12 months.
Reference: Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomized, phase 2, open-label, multicenter trial. Lancet Oncol 2015;16:1473-82.

***Monotherapy with everolimus for RCC is not covered on this plan.**

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Renal angiomyolipoma
1. The patient has a diagnosis of renal angiomyolipoma associated with tuberous sclerosis complex (TSC).
2. Patient has at least one lesion that is at least 3 cm in size
3. Evidence of growth of lesion(s) is present (≥5 mm increase in size per year)
If all criteria met, approve for 12 months.

Notes:

- TSC-associated renal angiomyolipoma (RAML) complications: renal hemorrhage, mass effect, CKD, anemia, HTN
- Growth of RAML associated with bleeding. If growing, risk of bleed is 41%. If not growing, risk is 8%.
- Other therapeutic options: embolization or nephrectomy (both increase risk for development of CKD).
- EXIST-2: everolimus versus placebo (required at least one lesion ≥3cm; placebo patients crossed over after progression)
  - Time to progression: HR 0.08, 95% CI 0.02-0.37, p<0.0001
  - Progression-free rate at 12 months: 92% vs 25%
  - No bleeding observed in study. No clear comparison of complications of RAML between groups, but most placebo patients crossed over to everolimus perhaps not leaving enough time for complications to develop.
- UpToDate: authors require evidence of growth (≥5 mm per year) before starting an mTOR inhibitor. Many RAMLs stop growing or grow very slowly in adults.
- Due to large difference in time to progression, EBRx will cover this indication but will follow the UpToDate recommendation that the tumor must have evidence of growth

References:

1. Kingswood JC et al. The effect of everolimus on renal angiomyolipoma in patients with tuberous sclerosis complex being treated for subependymal giant cell astrocytoma: subgroup results from the randomized, placebo-controlled, Phase 3 trial EXIST-1. Nephrol Dial Transplant. 2014 Jun;29(6):1203-10. PMID 24729041
2. Bissler JJ et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2013 Mar 9; 381(9869):817-24. PMID 23312829 NCT00790400
3. Bissler JJ et al. Everolimus long-term use in patients with tuberous sclerosis complex: Four-year update of the EXIST-2 study. PLoS One. 2017 Aug 9;12(8):e0180939. PMID 28792952 NCT00790400
4. Bissler JJ et al. Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis: extension of a randomized controlled trial. Nephrol Dial Transplant. 2016 Jan;31(1):111-9. PMID 26156073 NCT00790400
5. UpToDate “Renal Angiomyolipomas.” https://www.uptodate.com/contents/renal-angiomyolipomas?search=renal%20angiomyolipoma&source=search_result&selectedTitle=1~31&usage_type=default&display_rank=1

Subependymal giant cell astrocytoma (SEGA)
1. The patient has a diagnosis of subependymal giant cell astrocytoma (SEGA).
2. The patient is s/p surgery or else not a candidate for surgery.
3. The patient has one of the following: a SEGA lesion > 1 cm in diameter; serial radiological evidence

of SEGA growth; or new or worsening hydrocephalus.
If all criteria met, approve for 12 months.
References: 1. Franz DN, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicenter, R, PC phase 3 trial. Lancet. 2013. Jan 12;381(9861)125-132. 2. Krueger DA, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. NEJM. 2010 Nov 4;363(19):1801-11. 3. Bellmunt J, Pons F, Foreshew A, et al. Sequential targeted therapy after pazopanib therapy in patients with metastatic renal cell cancer: efficacy and toxicity. Clin Genitourin Cancer. 2014 Aug;12(4):262-9. doi: 10.1016/j.clgc.2014.03.002. Epub 2014 Mar 14. 4. Franz, David, et al. "Long-term efficacy and safety of everolimus for the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) in EXIST-1: approximately 3.5 years of exposure (P2. 235)." Neurology 84.14 Supplement (2015): P2-235.

Revision History		
Date	**Notes**	**Pharmacist's initials**
5/2009	Criteria written	JJ
5/11/12	Revision history table added	JJ
6/19/13	Revised Criteria. Removed renal cell carcinoma since no OS data. Did not add HER-2 positive breast cancer (No OS data admittedly in PI), renal angiomyolipoma with at least one angiomyolipoma (3cm), and advanced/metastatic pancreatic neuroendocrine tumor since no OS data. Added SEGA since the drug reduces seizure frequency. For those receiving it for renal cell CA who already had prior authorization, continue to allow. For others, these criteria will apply.	JJ
4/14/2015	I was asked again to look at afinitor. Notes: it is FDA- indicated for: • HER2-, hormone receptor+ breast cancer in combo w/ letrozole or anastrozole, • progressive neuroendocrine tumors of pancreatic origin (unresectable, locally advanced or metastatic), • advanced RCC after sunitinib or sorafenib failure, • renalangiomyolipoma and tuberous sclerosis complex • tuberous sclerosis complex who have subependymal giant cell astrocytoma (SEGA) that cannot be curatively resected. Reference 6 showed 1st line everolimus followed by sunitinib in RCC DID NOT MEET noninferiority and the PFS was less than the reverse order of	JJ

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	drugs. Reference 7: Everolimus in mRCC after pazopanib failed to improve PFS. The use of the drug is not supported in this manner. Reference 2: In mRCC pts who failed sunitinib or sorafenib, everolimus caused a statistically significant improvement in PFS, median 11m vs 4.6m(placebo), (95%CI, 3.1 to 5.4). The endpoint of OS is confounded because 73% of placebo patients crossed over to open-label everolimus.	
2/23/2016	Confirmatory and extended data available. FDA updated language. Ref 8	
8/19/2016	Changed SEGA PA criteria to statements. Added criteria for renal cell carcinoma in combination with lenvatinib based on DCWG/DUEC/Board vote.[9]	GBB
7/18/2019	Criteria reviewed: -added criteria for PNET -added criteria for renal angiomyolipoma (TSC associated) -added details of review of everolimus for breast cancer	SK
7/7/2020	Criteria reviewed. No change.	SK
9/28/2021	Criteria reviewed. No change.	SK

ADDITIONAL TRIAL INFORMATION FOR BREAST CANCER INDICATION:

- BOLERO 2 (double blind, everolimus/exemestane *vs* placebo/exemestane; n=724, 2:1 randomization, double-blind):
  - Progression free survival (PFS): median 7.8 mo vs 3.2 mo (p<0.001)[13]
  - Median overall survival (eve/exe vs plac/exe): 31 mo vs 26.6 (HR 0.89; 95% CI 0.73-1.1; p=0.1426)[14]
  - Post-trial everolimus use: specific data not given; crossover not specified as allowed in reports
  - Quality of Life: time to deterioration using EORTC QLQ-C30[15]
    - Time to 5% decrease in score: median 8.3 mo vs 5.8 mo (p=0.0084) [significant]
      →Baseline scores were ~65 in each group, so a 5% decrease would equal ~3-4 points
    - Time to 10-point decrease in score (generally-accepted minimally important difference): median 11.7 mo vs 8.4 mo (p=0.1017) [not significant]
- BOLERO 6 (**confirmatory study**; everolimus/exemestane *vs* everolimus *vs* capecitabine; n=309, 1:1:1 randomization, open label)[16]
  - Median PFS (everolimus/exemestane *vs* everolimus *vs* capecitabine): 8.4 mo vs 6.8 mo vs 9.6 mo [difference between eve/exe and eve groups was statistically significant]
  - Median OS (everolimus/exemestane *vs* everolimus *vs* capecitabine): 23.1 mo vs 29.3 mo vs 25.6 mo [no significant differences]
  - 24-month OS rate: 48% vs 59% vs 59%

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Everolimus (Zortress®)

Zortress is FDA-approved for:

- Liver transplant, in combination with corticosteroids and reduced dose tacrolimus; should not be administered earlier than 30 days post-transplant.
- Renal transplant, in combination with basiliximab induction and concurrent with corticosteroids and reduced doses of cyclosporine.

OFF LABEL:

- Carcinoid tumors
- Heart transplant, ≥3 post-transplantation. Data support substitution of everolimus for mycophenolate posttransplant for prophylaxis of organ rejection in heart transplant in combination with concomitant immunosuppression.
- Hodgkin lymphoma, relapsed or refractory
- Lung transplant
- Thymoma and thymic carcinomas, advanced, refractory
- Waldenstrom macroglobulinemia, relapsed or refractory

1. Zortress may be approved for use after a renal, cardiac, or liver transplant to prevent organ rejection.
If so, approve for 1 year.
*Make sure drug is dosed for this indication and *not dosed* for treatment of cancer (Afinitor dosing). • S/p renal transplant to prevent rejection: dose is 0.75mg twice daily, then dosed based on serum concentrations; used in combo with basiliximab induction and with cyclosporine and corticosteroids. • s/p heart transplant to prevent rejection: dose is 0.75 to 1.5mg twice daily, then dosed based on serum concentrations, in combo with cyclosporine and prednisone. • s/p liver transplant to prevent rejection: 1mg bid, then adjustments to target 3-8 ng/mL.
QL of 120units/30d. Zortress available in 0.25mg, 0.5mg, 0.75mg.

References:

Lexicomp: everolimus. Accessed 5/11/12.

Campistol JM, et al. Everolimus and long-term outcomes in renal transplant. *Transplantation.* 2011*;* 92:S3-s26.

Fullestad L, et al. Two-Year Outcomes in Thoracic Transplant Recipients After Conversion to Everolimus With Reduced Calcineurin Inhibitor Within a Multicenter,

Open-Label, Randomized Trial. *Transplantation*.2010;90:1581–1589.

Saliba F, De Simone P, et al. Renal function at two years in liver transplant patients receiving everolimus: results of a randomized, multicenter study. Am J Transplantation. 2013;13:1734-45.

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Revision history:

Date	What changed?	Pharmacist's initials
8/2010	Criteria created.	JJ
5/11/12	Dosing reference; revision history table added.	JJ
5/14/12	review article added and heart transplant reference added	JJ
2/26/14	Liver transplant rejection prevention added to criteria. Reference added. Everolimus showed similar efficacy but less worsening of SrCr than tacrolimus.	JJ
12/14/2020	I reformatted the criteria. No effective change made.	JJ
3/31/21	Applied EBRx criteria to UAS Plan. They had Afinitor criteria but not Zortress.	JJ

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Evolocumab (Repatha®)

140mg/mL (1mL) Autoinjector, solution cartridge, or prefilled syringe

EBRx PA Criteria

FDA-approved for:

- Homozygous familial hypercholesterolemia
- Hyperlipidemia, primary (including heterozygous familial hyperlipidemia)
- Prevention of cardiovascular events in patients with established CVD

Initial

1. Patient must have clinically evident atherosclerotic cardiovascular disease (defined as a history of myocardial infarction, nonhemorrhagic stroke (TIA does NOT qualify), or symptomatic peripheral artery disease).

2. Patient must have fasting LDL-C of ≥70mg/dL or a non-HDL-C of ≥100mg/dL WHILE TAKING an optimized regimen of lipid-lowering therapy
   - Must be a high-intensity statin equal to atorvastatin 20mg or higher (with or without ezetimibe) for at least 6 weeks

3. Patient must also have additional characteristics that places him/her at higher cardiovascular risk including:

   At least 1 of the following:

   - T1 or T2DM
   - Age ≥65
   - MI or non-hemorrhagic stroke within the past 6 months
   - Additional diagnosis of MI or non-hemorrhagic stroke excluding the one in the original history (item 1 above)
   - Current daily cigarette smoking
   - History of symptomatic peripheral artery disease,

   OR

   At least 2 of the following:

   - History of non-MI related coronary revascularization
   - Residual coronary artery disease with ≥40% stenosis in ≥2 large vessels
   - Most recent hsCRP>2.0mg/L
   - Most recent LDL-C >130mg/dL or non-HDL-C >160 mg/dL
   - Diagnosis of metabolic syndrome (At least 3 of the following:
     - waist circumference >40 inches for men or >35 inches for women
     - triglycerides ≥150 mg/dL
     - HDL-C <40 mg/dL for men or <50 for women
     - Systolic blood pressure ≥130mmHg or diastolic BP ≥85 mmHg or hypertension treated with medication
     - Fasting glucose ≥100 mg/dL

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Note: dose is 140mg every 2 weeks

Revision History

Date	Notes	Pharmacist's initials
1/16/2019	I wrote the criteria.	JJ
10/5/2020	I reviewed the criteria.	JJ
3/30/2021	Criteria reformatted.	JJ

References:

1. Sabatine, Marc S., et al. "Evolocumab and clinical outcomes in patients with cardiovascular disease." *N Engl J Med* 2017.376 (2017): 1713-1722.(FOURIER)
This n=27,564 RCT showed that in secondary prevention patients taking optimal cholesterol reducing drugs, evolocumab reduced the composite (cv death, MI, stroke, hospitalization for unstable angina or coronary revascularization), the composite [of CV death, MI or stroke], MI, ischemic stroke, coronary revascularization, ischemic stroke or TIA, and the Cholesterol Treatment Trialists Collaboration (CTTC) composite end point of coronary heart death, NF MI, stroke or coronary revascularization.
The primary endpoint occurred in 9.8% vs 11.3%placebo (HR 0.85; 95%CI 0.79-0.92). There was no reduction in all cause death or in CV death. The mean follow up was 2.2y. The patients had LDL>70mg/dL or non-HDL>100mg/dL AND established cardiovascular disease. Randomized to evolocumab SC 140mg q2w or 420mg monthly plus high- or moderate-intensity effective statin dose; or placebo SC q2w or qM plus high to mod statin dose (at least atorva 20mg).

Fam-trastuzumab deruxtecan-nxki (Enhertu®)

Vial 100mg

EBRx PA Criteria

FDA-approved for:

- Adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. NOT COVERED data is limited to a single arm trial. Reference: Modi Set al. N Engl J Med. 2020 Feb 13;382(7):610-621. PMID: 31825192. Follow NCT03523585 (phase 3 DESTINY-Breast02)
- Adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen. SEE CRITERIA

Criteria for new users
1. Diagnosis of locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma
2. Disease progression after at least two prior regimens which included a fluoropyrimidine, a platinum, agent, and trastuzumab
3. Tumor is HER2 positive (score of 3+ on immunohistochemical analysis or score of 2+ with positive results on in situ hybridization)
4. ECOG performance status is 0 or 1 (on a scale of 0 to 5, with higher numbers indicating greater disability)
If all criteria are met, approve for 12 months

Note:Dose: 6.4 mg/kg IV over 30-90 minutes every 3 weeks until disease progression

- Patients meeting the above criteria were randomized to either Enhertu or standard chemotherapy (irinotecan or paclitaxel) Overall survival was improved in the Enhertu group (12.5 mo versus 8.4 mo; HR 0.59, 95% CI 0.39-0.88). Response rate was also higher in the Enhertu group (40.5% vs 11.3%).
- Median duration of treatment was 4.6 months.

Reference:

Shitara K et al. DESTINY-Gastric01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med. 2020 Jun 18;382(25):2419-2430. doi: 10.1056/NEJMoa2004413. Epub 2020 May 29. PMID: 32469182.

Revision History:

Date	What changed	Pharmacist's initials
1/28/2021	Criteria written	SK

Febuxostat (Uloric®)

EBRx PA Criteria

FDA-approved for: Hyperuricemia in patients with gout who have an inadequate response to a maximally titrate dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.

Criteria for new users
1. The patient must: • have a documented hypersensitivity to allopurinol that prevents its use. A completed Medwatch form is required. OR • the patient must have failed or cannot tolerate maximally titrated allopurinol doses.[6]
2. The prescriber has discussed the black box warning relating to all-cause death and CV death risk increase compared to allopurinol.[7]

Note: Regarding the evidence on CV safety (reference 6).

- Noninferiority study comparing febuxostat vs allopurinol
- Overall 56.6% of patients discontinued trial treatment prematurely (57.3% FEB, 55.9% ALLO.
- Median duration of exposure was 728 days FEB, 719 days ALL
- Lower uric acid w/ FEB; rates of gout flares similar between groups 0.68 FEB, 0.63 ALLO, per patient-year.
- NI margin set at the upper bound of the one-sided confidence interval of the hazard ratio for the primary end point be less than **1.3**
- Results: Primary endpoint (composite CV death, NFM, NFstroke, urgent revasc due to UA 10.8% FEB, 10.4%ALLO (HR 1.03, 0.87-**1.23,** therefore reached noninferiority.
- Results: CV death 4.3%FEB, 3.2%ALLO, HR 1.34(95%CI 1.03-1.73, p=0.03)---Statistically significant increased CV death risk. NNH=91 people over 2 years.
- Results: Death from any cause: 7.8% FEB, 6.4% ALLO. HR 1.22 (95%CI 1.01-1.47, p=0.04)—Stat signif increased All cause death. NNH=72 people over 2 years.

References:

1. Stamp LK, O'Donnell JL, et al. Using Allopurinol Above the Dose Based on Creatinine Clearance Is Effective and Safe in Patients With Chronic Gout, Including Those With Renal Impairment. ARTHRITIS & RHEUMATISM. Vol. 63, No. 2, February 2011, pp 412–421.
2. El-Zawawy H, Mandell BF. Managing gout: How is it different in patients with chronic kidney disease? C L E V E L A N D C L I N I C J O U R N A L O F M E D I C I N E. D E C E M B E R 2 0 1 0;7 7(12) :919-928.
3. Schumacher HR, et al. Effects of Febuxostat Versus Allopurinol and Placebo in Reducing Serum Urate in Subjects With Hyperuricemia and Gout: A 28-Week, Phase III, Randomized, Double-Blind, Parallel-Group TrialArthritis & Rheumatism (Arthritis Care & Research) Vol. 59, No. 11, November 15, 2008, pp 1540–1548.

4. Becker MA, Schumacher HR, et al. Clinical Efficacy and Safety of Successful Longterm Urate Lowering with Febuxostat or Allopurinol in Subjects with Gout. J Rheumatol. 2009;36:1273–82.
5. Becker mA, Schumacher HR, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353:2450-61.
6. Center for Drug Evaluation and Research. “FDA Adds Boxed Warning for Increased Risk of Death with Gout Medicine.” *U.S. Food and Drug Administration*, FDA, 17 Nov. 2017, www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-increased-risk-death-gout-medicine-uloric-febuxostat.
7. White, William B., et al. "Cardiovascular safety of febuxostat or allopurinol in patients with gout." *New England Journal of Medicine* 378.13 (2018): 1200-1210.

Revision History:

Date	What changed?	Pharm.D.
3/30/09	Excluded per JJ’s directory	JJ
8/09	changed to covered w/ PA 8/09	JJ
8/09	PA criteria: documented hypersensitivity to allopurinol. All other requests for coverage to be denied.	JJ
4/5/10	additional criteria of CrCl<30ml/min was included in this PA—cannot find documentation on this.	JJ
5/14/12	References added; revision hx table added	JJ
2/25/19	I added reference 6. I added item 2 regarding CV black box warning. I added the box and calculated the NNH for CV death and all cause death.	JJ
11/24/19	Added the patient must have failed allopurinol therapy based off of the black box warning; Converted document to new template formation.	DD/JJ
2/9/2021	I clarified the criteria; combined the old 1&2 to be either 1 or 2, AND 3.	JJ

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Fenfluramine (Fintepla®)

EBRx PA Criteria

is FDA-approved for: Treatment of seizures associated with Dravet syndrome in patients aged 2y+.

Criteria for new users
1. The patient must have the diagnosis of seizures associated with Dravet syndrome.
2. The patient must be ≥2 years old.
3. The patient must have at least one other antiepileptic (AEP) drug including clobazam or valproate (or both), or others such as levetiracetam, stiripentol, topiramate.
4. The patient must have no history or valvular heart disease or pulmonary hypertension
5. The patient is NOT TAKING carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, or phenytoin.
Note: Please note the seizure frequency in a week.
If fulfills all of the above, the PA is good for 6 months.

Criteria for continuation
1. The patient should have on the profile at least one other AEP drug and be adherent. (valproate and/or clobazam)
2. the patient must have had a decrease in seizure frequency by at least 25% (arbitrary; in the trial the lowest dose showed a reduction by 32%) from the first request. (This is why it was important to note the sz frequency at the original request of this drug.)
If the continuation criteria are fulfilled, the PA is good for 12m.

Note: Please note if the patient is taking stiripentol. It is a CYP450 inhibitor and the max dose is lower with concomitant use.

Quantity Limits:

Revision History:

Date	What changed	Pharmacist's initials
8/20/2020	I wrote the criteria.	JJ

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Fentanyl (Actiq/Fentora)

(Lazanda Spray was excluded from coverage 5/15/12 as a new drug.)

(PA required only for quantity>7.)

1. Does the patient have a diagnosis of cancer?	☐ Yes ☐ No **If yes, go on to next question. If no, stop and deny coverage.**
2. Is the patient opioid tolerant (taking at least 60 mg morphine per day, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg oxycodone daily, at least 8mg oral hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer)?	☐ Yes ☐ No **If yes, go on to next question. If no, stop and deny coverage.**
3. Has the patient received an MAO-I inhibitor within the past 14 days?	☐ Yes ☐ No **If yes, stop and deny coverage at this time. If no, go to next question.**
4. Is the patient able to swallow oral tablets?	☐ Yes ☐ No **If yes, stop and deny coverage at this time. If no, go to the approval statement below.**
If questions 1, 2, are answered "yes", and question 3 & 4 are answered "no", then approve PA.	
If approved for coverage, PA is good for 1 year.	
Quantity limits: 90 units/30 days	

References:

1. **Actiq Package Insert. Current as of 11-13-06.**
2. **Coluzzi PH, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). Pain. 2001; 91:123-130.**

Notes: No grandfathering.

Revision History:

Date	What changed?	Pharmacist's initials
2/6/07	Actiq criteria written; Fentora added.	JJ

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Onsolis (fentanyl buccal film)

Does the patient have a diagnosis of cancer?	☐ Yes ☐ No
Is the patient currently taking a long acting opioid for maintenance pain control?	☐ Yes ☐ No
Is the patient opioid tolerant?	☐ Yes ☐ No
Is the patient able to swallow tablets?	☐ Yes ☐ No
Is the patient unable to use other fentanyl buccal lozenges available without a Prior Authorization? Reason_____	☐ Yes ☐ No

If yes to questions 1-3, and no to 4 and 5 (with a reasonable explanation of why other agents cannot be used), approve x6 months.

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Fidaxomicin (Dificid®)

200 mg tablets, 40mg/mL oral suspension

EBRx PA Criteria

FDA-approved for: Clostridioides (formerly Clostridium) difficile infection in adults and peds patients >6 months old.

Criteria for new users
1. The patient must have the diagnosis of C Dif infection.
2. The patient must still have the diagnosis of symptomatic C Dif infection after taking vancomycin oral 125mg QID for 10 days for an initial (severe or non severe) episode, and after the 1st recurrence of failing pulsed oral vancomycin 125mg QID for 10-14 days (second course) then 2 times per day for a week, then once daily for a week, and then every 2-3 days for 2-8 weeks.

Quantity Limits: 200mg BID for 10 days or 20 tablets or the equivalent for suspension.

References:

1. McDonald, L. Clifford, et al. "Clinical practice guidelines for Clostridium difficile Infection in Adults and Children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)." *Clinical Infectious Diseases* 66.7 (2018): e1-e48.

2. Louie TJ, et al. Fidaxomicin versus vancomycin for clostridium difficile infection. N Engl J Med 2011;364:422-31.

3. Dificid package insert. http://www.dificid.com/upload/dificid.pdf , accessed 7/12/2011.

4. McDonald, L. Clifford, et al. "Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)." *Clinical Infectious Diseases* 66.7 (2018): e1-e48.

Date	What changed?	Pharmacist's initials
10/11/11	Criteria written	JJ
5/14/12	Revision hx table added	JJ
4/25/18	I updated the criteria. I removed the requirement to fail metronidazole, to have a mild-mod diagnosis of Cdif toxin +, and I added the reference where these guidelines came from. I also removed the reference for the 2010 Cdif Guidelines. Cohen SH, et al. Clinical Practice guidelines for clostridium difficile infection in adults: 2010 update by the society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5). Available on the IDSA Website: http://www.idsociety.org/content.aspx?id=4430#cd , accessed 7/12/2011.	JJ
3/30/21	I updated the criteria according to the 2017 SHEA/IDSA guidelines	JJ

Fingolimod (Gilenya®)

0.25mg, 0.5mg tablets

EBRx PA Criteria

is FDA-approved for: relapsing multiple sclerosis

Criteria for new users
1. Patient must have the diagnosis of relapsing MS with highly active disease as indicated by the prescriber (high frequency of relapses, MRI changes).
2. Patient must be at low risk for progressive multifocal leukoencephalopathy (PML) including those who are antibody positive as long as the anti-JCV antibody index is below 0.9.
3. No concurrent therapy with other RRMS drug therapies.

Note: Dose is 0.5mg QD.

QL: 30/30; specialty drug. No fills >31 ds.

References:

1. PI. Gilenya. http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf Accessed 1/13/12.

2. Cohen JA, et al. Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis. N Engl J Med 2010;362:402-15.

3. Drug Effectiveness Review Project. Disease-modifying drugs for MS. Final Update 1 Report, August 2010.

4. AAN. Practice Guideline: Disease-modifying Therapies for Adults with multiple sclerosis. American Academy of Neurology 4/24/2018. https://www.aan.com/Guidelines/Home/GetGuidelineContent/900

Revision History:

Date	Notes	Pharmacist's initials
1/13/12	Criteria written	JJ
5/14/12	Revision hx table inserted	JJ
5/5/14	QL of 1/1 added to fingolimod.	JJ
9/19/19	I changed the criteria to eliminate failure or intolerance to interferon or glatiramer. Added reference 4.	JJ
7/17/2020	Reviewed. No changes.	JJ
3/31/2021	Reformatted criteria	JJ

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Gemtuzumab ozogamicin (Mylotarg®)

4.5 mg vials

EBRx PA Criteria

MEDICAL PRIOR AUTHORIZATION – EXCLUDED FROM PHARMACY

FDA-approved for:

- Treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML)
  - In combination with daunorubicin and cytarabine (**CURRENTLY ONLY COVERED INDICATION**)
    OR
  - As monotherapy NOT COVERED (see venetoclax, glasdegib) in older adults not suited for intensive chemotherapy, overall survival benefit over best supportive care (transfusion, hydroxyurea) was minimal (median 4.9 mo vs 3.6 mo). Complete response (CR) rate with gemtuzumab was also low at 8.1%. Other therapies have longer overall survival and higher CR rates (e.g. decitabine or azacitidine with or without venetoclax, glasdegib).

    Reference: Amadori S et al. Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial. J Clin Oncol. 2016 Mar 20;34(9):972-9. PMID 26811524
- Treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older NOT COVERED. Data limited to a single arm, phase II trial (Taksin AL et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the alfa group. Leukemia. 2007 Jan;21(1):66-71. PMID 17051246)

Criteria for new users
The patient **must have** a diagnosis of acute myeloid leukemia (AML) and fulfill all of the following criteria: • AML is previously untreated. • Pt does not have diagnosis of acute promyelocytic leukemia (aka APL or M3 AML) • AML is not therapy related or myelodysplastic syndrome (MDS)-related • Cytogenetic risk is favorable or intermediate (not poor risk; see below for definitions) • AML blasts express CD33 (CD33-positive AML) • ECOG 0-2 • The patient does NOT have CNS involvement of AML • The patient does NOT have liver or renal abnormalities defined as AST or ALT ≥ 2.5 x upper limit of normal (ULN), serum bilirubin ≥ 2 x ULN, OR serum creatinine ≥ 2.5 x ULN.
If patient meets criteria above, approve medical PA for 4 months. Medication is excluded from pharmacy benefit. **For patients who do not achieve an adequate response during first induction cycle, no further gemtuzumab is indicated. Medication is approved ONLY in**

combination with cytarabine and daunorubicin.

Dosing: IV:

- **Induction Cycle**: gemtuzumab 3 mg/m^2 (**up to one 4.5 mg vial**) on Days 1, 4, and 7 in combination with daunorubicin (60 mg/m^2 on Days 1, 2, and 3) and cytarabine (200 mg/m^2 as continuous infusion for 7 days). **For patients who do not achieve an adequate response during first induction cycle, no further gemtuzumab is indicated.**
- **Consolidation Cycle (given x 2 cycles):** gemtuzumab 3 mg/m^2 (**up to one 4.5 mg vial**) on Day 1 in combination with daunorubicin (60 mg/m^2 for 1 day [first course] or 2 days [second course]) and cytarabine (1000 mg/m^2 per 12 h, infused over 2 h on days 1–4).

Risk stratification by genetics per NCCN Guidelines for Acute Myeloid Leukemia (Version 1.2020)

RISK STRATIFICATION BY GENETICS IN NON-APL AML[1,2]

Risk Category*	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Biallelic mutated *CEBPA* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,§ monosomal karyotype‖ Wild-type *NPM1* and *FLT3*-ITD^{high}† Mutated *RUNX1*¶ Mutated *ASXL1*¶ Mutated *TP53*#

Revision History:

Date	What changed	Pharmacist's initials
2/21/18	I wrote the criteria. Current approval is only FOR TX OF NEWLY-DIAGNOSED CD33-positive AML in adults in combo with 3+7 regimen. Not covered for relapsed or refractory AML or newly diagnosed AML as monotherapy (excluded code 2,8).	JK
8/26/19	Criteria reviewed. Added to criteria that AML should not be APL, treatment or MDS related, or poor risk cytogenetics. This is likely going to be given inpatient.	SK

2/10/2020	Criteria reviewed. No change	SK
5/25/2021	Criteria reviewed. No change. The covered indication is likely to be initiated inpatient.	SK

Ref:

1. Castaigne, Sylvie, et al. "Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study." The Lancet 379.9825 (2012): 1508-1516. PMID 22482940
2. Lexicomp and gemtuzumab package insert accessed 7/23/19.

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Glatiramer (Glatopa®)

EBRx PA Criteria

FDA-approved for: relapsing multiple sclerosis

Criteria for new users
4. Patient must have the diagnosis of relapsing MS with highly active disease as indicated by the prescriber (high frequency of relapses, MRI changes).
5. No concurrent therapy with immunosuppressive drugs
6. No concurrent therapy with other RRMS drug therapies.

Note: Dose is 20mg SC daily.

Quantity Limits:

References:

1. Lexicomp. Glatiramer. Accessed 9/18/19.
2. UpToDate. DMT for RRMS. Accessed 9/18/19.
3. AAN. Practice Guideline: Disease-modifying Therapies for Adults with multiple sclerosis. American Academy of Neurology 4/24/2018. https://www.aan.com/Guidelines/Home/GetGuidelineContent/900

Revision History:

Date	Task	Pharmacist
5/20/14	JJ wrote PA according to AR Insurance Board minutes 1/30/14.	JJ
9/19/2019	I updated the criteria. Added reference 3.	JJ
2/26/2020	I reviewed the criteria. No changes.	JJ
7/17/2020	I reviewed. Removed the requirement for low PML risk. Not needed.	JJ

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Granisetron sustained-release injection (Sustol®)

EBRx PA Criteria

FDA-approved for:

in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens

Criteria for new users
1. Patient must have a cancer diagnosis
2. Patient must be receiving moderately emetogenic chemotherapy or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens
3. Patient must have previous failure of an oral 5HT antagonist given daily on a scheduled basis OR palonosetron given 30-60 minutes prior to chemotherapy
4. Creatinine clearance must be >30 ml/min
If above criteria met, approve for 6 months maximum. Use of Sustol with successive chemotherapy cycles for more than 6 months is not recommended per package insert.
Dose: -10 mg SQ at least 30 minutes before the start of emetogenic chemotherapy on day 1. -Do not administer more frequently than once every 7 days -Use with successive emetogenic chemotherapy cycles for more than 6 months is not recommended as safety and efficacy have not been verified beyond this time frame. Evidence: A randomized, double-blind study compared Sustol to palonosetron in patients receiving moderately emetogenic chemotherapy or an anthracycline+cyclophosphamide regimen. Dexamethasone was also given and neurokinin 1 antagonists were NOT given. Sustol was non-inferior to palonosetron for prevention of acute and delayed chemotherapy-induced nausea/vomiting.[1] Another randomized, double-blind, double dummy trial compared Sustol/Emend/dexamethasone to ondansetron IV/Emend/dexamethasone in patients receiving highly emetogenic chemotherapy. Dexamethasone was also given on days 2-4 at standard doses. The Sustol group was superior for prevention of delayed n/v (24 to 120h after chemotherapy was given; complete response 65% vs 57%; p=0.014). However, a major

limitation of this study is that Sustol has a longer half-life than ondansetron (24h vs 3-6h) so coverage in the delayed phase was different between groups and explains the superior effect of Sustol for prevention of n/v in the delayed phase.[2]

References:

1. Raftopoulos H et al. Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, noninferiority phase 3 trial. Support Care Cancer. 2015 Mar;23(3):723-32. PMID 25179689
2. Schnadig ID et al. APF530 (granisetron injection extended-release) in a three-drug regimen for delayed CINV in highly emetogenic chemotherapy. Future Oncol. 2016;12(12):1469-1481. PMID 26997579
3. Sustol monograph. LexiComp. Accessed 5/23/19

Revision History:

Date	What changed	Pharmacist's initials
5/20/19	Criteria written	sk
6/15/2020	Criteria reviewed. No changes.	sk

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Granisetron transdermal patch (Sancuso®)

34.4 mg/patch (one patch delivers 3.1 mg/24 hours)

EBRx PA Criteria

FDA-approved for:

Prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days.

Criteria for new users
1. Must have a documented cancer diagnosis
2. Must be receiving a moderately or highly emetogenic chemotherapy regimen
3. Must have previous failure of an oral 5HT antagonist given daily on a scheduled basis OR palonosetron given 30-60 minutes prior to chemotherapy [CHART DOCUMENTATION REQUIRED]
If above criteria met, approve for 1 year
QL: 5 patches per 30 days
Dose: -Each patch contains 34.4 mg of granisetron which delivers 3.1 mg per 24 hours. -Apply a single patch to the upper outer arm a minimum of 24 hours before chemotherapy. The patch may be applied up to a maximum of 48 hours before chemotherapy as appropriate. Remove the patch a minimum of 24 hours after completion of chemotherapy. -The patch can be worn for up to 7 days depending on the duration of chemotherapy. Evidence: A randomized, double-blind, double-dummy study compared granisetron patch to oral granisetron (given daily) in patients receiving multi-day chemotherapy (highly or moderately emetogenic) found the patch to be non-inferior to oral granisetron for prevention of *acute* chemotherapy-induced nausea and vomiting (CINV).[1] Another trial compared granisetron patch to palonosetron in patients receiving moderately emetogenic chemotherapy and found the patch to be non-inferior to palonosetron for prevention of *acute* CINV.[2]

References:

1. Boccia RV et al. cacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, phase III study. Support Care Cancer. 2011 Oct;19(10):1609-17. PMID 20835873
2. Seol YM et al. Transdermal granisetron versus palonosetron for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: a multicenter, randomized, open-label, cross-over, active-controlled, and phase IV study. Support Care Cancer. 2016 Feb;24(2):945-952. PMID 26265119

Revision History:

Date	What changed	Pharmacist's initials
5/20/19	Criteria written	SK
11/25/19	Added requirement for chart documentation of failure of oral 5HT antagonist and/or palonosetron	SK
3/29/2021	Criteria reviewed. No changes	SK

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Recombinant Human Growth Hormone (Somatropin®)

EBRx PA criteria

Gray indicates it is NOT A COVERED USE.

Genotropin, Nutropin, Humatrope, Norditropin, Omnitrope, Serostim, Saizen, Tev-Tropin, Zorbitive

Indication	Drug
Pediatric: Growth failure due to inadequate endogenous growth hormone (GH)secretion □ age < 18 □ short stature (height less than -2.25 SD for age based on sex specific standards) □ must confirm GH deficiency with provocative GH stimulation test □ must have open epiphyses (confirm with x-ray of a long bone) ***Approve if patient meets above criteria*** *If pt is >18 yrs, please see adult criteria below	□Genotropin □ Humatrope □ Norditropin □Nutropin □Omnitrope □Saizen □Tev-Tropin
Pediatric: Short stature associated with Turner syndrome *Not a covered benefit. Treatment in one trial increased final height by approximately six cm over an untreated control group. Despite this increase, the final height of treated women was still outside the normal range*	□ Genotropin □ Humatrope □ Norditropin □Nutropin □Omnitrope
Pediatric: Growth failure in children born small for gestational age who fail to manifest catch-up growth by either 2 years of age(a) or by 2-4 years of age (b) *Not a covered benefit. These children are not GHD and treatment with GH is likely to yield only modest gains in height. Adult height will usually be below average despite therapy.*	□ Genotropin (a) □ Humatrope (b) □ Norditropin (b) □ Omnitrope (a)
Pediatric: Idiopathic Short Stature (ISS) *Not a covered benefit. These children are not GHD and when health related quality of life was studies, no significant improvement was found in GH treated children, nor was there any evidence that GH treatment impacts psychological adaptation or self-perception.*	□ Genotropin □ Humatrope □ Nutropin □ Omnitrope

Results suggest that short-term height gains can range from none to approximately 0.7 SD over one year.	
Pediatric: Growth failure due to chronic renal insufficiency up to time of renal transplant *Not a covered benefit. GH treatment increased height in children with CKD by about 4 cm after 1 year and by a further 2 cm after 2 years of treatment compared with no treatment. Studies were too short to determine if continuing treatment resulted in an increase in final adult height.*	□ Nutropin
Pediatric: Growth failure due to Prader Willi syndrome □ Open epiphyses o Confirm with x-ray of long bone upon initiation of therapy o If 18-25 yrs, must have yearly x-ray to verify open epiphyses as epiphyses usually close around this time □ Diagnosis of Prader Willi syndrome from DNA testing □ must NOT have h/o severe respiratory impairment or upper airway obstruction □ must NOT have sleep apnea □ must Not be severely obese (>225% IBW) Initial Approval: 1 year Reauthorization: Pt must continue to meet above criteria	□ Genotropin □ Omnitrope
Pediatric: Short stature or growth failure associated with short stature homeobox gene (SHOX) deficiency *Not a covered benefit. While RCT have shown significant increase in height over 2 years with GH treatment vs placebo[7], there are no good studies demonstrating if normal adult height is achieved.*	□ Humatrope
Pediatric: Short stature associated with Noonan syndrome Not a covered benefit. While a clinical trial showed an initial increase in height standard deviation score, the accelerating effect of GH on bone maturation seemed to compromise the final height prognosis	□ Norditropin
Adult: GH deficiency of either childhood or adult onset etiology	□Genotropin

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Childhood etiology 1. <u>Open epiphyses</u> (usually close between 18-25 yrs) o Confirmed GH deficiency o X-ray of long bone shows open epiphyses (pts must have yearly x-ray to confirm epiphyses still open during this time) Initial Approval: 1 year Reauthorization: must continue to provide evidence of open epiphyses 2. <u>Closed epiphyses</u> □ must confirm GH deficiency with provocative GH stimulation test [A child's GH stim test would need to be <10ng/mL to represent deficiency.] □ If a transition patient (receiving GH when <18), pt must have been off GH at least one month before GH test to determine if true GHD persists □ Must score ≥ 11 on "Quality of Life Assessment of Growth Hormone Deficiency in Adults" questionnaire during GH-free period Initial Approval: 1 year Reauthorization: Score on "Quality of Life Assessment of Growth Hormone Deficiency in Adults" questionnaire must have increased by ≥ 7 points. ***Adult onset*** 1. <u>Idiopathic:</u> o Must confirm GH deficiency with TWO provocative GH stimulation tests because idiopathic GHD in adults is very rare [A positive GHD stim test would be <5ng/mL.] 2. <u>Acquired:</u>	□ Humatrope □ Norditropin □Nutropin □Omnitrope □Saizen

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○ If pt has a diagnosis of structural hypothalamic/pituitary disease, surgery or irradiation to pituitary, or head trauma then only one provocative GH stimulation test is necessary. A GH stim test would need to be <5ng/mL to be positive; also a panhypopituitary patient would have other drugs representative of panhypopituitaryism.] Initial Approval: 1 year Reauthorization: Score on "Quality of Life Assessment of Growth Hormone Deficiency in Adults" questionnaire must have increased by ≥ 7 points.	
Adult: Short Bowel Syndrome □ Must be receiving parenteral nutrition and have an optimized diet □ Must be receiving glutamine concurrently Initial Approval: 3 months Reauthorization: tx must have resulted in the elimination of 1 or more days of TPN infusion	□ Zorbtive
Adult: HIV with wasting or cachexia with concomitant antiretroviral therapy □ Must be receiving concurrent HAART therapy □ ≥10% unintentional weight loss or low BMI (<20kg/m^2) or body weight <90% of IBW □ Exclude if fasting blood glucose >121 mg/dL , malignancy, or active AIDS-defining opportunistic infection Initial Approval: 3 months Reauthorization: pt must have ≥ 3kg weight gain or increased exercise capacity	□Serostim

GH (somatropin) will not be approved for the following uses:

1. Kids: Idiopathic short stature (nonGH deficient short stature)
2. Enhancement of athletic performance
3. Ageing or age-related conditions

DENY if any of the following:

- Active malignancy OR malignancy in the past year
- Age > 65 yrs

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4. Down's Syndrome
5. Fanconi's syndrome
6. Bloom syndrome

Pediatric: GH deficiency

- Short stature is defined by height SD score < -2.25, and associated with growth rates unlikely to permit attainment of adult height in normal range
- Hypothalamus secretes GH-releasing hormone (GHRH), which stimulates the pituitary to secrete GH. Somatostatin is secreted by the hypothalamus to inhibit GH secretion. When GH pulses are secreted into the blood, then insulinlike growth factor (IGF)-1 is released. GHD may result from disruption of the GH axis at numerous places—in the higher brain, the hypothalamus, or the pituitary gland.
- Therapy should be discontinued when patient has reached satisfactory adult height, when epiphyses have fused, or when patient ceases to respond.
- Catch-up growth for children treated early is excellent, with a normal final height attained.[11]
- A final height of 30cm can be expected on average, but this is affected by variables such as birthweight, age at start of treatment, extent of deficiency, duration of treatment, frequency of GH injections, height at start of treatment, and height at the start of puberty. [11]

Pediatric: Turner Syndrome (TS)

- TS is the cause of short stature in girls and primary amenorrhea in young women that is usually caused by loss of part or all of an X chromosome GH is initiated once height is below the 5th percentile for age, which usually occurs between 2-5 yrs.
- Treatment with GH is stopped once epiphyseal fusion occurs, satisfactory height is obtained, or little potential for growth remains (bone age ≥14 yr and growth velocity <2cm/year)[12]
- Short stature seen in TS is caused by SHOX gene haploinsufficiency, leading most children to have an avg adult stature 20cm shorter than their target height[12]
- Girls with TS generally have normal GH levels [12]
- "Recombinant human growth hormone (hGH) doses between 0.3 to 0.375 mg/kg/wk increase short-term growth in girls with Turner syndrome by approximately three

(two) cm in the first (second) year of treatment. Treatment in one trial increased final height by approximately six cm over an untreated control group. Despite this increase, the final height of treated women was still outside the normal range. Additional trials of the effects of hGH carried out with control groups until final height is achieved would allow better informed decisions about whether the benefits of hGH treatment outweigh the requirement of treatment over several years at considerable cost." –Cochrane Review[2]

Pediatric: Small for Gestational Age

- The mechanism underlying postnatal growth failure in children who fail to catch up in growth by age 2 is poorly understood, but an irreversible deficit in cell number, inadequate calorie intake during the first years of life, and abnormalities in GH secretion have been hypothesized. Classic GH deficiency is rarely found.
- Most children catch up in growth during the first 6-12 months in life. If they have not caught up by age 2, they are unlikely to do so later.
- Growth hormone treatment is likely to yield only modest gains in height compared with no treatment (an increase in adult height of approximately 6 cm, provided the treatment is begun early and continued for at least seven years). Adult height will usually be below average despite therapy.

Pediatric: Growth failure due to CRI up to time of renal transplant

- Growth retardation is a common problem in children with chronic kidney disease (CKD) and is due to abnormalities in the GH-IGF axis.
- "This review of 16 studies enrolling 809 children found that rhGH increased height in children with CKD by about 4 cm after 1 year and by a further 2 cm after 2 years of treatment compared with no treatment. Studies were too short to determine if continuing treatment resulted in an increase in final adult height." – Cochrane Review

Pediatric: Prader-Willi Syndrome (PWS)

- genetic disorder characterized by excessive appetite, severe hypotonia, emotional problems and delays in development
- Most patients have hypothalamic-pituitary dysfunction, with abnormal growth hormone secretion and hypogonadotrophic hypogonadism.[4]

- Treatment with GH is associated with a significant decrease in fat% and improved HDL/LDL ratio in prepubertal children.
    - From randomized control trial measuring surrogate endpoints (no clinical outcomes) in 85 infants and prepubertal children (6mo-3yrs) of GH vs. placebo[13]
        - Decline in fat % ($p<0.001$)during 24 months of study
        - Improved HDL/LDL ratio ($p=0.04$)
        - No significant changes seen in BP or fasting glucose
- Treatment with GH prevents deterioration of certain cognitive skills
    - From randomized controlled trial of 50 prepubertal children (3.5-14yrs) of GH vs. placebo[14]
        - Baseline tests of vocabulary, similarity, and block design measured for both groups and found to be similar
        - While there was no significant change (increase or decrease) in cognitive function for the GH treated group, the placebo group had a decrease in cognitive functioning on the similarities ($p=0.04$) and vocabulary tests ($p=0.03$) at 2 years
        - After two years, all participants received GH and all subjects analyzed again after 4 years, at which time there was a significant cognitive improvement in similarities ($p=0.01$) and block design ($p=0.03$) tests compared to baseline scores.
    - Per AACE guidelines[1], "GH results in appreciable acceleration of growth, decrease in fat mass, increase in lean body mass, and increase in the ratio of lean to fat tissue. Some studies report an improvement in physical activity and agility. The data show substantial improvement in near final adults height after GH treatment"

Pediatric: Short stature or growth failure associated with short stature homeobox gene (SHOX) deficiency

- "The SHOX gene encodes a transcription factor responsible for a significant proportion of long-bone growth. Patients with mutations or deletions of SHOX (including those with TS) have variable degrees of GH impairment.

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- While RCT have shown significant increase in height over 2 years with GH treatment vs placebo[7], there are no good studies demonstrating if normal adult height is achieved.

- mutations in the SHOX gene are responsible for up to 4 percent of cases of apparent "idiopathic" short stature

Pediatric: Pediatric: Short stature associated with Noonan syndrome

- relatively common autosomal dominant disorder that causes GH resistance

- Noonan syndrome (NS) is characterized by short stature, typical facial dysmorphology and congenital heart defects

- While there are a few clinical trials that show increase in height, only one had a placebo group. This trial found that while there was an initial increase in height standard deviation score, the accelerating effect of GH on bone maturation seemed to compromise the final height prognosis. [15]

Pediatric: Idiopathic Short Stature

- "Results suggest that short-term height gains can range from none to approximately 0.7 SD over one year. One study reported health related quality of life and showed no significant improvement in GH treated children compared with those in the control group, whist another found no significant evidence that GH treatment impacts psychological adaptation or self-perception in children with ISS." -- Cochrane Review[5]

Adult: GH deficiency of either childhood or adult onset etiology

- "Idiopathic GHD in adults is very rare, and stringent criteria are necessary to make this diagnosis. Because in the absence of suggestive clinical circumstances there is a significant false-positive error rate in the response to a single GH stimulation test, we suggest the use of two tests before making this diagnosis." Endocrine Society Clinical Practice guideline 2011

- Larger doses of somatropin may be required for women taking oral estrogen replacement

- Adults with GHD may have reduced lean body mass, increased fat mass, decreased bone mass, reduced physical and cardiac performance, and an abnormal lipid profile. [11]

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- Short term (4 month) improvements have been seen in lean body mass, exercise capacity, and muscle strength. In some studies, QoL measures (energy, mood, physical mobility) improved with treatment. [11]

- The NICE Guidelines require adults to have an impaired QoL due to the GHD. This is judged using the "Quality of Life Assessment of Growth Hormone Deficiency in Adults" questionnaire. A person should score at least 11 to initiate treated and be evaluate after 9 months. If the score has not improved by 7 points, therapy should be discontinued.

Adult: Short Bowel Syndrome

- Short bowel syndrome is a malabsorption disorder caused by the surgical removal of the small intestine, or by the complete dysfunction of a large segment of bowel

- The rational for treating short bowel patients with human recombinant growth hormone and/or glutamine is the hope of reducing parenteral nutrition dependency

- Studies have shown that GH with or without glutamine appears to increase weight, lean body mass, energy absorption, and nitrogen absorption, however, the benefits of treatment don't continue after treatment is stopped. [16]

- One RCT looked at the effect of GH on parenteral nutrition requirements[8]

    - Prospective, double-blind, randomized, placebo controlled trial of 41 adults randomized to either: GH + glutamine placebo, GH placebo + glutamine, or GH +glutamine . All pts had dietary optimization.

    - only patients taking human growth hormone with glutamine maintained statistically significant parenteral nutrition reductions at 3 month follow-up ($p<0.005$)

    - GH + glutamine + diet reduced and maintained average PN infustion time to only 1-2 x per week over the course of the study (down from previous schedule of 5-6 days/week)

- A study by Rovera et al. has demonstrated that the single most important factor to enhance quality of life in PN-dependent patients is the elimination of 1 or more days required for nutrient infusion[17]

Adult : HIV with wasting or cachexia with concomitant antiretroviral therapy

- Wasting is defined as a ≥10% involuntary weight loss. It is designated an AIDS-defining condition and an independent predictor of mortality.

- Treatment options include nutritional advice, exercise, testosterone (for men, although low doses have been studied in women), appetite-stimulating drugs, and growth hormone

- A meta-analysis of 18 studies concluded that GH may have advantages over testosterone and anabolic steroids in terms of improvements in functional capacity and QOL.[18]

    - Work output was reported in 2 studies

        - Improvement of 0.97KJ at 12 weeks vs. improvement of 0.20KJ in the placebo group (p=0.039)

        - Median improvement of 2.60KJ at 12 weeks vs. median decrease of 0.25KJ in placebo grp (p<0.01)

    - QOL was reported in 3 studies

        - Using BACRI scale, GH treatment group reported significant increase in QOL at week 12 (p=0.029 for QOD dosing and 0.039 for QD dosing)

        - Using HIV-PARSE in another study, no significant difference was found in QOL

In the 3rd study, 4 treatment groups were compared (GH + IGF, GH alone, IGF alone, or placebo) The MOS-HIV scale detected a significant increase in total QOL at 12 weeks in the GH group alone p=0.02). This study also found a significant correclation between change in LBM and change in QOL (p=0.003).

Testing overview:

growth hormone stimulation tests

insulin tolerance test

growth hormone releasing hormone (GHRH)-arginine test

GHRH plus GH-releasing peptide-6 (GHRP-6) test

glucagon stimulation test

insulin-like growth factor I

Blood tests:

growth hormone (GH) stimulation tests

Endocrine Society (ES) recommendations in adults

- consider using 2 GH stimulation tests due to significant false-positive error rate of test

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- insulin tolerance test (ITT) and growth hormone releasing hormone (GHRH)-arginine test have sufficient sensitivity and specificity to establish diagnosis (ES Grade 1++++)
    - ITT
        - considered "gold standard"
        - use caution in patients with seizure disorders or cardiovascular disease
        - careful monitoring required in all patients
    - GHRH-arginine testing
        - may show false-normal GH response in patients with clearly established, recent (within 10 years) hypothalamic causes of suspected growth hormone deficiency (GHD) (such as irradiation of hypothalamic-pituitary region)
        - GHRH unavailable in United States
- glucagon stimulation test can be used when GHRH is not available and ITT is contraindicated or not practical (ES Grade 2++)
    - monitor GH for ≥ 3 hours due to delayed release
    - monitor for delayed hypoglycemia due to secondary stimulation of endogenous insulin release
    - obesity may blunt GH response
- growth hormone stimulation tests optional if deficiencies in ≥ 3 pituitary axes (ES Grade 1+++)
    - this situation strongly suggests GHD
    - presence of ≥ 3 other pituitary hormone deficiencies with low serum insulin-like growth factor I level may be as specific as any GH stimulation test
    - some insurers may require results of GH stimulation test
- Reference - J Clin Endocrinol Metab 2011 Jun;96(6):1587

--Dyna Med

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Revision History:

Date	Changes	Pharmacist
7/5/2012	Document Created	CK
7/30/12	Document updated to include committee agreement and shows gray that indicates not covered.	JJ
2-28-2017	I ungrayed part of the document regarding adults and kids with closed epiphyses. They will need to have GH stimulation tests to confirm their diagnoses.	JJ

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Antihemophilic factor (RECOMB Porc) RPF VIII

for injection 500 units (Factor 8)

EBRx PA Criteria

is FDA-approved for: the treatment of bleeding episodes in adults with acquired hemophilia A.

NOTE: NOT indicated for treatment of congenital hemophilia A or von Willebrand disease.

Criteria	
1. The patient must have bleeding.	☐Yes ☐No
2. The patient must have the diagnosis of ACQUIRED hemophilia A.	☐Yes ☐No

Revision History:

Date	What changed	Pharmacist's initials
2/26/15	I wrote the criteria.	JJ

Factors for Hemophilia—Currently all the factors are covered per EBRx as long as they have the correct diagnosis for the drug they are trying to access. This is the only criteria for now.

Brand	Indication		Dosing	Supplied As (units)	Unit Cost	Vial Cost
Factor IX Human						
AlphaNine SD	*Hemophilia B (congenital factor IX def or Christmas dz)		15 to 30 units/kg/dose twice weekly* 25 to 40 units/kg/dose twice weekly* 40 to 100 units/kg/dose 2 to 3 times weekly*	500 1000 1500	$1.58 $1.58 $1.58	$790 $1,580 $2,370

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Mononine	*hemophilia B (congenital factor IX def or Christmas dz)		15 to 30 units/kg/dose twice weekly* 25 to 40 units/kg/dose twice weekly* 40 to 100 units/kg/dose 2 to 3 times weekly*	250 500 1000	$1.20 $1.20 $1.52	$300 $600 $1,520
Factor IX Recombinant						
BeneFIX	* hemophilia B (congenital factor IX def or Christmas dz); ^hemophilia B			250 500 1000 2000	$1.64 $1.64 $1.64 $1.64	$410 $820 $1,640 $3,280
Ixinity	* hemophilia B (congenital factor IX def or Christmas dz); ^hemophilia B			500 1000 1500	$1.78 $1.78 $1.78	$890 $1,780 $267
Rixubis	#hemophilia B		40 to 60 (80 in children) units/kg twice weekly; may titrate dose depending upon age, bleeding pattern, and physical activity			
Factor IX Recombinant factor IX-Fc fusion						
Alprolix (fusion of factor IX to a monomeric human immunoglobulin Fc domain (rFIXFc); t 1/2 =54-90h	#hemophilia B		50 units/kg once weekly or 100 units/kg once every 10 days; adjust dose based on individual response	500 1000 2000 3000	$3.42 $3.42 $3.42 $3.42	$1,710 $3,420 $6,840 $10,260
Factor IX Recombinant, Albumin Fusion Protein—for Hemophilia B (congenital factor IX def); t1/2=102h						
Idelvion	*^#hemophilia B		25 to 40 (55 in children) units/kg once every 7 days; if well controlled may switch to 50 to 75 units/kg once every 14 days.	250 500 1000 2000	$5.10 $5.10 $5.10 $5.10	$1,275 $2,550 $5,100 $10,20

						0
Factor IX DNA Recombinant, Pegylated; t ½=85h single dose, 110h after multiple QW doses.						
Rebinyn-- FOR IV INFUSION ONLY	*^Hemophilia B		On-demand treatment: 40-80 IU/kg Perioperative prophylaxis: 40 IU/kg single dose, 80 IU/kg, then 40 IU/kg prn perioperatively in 1-3d intervals.	500 1000 2000	$4.80 $4.80 $4.80	$2400 $4800 $9600
Factor VIII and Von Willebrand Factor						
Alphanate	*hemophilia A (factor VIII def)		15 to 30 units/kg/dose twice weekly (Peds) 25 to 40 units/kg/dose twice weekly (Peds) 40 to 100 units/kg/dose 2 to 3 times weekly (Peds)	250 500 1000 1500 2000	$1.38 $1.38 $1.38 $1.38 $1.38	
Humate-P	*hemophilia A			250/600 500/1200 1000/2400	1.40 1.40	
Wilate	*von Willebrand disease			500-500 1000-1000	1.56 1.56	
Factor VIII (Recombinant)						
Advate	*^# hemophilia A		20 to 40 units/kg every other day (3 to 4 times weekly). Alternatively, an every-third-day dosing regimen may be used to target factor VIII trough levels of ≥1%	250 500 1000 2000 3000 4000	$1.82 $1.82 $1.82 $1.82 $1.82 $1.82	$455 $910 $1,820 $3,640 $5,460 $7,280
Afstyla Kit	*^# hemophilia A		20-50 IU/kg 2 to 3 times weekly	250 500 1000	1.98 1.98 1.98	$495 $990 $1980

				1500 2000 2500 3000	1.98 1.98 1.98 1.98	$2970 $3960 $4950 $5940
Helixate	*^# hemophilia A; also to reduce risk of joint damage in children w/o preexisting joint damage		25 units/kg 3 times weekly	250 500 1000 2000 3000	$1.76 $1.76 $1.76 $1.56 $1.76	$440 $880 $1,760 $3,120 $5,280
Kogenate	*^# hemophilia A; also to reduce risk of joint damage in children w/o preexisting joint damage		25 units/kg 3 times weekly	250 500 1000 2000 3000	$1.75 $1.75 $1.75 $1.75 $1.75	$438 $875 $1,750 $3,500 $5,250
Kovaltry	*^# hemophilia A		20 to 40 units/kg 2 or 3 times weekly			
Novoeight	*^# hemophilia A		20 to 50 units/kg 3 times weekly or 20 to 40 units/kg every other day	250 500 1000 1500 2000 3000	$1.98 $1.98 $1.98 $1.98 $1.98 $1.98	$495 $990 $1,980 $2,970 $3,960 $5,940
Nuwiq	*^# hemophilia A		30 to 40 units/kg every other day	250 500 1000 2000	$2.03 $2.03 $2.03 $2.03	$508 $1,015 $2,030 $4,060
Recombinate	*^# hemophilia A			220-400 401-800 801-1240	1.82	

				1241-1800 1801-2400		
Xyntha*	*^# hemophilia A		Treatment experienced patients: 25 to 35 units/kg 3 times weekly	250 500 1000 2000	$1.82 $1.82 $1.82 $1.82	$455 $910 $1,820 $3,640
Longer lasting products						
Eloctate (see below) Recombinant; Fc fusion						
Afstyla Recombinant; single chain						
Adynovate Recombinant' PEGylated						
Esperoct Recombinant, glycoPEGylated						
Antihemophilic Factors (Recombinant [Fc Fusion Protein])						
Eloctate (long acting)	*^# hemophilia A; not for VW disease		50 units/kg every 4 days; may adjust within the range of 25 to 65 units/kg at 3- to 5-day intervals based on patient response	250 500 750 1000 1500 2000 3000	$2.38 $2.38 $2.38 $2.38 $2.38 $2.38 $2.38	$595 $1,190 $1,785 $2,380 $3,570 $4,760 $7,140
Von Willebrand						
Vonvendi	* von Willebrand disease		Initial: 40 to 80 units/kg Subsequent: 40 to 60 units/kg every 8-24 hours	650 1300	$2.38	$1547 $3094

DEFINITIONS — Hemophilia typically refers to an inherited bleeding disorder caused by deficiency of coagulation factor VIII (hemophilia A), factor IX (hemophilia B or Christmas disease), or factor XI (hemophilia C or Rosenthal syndrome).

●**Acquired factor deficiencies** – Acquired coagulation factor deficiencies caused by an autoantibody (often to factor VIII) are sometimes referred to as acquired hemophilia. The terms "acquired factor inhibitor" or "acquired factor deficiency" are preferable to avoid potential mislabeling the patient as having hemophilia A or B. Management of these conditions is discussed separately. (See "Acquired inhibitors of coagulation".)

●**Inhibitors** – In hemophilia, inhibitor refers to an autoantibody that typically forms in response to infused factor. Inhibitors are most common in individuals with very low baseline factor levels. (See "Factor VIII and factor IX inhibitors in patients with hemophilia".)

●**Severity** – Hemophilia is characterized as mild, moderate, or severe, based on the residual or baseline factor activity level (also referred to as "factor level"); this is expressed as a percent of normal or in international units (IU)/mL [1]. Factor levels typically correlate with the degree of bleeding symptoms [2,3].

•**Severe hemophilia** – Severe hemophilia is defined as <1 percent factor activity, which corresponds to <0.01 IU/mL.

•**Moderate hemophilia** – Moderate hemophilia is defined as a factor activity level ≥1 percent of normal and <5 percent of normal, corresponding to ≥0.01 and <0.05 IU/mL.

•**Mild hemophilia** – Mild hemophilia is defined as a factor activity level ≥5 percent of normal and <40 percent of normal (≥0.05 and <0.40 IU/mL).

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EBRx Hepatitis C Coverage Policy

AASLD HCV Treatment Guidelines SUMMARY

Jill Johnson, Pharm.D.

10/20/16, 9/22/17TW, 1/30/18JJ, 4/7/2021JJ

At this time (4/7/21):

UAS covers Epclusa, Vosevi, generic sofosbuvir/velpatasvir, ledipasvir/sofosbuvir

EBD covers Mavyret, Zepatier, generic sofosbuvir/velpatasvir

A. For any treatment to eradicate chronic hepatitis C virus (HCV)infection, the following criteria must be met regardless of which regimen is requested:

1. The patient must test positive for chronic HCV infection. Two options: • HCV antibody ≥6m before a positive HCV RNA (viral load), OR • 2 HCV RNA levels 6 months apart ☐The viral load must be documented._____ ☐The genotype and subtype must be documented._____	The diagnosis of CHRONIC HCV must be made. 15-25% seroconvert on their own and the patient clears the infection. We only treat chronic HCV infection.
2. The patient must be free of using illicit drugs for the past 6 months. ☐A patient-signed statement attesting to this is acceptable.	Any positive drug screen for injectable drug use during treatment stops access to the HCV drugs. Reinfection is a risk for IV drug users.
3. The patient must be free of abusing ethanol for the past 6 months. (defined as >3 glasses/d (1 glass is equivalent to beer 284 mL, wine 125 mL, or distilled spirits 25 mL for females and >4 glasses/d for males). ☐A patient-signed statement attesting to this is acceptable.	
4. If the patient has cirrhosis, there must be NO signs of decompensation (ascites, episodes of spontaneous bacterial peritonitis, hepatic encephalopathy,), unless the patient is currently listed for liver transplant. ☐The drug profile for the past 1 year must be submitted.	Unless currently LISTED on the liver transplant list. Patients with decompensation will not be treated unless currently listed on a verifiable list

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	from a liver transplant center.
5. The patient with liver disease due to any cause other than HCV infection (chronic hepatitis B infection, autoimmune hepatitis, alcoholic hepatitis, hemochromatosis, Wilson's disease, alpha 1 antitrypsin deficiency,) should be referred to a gastroenterologist.	
6. The extent of fibrosis may be shown by liver biopsy, FIB-4, APRI, Fibroscan (transient elastography), or Fibrotest to demonstrate the patient has a Metavir score of F3 or F4.	
7. Patients with extrahepatic manifestations of chronic HCV infection are candidates for therapy regardless of corresponding Metavir score as long as they meet the other requirements above.	
8. If the patient was provided HCV eradication therapy and abandoned therapy, they are not eligible for a 2nd course of treatment. If the patient completed but relapsed or had intolerance to the 1st course of therapy, then they would be eligible for subsequent treatment depending on what is requested and the clinical evidence. ☐A review of the drug profile for fills provided in the past for HCV eradication drug therapy. Further explanation by the patient/physician may be required.	

B. Other questions which must be collected on EVERY patient seeking drug therapy for HCV infection:

1. Is the patient currently on the liver transplant list? (Decompensated, metavir F4 patients are eligible for treatment, absent contraindications listed in #5 above.)	
2. Has the patient previously received any treatment for HCV infection? If so, what regimen and duration? ☐This info must be captured even if drug was supplied by the manufacturer.	This answer is needed to determine treatment eligibility.
3. HIV positive patients must have absolute CD4 counts above 500 and not require HAART therapy or currently receive HAART therapy if the absolute CD4 count is below 200, to be eligible for HCV eradication treatment. ☐If HIV positive, the absolute CD4 count must be submitted from the past 6 months.	

C. Likelihood of progressing without treatment

The premise for the policies below is multifactorial.

First, chronic HCV is a progressive disease that takes decades to develop cirrhosis or hepatocellular carcinoma and only 20% develop cirrhosis over 20-30 years and 5% die from cirrhosis or liver cancer. Second, achieving a sustained viral response 12 or 24 weeks after the end of drug

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therapy (SVR12 or SVR24) is not a cure. SVR is a surrogate marker for the actual outcome of liver morbidity or mortality (including decompensated liver cirrhosis, hepatocellular carcinoma, liver transplantation, or death from liver related causes). Thus the objective is not how many patients develop SVRs but how many are spared from ESLD. None of the drug trials evaluated these outcomes. All the studies linking SVR to clinical outcomes are observational studies and are subject to confounding. Additionally, patients who achieve SVR remain at risk for developing HCC, although the risk is lower than if SVR had not been achieved. To date (2/10/15), all data showing a decrease in liver morbidity or mortality included interferon + ribavirin in the HCV eradication therapy. There are no data to show a non-interferon containing regimen for HCV eradication reduces liver-related morbidity or mortality. However, the available observational studies with interferon show achieving an SVR24 correlates to improved quality of life and reduction in fatigue, and approximately an 80% decrease in decompensated liver disease, HCC, liver transplant, and all-cause mortality. It appears that some risk for HCC remains, even in those achieving SVR.

Condition	Number of individuals
Infection with hepatitis C	100
Develop symptoms	20-30
Remain asymptomatic	70-80
Develop chronic infection	75-85
Develop chronic liver disease	60-70
Develop cirrhosis over 20-30 years	5-20
Die from cirrhosis or liver cancer	1-5

Drugs for HCV

Brand	Components	Common dose	FDA Approval
Zepatier	Elbasvir 50mg/grazoprevir 100mg	1 tablet QD	**CONTRAINDICATED CHILD-PUGH B OR C** **Treatment with or w/o Riba for GT 1 or 4 in adults**
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	1 tablet QD	**NO DOSE ADJ FOR ANY CHILD-PUGH ABC** **Treatment with or w/o Riba for chronic HCV GT 1, 4, 5, or 6 infection**
Viekira Pak (company's	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg, + BID	2 tabs QD plus	**CONTRAINDICATED CHILD PUGH B OR C** **Treatment of chronic HCV in adults,**

website has only XR info)	dasabuvir 250mg and wt-based Riba	dasabuvir 1 BID (comes in a pack)	• **GT 1b w/o cirrhosis or w/ compensated cirrhosis, or** • **GT 1a w/o cirrhosis or w/ compensated cirrhosis for use in combo w/Riba**
Viekira XR 24hour	Ombitasvir 8.33mg/paritaprevir 50mg/ ritonavir 33.33 mg/ dasabuvir 200mg	3 tabs QD X 12w	**CONTRAINDICATED CHILD PUGH B OR C**
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	1 tablet QD	**NO DOSE ADJ FOR ANY CHILD-PUGH ABC** **Treatment of chronic HCV in adults, GT 1,2,3,4,5, or 6 w/o cirrhosis or w/ compensated cirrhosis or in combo w/ RBV in patients w/ decompensated cirrhosis**
Technivie	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg + wt-based Riba	2 tablets QD	**CONTRAINDICATED CHILD PUGH B OR C** **Treatment of chronic HCV, GT4 without cirrhosis**
Mavyret	Glecaprevir 100 mg/pibrentasvir 40 mg	3 tablets QD	**CONTRAINDICATED IN CHILD-PUGH B OR C** **Tx of chronic HCV in adults w/ GT 1,2,3,4,5, or 6 w/ no cirrhosis or compensated cirrhosis Child-Pugh A. Also pts w/ GT1 previously tx w/ NS5A inhibitor or an NS3/4A protease inhibitor, but not both.**
Vosevi	Sofosbuvir 400 mg, velpatasvir 100 mg, voxilaprevir 100 mg	1 tablet QD	**USE NOT REC IN CHILD PUGH B OR C** **Adult pt w/ Chronic HCV w/o cirrhosis or w/ compensated cirrhosis GT 1-6. Only approved for GT1-6 AND HCV tx exp w/ NS5A inhibitor or GT1a or 3 tx exp w/ SOF w/o an NS5A inhibitor.**

Combinations Available for tx of moderate or greater levels of cirrhosis: Harvoni, Sovaldi, Epclusa

Combinations available for pts tx experienced with NS5A inhibitors: Vosevi, Mavyret

Tx for pts tx experienced with NS3/4A PI: Epclusa, Vosevi, Mavyret (select patients)

INITIAL THERAPY

PM=polymorphism, TN=treatment naïve, SVR=sustained viral response, RAV=resistant-associated variant

	Daily Drug Combination	Duration (w)	Notes
	GT1a, TN, NO Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class I, A
Mavyret	Glecaprevir 300mg/pibrentasvir 120 mg	8	Class I, A

Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg (HIV-uninfected, whose HCV RNA is <6mil IU/mL	8	Class I, B
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	GT1a, TN, COMPENSATED Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg, for patients w/o baseline NS5A RASs for elbasvir	12	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	8	Class I,B
	GT1b, TN, NO Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class I, A;
Mavyret	Glecaprevir 300mg/pibrentasvir 120 mg	8	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg for patients who are HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8	Class 1, B
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	GT1b, TN, COMPENSATED Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	8	Class I, B
	GT2, TN, NO Cirrhosis		
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8	Class I, A

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	GT2, TN, COMPENSATED Cirrhosis		
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	8	Class I, B

Brand drug	Daily Drug Combination	Duration (w)	Notes
	GT3, TN, NO Cirrhosis		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	GT3, TN, COMPENSATED Cirrhosis		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	8	Class I, B
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg, for patients w/o baseline NS5A RAS Y93H for velpatasvir	12	Class I, A
	ALTERNATIVES		
Epclusa+ribavirin	Sofosbuvir 400mg/velpatasvir 100mg + weight-based ribavirin for patients w/ baseline NS5A RAS Y93H for velpatasvir	12	IIa,A
Vosevi	Sofosbuvir 400mg/velpatasvir 100mg/voxilaprevir 100mg when Y93H is present	12	Class IIa, B
	GT4 TN, NO Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	GT4, TN, COMPENSATED Cirrhosis		
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	8	Class I, B
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class IIa, B

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Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class II, B
	GT 5 or 6 with and without Cirrhosis		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class IIa, B

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TREATMENT-EXPERIENCED

	Daily Drug Combination	Duration (w)	Notes
	Sofosbuvir-based treatment failures, with or w/o compensated cirrhosis		
Vosevi	Sofosbuvir 400mg/velpatasvir 100mg/voxilaprevir 100mg (for GT3 add wt-based ribavirin if cirrhosis is present)	12	Class I, A
	ALTERNATIVES		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg , except for NS3/4 protease inhibitor inclusive combination DAA regimen failures NOT recommended for GT3 infection w/ sofosbuvir/NS5A inhibitor experience	16	Class I, A
	Glecaprevir/Pibrentasvir Treatment Failures (All Genotypes), with or w/o compensated cirrhosis		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg + sofosbuvir 400mg + wt-based ribavirin	16	Class IIa, B
Vosevi	Sofosbuvir 400mg/velpatasvir 100mg/voxilaprevir 100mg	12	Class IIa, B
	For patients with compensated cirrhosis, addition of wt-based ribavirin is recommended	12	Class IIa, C
	Multiple DAA treatment failures (All Genotypes), including Sofosbuvir/Velpatasvir/Voxilaprevir OR Sofosbuvir + Gelcaprevir/Pibrentasvir		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg + Sofosbuvir 400mg + wt-based ribavirin	16	Class IIa, B
Vosevi	Sofosbuvir 400mg/velpatasvir 100mg/voxilaprevir 100mg + wt-based ribavirin	24	Class IIa, B

DECOMPENSATED CIRRHOSIS: (Patients who have decompensated cirrhosis are NOT COVERED UNLESS ON THE LIVER TRANSPLANT LIST due to unclear, clinically meaningful improvements in health.) [See AASLD guidelines accessed 4/7/2021.]

Clinical trial data demonstrate that in the population of persons with decompensated cirrhosis, most patients receiving direct-acting antiviral (DAA) therapy experience improvement in clinical and biochemical indicators of liver disease between baseline and post-treatment week 12, including patients with CTP

class C cirrhosis (Manns, 2016); (Welzel, 2016); (Charlton, 2015); (Curry, 2015). Improvements, however, may be insufficient to avoid liver-related death or the need for liver transplantation (Belli, 2016), highlighting that not everyone benefits from DAA therapy (Fernandez-Carrillo, 2016). Most deaths among those receiving DAA therapy relate to the severity of underlying liver disease. Predictors of improvement or decline have not been clearly identified, although patients with a Model for End-Stage Liver Disease (MELD) score >20 or severe portal hypertension complications may be less likely to improve and might be better served by transplantation than antiviral treatment (El-Sherif, 2018); (Terrault, 2017); (Belli, 2016).

Real-world data comparing DAA response rates demonstrate that patients with cirrhosis and hepatocellular carcinoma (HCC) have lower SVR rates than cirrhotics without HCC (Beste, 2017); (Prenner, 2017). In a large VA study including sofosbuvir, ledipasvir/sofosbuvir, and paritaprevir/ritonavir/ombitasvir plus dasabuvir regimens (± ribavirin), overall SVR rates were 91% in patients without HCC versus 74% in those with HCC (Beste, 2017). After adjusting for confounders, the presence of HCC was associated with a lower likelihood of SVR (AOR=0.38). Whether this lower SVR can be overcome with an extended duration of therapy is unknown.

In a more recent large, multicenter, real-world cohort of 642 patients with advanced cirrhosis (defined as cirrhosis and MELD score ≥10) treated with a variety of DAA regimens, the overall SVR12 rate was 90.5%. Age <60, male sex, ascites, albumin level <3.5 mg/dl, hepatocellular carcinoma, proton-pump inhibitor use, MELD score <16 and CTP class B/C were significantly associated with decreased odds of SVR12. In long-term follow up, at a median of 4 years after the end of treatment, a clinically meaningful decrease in MELD score of ≥3 occurred in 29% and a final MELD score of <10 was achieved in 25%. These data highlight that a proportion of patients with advanced cirrhosis who receive DAA therapy may not achieve significant long-term improvement in liver function (Verna, 2020).

Combinations Available for tx of moderate or greater levels of cirrhosis: Daklinza, Harvoni, Sovaldi, Epclusa,

Combinations available for pts tx experienced with NS5A inhibitors: Vosevi, Mavyret

Tx for pts tx experienced with NS3/4A PI: Epclusa, Vosevi, Mavyret (select patients)

INITIAL THERAPY

PM=polymorphism, TN=treatment naïve, SVR=sustained viral response, RAV=resistant-associated variant,

	Daily Drug Combination	Duration (w)	Notes
	GT1a, TN, NO Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class I, A
Mavyret	Glecaprevir 300mg/pibrentasvir 120 mg	8	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg (for non-black, HIV-uninfected, whose HCV RNA is <6mil IU/mL	8	Class I, B
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	ALTERNATIVE		
Zepatier	Elbasvir 50mg/grazoprevir 100mg plus wt-based ribavirin	16	Class IIa, B, RAV+
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg, PLUS BID dasabuvir 250mg and wt-based Riba	12	Class I, A
Olysio+Sovaldi	Simeprevir 150mg/sofosbuvir 400mg	12	Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg/ sofosbuvir 400mg	12	Class I, B
	GT1a, TN, COMPENSATED Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class I, A; RAV-
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	12	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A

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Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	ALTERNATIVE		
Zepatier	Elbasvir 50mg/grazoprevir 100mg PLUS wt-based ribavirin	16	Class IIa, B; RAV+
	GT1b, TN, NO Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class I, A;
Mavyret	Glecaprevir 300mg/pibrentasvir 120 mg	8	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg for patients who are non-black, HIV uninfected, and whose HCV RNA level is <6 million IU/mL	8	Class 1, B
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	ALTERNATIVEs		
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ ombitasvir 25mg, PLUS BID dasabuvir 250mg	12	Class I, A
Olysio+Sovaldi	Simeprevir 150mg PLUS sofosbuvir 400mg	12	Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg	12	Class I, A
	GT1b, TN, COMPENSATED Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	12	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A

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Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	ALTERNATIVE		
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ ombitasvir 25mg, PLUS BID dasabuvir 250mg	12	Class I, A
	GT2, TN, NO Cirrhosis		
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8	Class I, A
	ALTERNATIVE		
Daklinza+Sovaldi	Daclatasvir 60mg/sofosuvir 400mg	12	Class IIa, B
	GT2, TN, COMPENSATED Cirrhosis		
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	12	Class I, B
	ALTERNATIVE		
Daklinza + Sovaldi	Daclatasvir 60mg + sofosbuvir 400mg	16-24	Class IIa, B

	Daily Drug Combination	Duration (w)	Notes
	GT3, TN, NO Cirrhosis		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A

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	ALTERNATIVE		
Daklinza+Sovaldi	Daclatasvir 60mg + sofosbuvir 400mg	12	Class I, A
	GT3, TN, COMPENSATED Cirrhosis		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	12	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	ALTERNATIVES		
Vosevi	Sofosbuvir 400mg/velpatasvir 100mg/voxilaprevir (100mg when Y93H is present	12	Class IIa, B
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg w/ or w/o wt-based riba	24	Class IIa, B
	GT4 TN, NO Cirrhosis		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class IIa, B
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class IIa, B
	ALTERNATIVES		
Technivie	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg, PLUS wt-based Riba	12	Class I, A
	GT4, TN, COMPENSATED Cirrhosis		
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A

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Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	12	CLASS I, B
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class IIa, B
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A
	ALTERNATIVE		
Technivie	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg, PLUS wt-based Riba	12	Class I, A
	GT 5 or 6 with and without Cirrhosis		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8: no cirrhosis 12: w/ cirrhosis only Child-Pugh A	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class IIa, B

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TREATMENT-EXPERIENCED

	Daily Drug Combination	Duration (w)	Notes
	GT1a, PEG-IFN/Ribavirin TE, NO Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	ALTERNATIVES		
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg, PLUS BID dasabuvir 250mg and wt-based Riba	12	Class I, A
Olysio+Sovaldi	Simeprevir 150mg/sofosbuvir 400mg	12	Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg/ sofosbuvir 400mg	12	Class I, B
Zepatier+Ribavirin	Elbasvir 50mg/grazoprevir 100mg + wt-based riba if baseline NS5A RASs for elbasvir	16	Class IIa, B
	GT1a, PEG-IFN/Ribavirin TE, COMPENSATED Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg, without baseline NS5A RASs for elbasvir	12	Class I, A

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Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	12	Class I, B
	ALTERNATIVES		
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg PLUS wt-based Riba	12	Class I, A
Zepatier+Ribavirin	Elbasvir 50mg/grazoprevir 100mg + wt-based ribavirin with baseline NS5A RASs for elbasvir	16	Class I, B
	GT1b, PEG-IFN/Ribavirin TE, NO Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8	Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	ALTERNATIVES		
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ ombitasvir 25mg, + BID dasabuvir 250mg	12	Class I, A
Olysio+Sovaldi	Simeprevir 150mg PLUS sofosbuvir 400mg	12	Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg	12	Class I, B
	GT1b, PEG-IFN/Ribavirin TE, COMPENSATED Cirrhosis		
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	12	Class I, B

	ALTERNATIVES		
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg + Wt-based ribavirin	12	Class I, A
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ ombitasvir 25mg, +BID dasabuvir 250mg	12	Class I, A
	GT1, PI-experienced (telaprevir, boceprevir, simeprevir) + Peginterferon/Riba-experienced, NO cirrhosis		
Harvoni	Ledipasvir 90mg/sofosbuvir 400mg	12	Class I, A
Epclusa	Sofosbuvir 400mg/ velpatasvir 100mg	12	Class I, A
Mavyret	Glecaprevir 300mg/pibrentasvir 120mg	12	Class IIa, B
	ALTERNATIVES		
Zepatier+Ribavirin	Elbasvir 50mg/grazoprevir 100mg + Wt-based riba for all GT 1b and 1a patients without baseline NS5A RASs for elbasvir	12	Class IIa, B
Zepatier+Ribavirin	Elbasvir 50mg/grazoprevir 100mg + Wt-based riba for GT 1a with baseline NS5A RASs for elbasvir	16	Class IIa, B
	GT1, PI-experienced (telaprevir, boceprevir, simeprevir) + Peginterferon/Riba-experienced, WITH COMPENSATED cirrhosis		
Epclusa	Sofosbuvir 400mg/ velpatasvir 100mg	12	Class I, A
Mavyret	Glecaprevir 300mg/pibrentasvir 120mg	12	Class IIa, B
	ALTERNATIVES		
Harvoni+Ribavirin	Ledipasvir 90mg/sofosbuvir 400mg + wt-based ribavirin	12	CLASS I, A
Zepatier+Ribavirin	Elbasvir 50mg/grazoprevir 100mg + Wt-based riba for all GT 1b and 1a patients without baseline NS5A RASs for elbasvir	12	Class IIa, B

Zepatier+Ribavirin	Elbasvir 50mg/grazoprevir 100mg + Wt-based riba for GT 1a with baseline NS5A RASs for elbasvir	16	Class IIa, B
	GT1, Non-NS5A inhibitor, Sofosbuvir-containing regimen-experienced, WITHOUT cirrhosis		
Vosevi	Sofosbuvir 400mg/velpatasvir 100mg/ voxilaprevir 100mg for GT 1a only	12	Class IA
Mavyret	Glecaprevir 300mg/pibrentasvir 120mg	12	Class IIa, B
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg for GT 1b only	12	Class IIa, B
	ALTERNATIVEs		
Harvoni+ribavirin	Ledipasvir 90mg/sofosbuvir 400mg + Wt-based ribavirin, except simeprevir failures	12	Class IIa, B
	GT1, Non-NS5A inhibitor, Sofosbuvir-containing regimen-experienced, WITH COMPENSATED cirrhosis		
Vosevi	Sofosbuvir 400mg/velpatasvir 100mg/ voxilaprevir 100mg for GT 1a only	12	Class IA
Mavyret	Glecaprevir 300mg/pibrentasvir 120mg	12	Class IIa, B
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg for GT 1b only	12	Class IIa, B
	GT1, NS5A inhibitor DAA-experienced, WITH OR WITHOUT COMPENSATED cirrhosis		
Vosevi	Sofosbuvir 400mg/velpatasvir 100mg/ voxilaprevir 100mg for GT 1a only	12	Class IA
	ALTERNATIVE		
Mavyret	Glecaprevir 300mg/pibrentasvir 120mg except NS3/4 protease inhibitor inclusive DAA combo regimens	16	Class IIa, B

	GT2 PEG-IFN/Ribavirin TE without Cirrhosis		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8	Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A
	ALTERNATIVE		
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg	12	Class IIa, B
	GT2 PEG-IFN/Ribavirin TE; COMPENSATED Cirrhosis		
Epclusa	Sofosbuvir 400mg/velpatasvir 10mg	12	Class I, A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	12	Class I, B
	ALTERNATIVE		
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg	16-24	Class IIa, B
	GT2 Sofosbuvir PLUS Riba TE (regardless of cirrhosis status)		
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg w/ wt-based riba	12	Class I, B
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg. (tx duration for no cirrhosis or Child-Pugh A cirrhosis)	12	Class IIb, B
	GT3 PEG-IFN/Ribavirin TE without Cirrhosis		
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A

	ALTERNATIVES		
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg	12	Class I ,A
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	16	Class IIa, B
Vosevi	Sofosbuvir 400mg/velpatasvir 100mg/ voxilaprevir 100mg when Y93H is present	12	Class IIb, B
	GT3 PEG-IFN/Ribavirin TE; COMPENSATED Cirrhosis		
Zepatier+Sovaldi	Elbasvir 50mg/grazoprevir 100mg + sofosbuvir 400mg	12	Class I, B
Vosevi	Sofosbuvir 400mg/ velpatasvir 100mg/ voxilaprevir 100mg	12	Class IIb, B
	ALTERNATIVEs		
Epclusa+ Ribavirin	Sofosbuvir 400mg/velpatasvir 10mg + Wt based ribavirin	12	Class I, B
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child-Pugh A)	16	Class IIa, B
	GT3 , DAA-experienced (including NS5A inhibitors), (regardless of cirrhosis status)		
Vosevi	Sofosbuvir 400mg/ velpatasvir 100mg,/ voxilaprevir 100mg	12	Class I, A
	If CIRRHOSIS, and prior NS5A inhibitor failure, Wt-based ribavirin is recommended	12	Class IIa, C
	GT4 PEG-IFN/Ribavirin TE without Cirrhosis		
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, A

Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg	8	Class I, B
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class IIa, B
Harvoni	Ledipasvir 90mg/sofosbuvir 400mg	12	Class IIa, B
	ALTERNATIVES		
ViekiraPak + Riba	Paritaprevir 150mg/ritonavir 100mg/ ombitasvir 25mg + Wt-based ribavirin	12	Class I, A
Zepatier + Riba	Elbasvir 50mg/ grazoprevir 100mg + Wt-based ribavirin (for pts w/ prior on-treatment virologic failure while on Peg/riba	16	Class IIa, B
	GT4 PEG-IFN/Ribavirin TE; COMPENSATED Cirrhosis		
Epclusa	Sofosbuvir 400mg/velpatasvir 10mg	12	Class I, A
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12	Class IIa, B; for virologic relapse after prior PEG-IFN/riba. GT4 with prior on-treatment virologic failure while on PegIFN/Riba should have 16w and have ribavirin added.
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg (Child Pugh A)	12	Class IIa, B
	ALTERNATIVE		
Technivie	Paritaprevir 150mg/ritonavir 100mg/ombitasvir 25mg + wt-based Ribavirin	12	Class I, A
Zepatier	Elbasvir 50mg/grazoprevir 100mg	16	GT4 with prior on-treatment virologic failure while on PegIFN/Riba should have 16w and have ribavirin added.
Harvoni	Ledipasivr 90mg/sofosbuvir 400mg + Wt-based ribavirin	12	Class IIa, B

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	GT4, DAA (includingNS5A inhibitor-TE (regardless of cirrhosis status)		
Vosevi	sofosbuvir, velpatasvir, voxilaprevir	12	Class I, A
	GT5 or 6 PEG-IFN/Ribavirin TE (regardless of cirrhosis status)		
Mavyret	Glecaprevir 300 mg/pibrentasvir 120 mg no cirrhosis/compensated cirrhosis Child-Pugh A	8/12	Class IIa, B
Harvoni	Ledipasvir 90mg/sofosbuvir 400mg	12	Class IIa, B
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12	Class I, B
	GT5 or 6, TE with DAA (including NS5A inhibitors) (regardless of cirrhosis status)		
Vosevi	sofosbuvir, velpatasvir, voxilaprevir	12	Class IIa, B

DECOMPENSATED CIRRHOSIS: (NOT COVERED UNLESS ON THE LIVER TRANSPLANT LIST) [See below from 9/2017 AASLD guidelines.]

Clinical trial data demonstrate that in the population of persons with decompensated cirrhosis, most patients receiving direct-acting antiviral (DAA) therapy experience improvement in clinical and biochemical indicators of liver disease between baseline and post-treatment week 12, including patients with CTP class C cirrhosis (Manns, 2016); (Curry, 2015); (Charlton, 2015); (Welzel, 2016). However, improvements may be insufficient to avoid liver-related death or the need for liver transplantation (Belli, 2016), highlighting that not everyone benefits from DAA therapy (Fernandez-Carrillo, 2016). Most deaths among those receiving DAA therapy relate to the severity of underlying liver disease. The predictors of improvement or decline have not been clearly identified, though patients with a Model for End-Stage Liver Disease (MELD) score >20 or severe portal hypertension complications may be less likely to improve and might be better served by transplantation than treatment (Terrault, 2017); (Belli, 2016).

Real-world data comparing DAA response rates demonstrate that patients with cirrhosis and hepatocellular carcinoma (HCC) have lower SVR rates than cirrhotics without HCC (Prenner, 2017); (Beste, 2017). In a large VA study including sofosbuvir, ledipasvir/sofosbuvir, and paritaprevir/ritonavir/ombitasvir plus dasabuvir regimens (with and without ribavirin), overall SVR rates were 91% in patients without HCC vs 74% in those with HCC (Beste, 2017). After adjusting for confounders, the presence of HCC was associated with a lower likelihood of SVR (AOR=0.38). Whether this lower rate of SVR can be overcome with an extended duration of therapy is unknown.

Hydroxyprogesterone Caproate

IM in oil 1.25g/5mL (250mg/mL)

EBRx PA Criteria

FDA-approved for:

1. Preterm birth; to reduce the risk of preterm birth in women with a singleton pregnancy and who have a history of singleton spontaneous preterm birth. Use is not intended for women with multiple gestations or other risk factors for preterm birth.

2. in non-pregnant women: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV);

3. in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer;

4. as a test for endogenous estrogen production and for the production of secretory endometrium and desquamation.

Criteria for new users seeking hydroxyprogesterone caproate IM in oil for prevention of preterm birth
1. Patient must be pregnant with a singleton pregnancy
2. Patient must have a history of singleton spontaneous preterm birth
NOTE: Dose is 250mg once weekly for 22 weeks beginning at 16 weeks, 0 days and lasting until 37 weeks gestation or until delivery, whichever comes first.

Criteria for non-pregnant women for the treatment of advanced adenocarcinoma of the uterine corpus, State III or IV
1. Patient must be non-pregnant and have the diagnosis of advanced stage III or IV adenocarcinoma of the uterine corpus.
NOTE: The dose is 1g or more (1-7g/week), stopped when relapse occurs or after 12 weeks with no objective response.

Criteria for amenorrhea and/or abnormal uterine bleeding
1. Patient must be premenopausal and have amenorrhea and/or abnormal uterine bleeding cyclically.

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NOTE: The dose is 375mg IM once monthly for a maximum of 4 cycles.

Quantity Limits:

Revision History:

Date	What changed	Pharmacist's initials
12/14/2016	I wrote the criteria. I omitted the last FDA approval due to this use will not likely go through the pharmacy benefit and would likely occur in the hospital or a doctor's office.	JJ

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Ibrutinib (Imbruvica®)

70, 140mg capsules

140, 280, 420, 560 mg tablets

EBRx PA Criteria

FDA-approved for:

- Treatment of adults with mantle cell lymphoma (MCL) who have received at least 1 prior therapy (accelerated approval)
- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
- Treatment of CLL/SLL patients with 17p deletion.
- Treatment of Waldenstrom macroglobulinemia
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy (accelerated approval)—**NOT A COVERED USE FOR EBRX** Data is limited to single arm trial only
- Chronic graft versus host disease after failure of one or more lines of systemic therapy

CLL or SLL: Criteria for new users
1. Diagnosis of CLL or SLL
2. Presence of indication for treatment [including but not limited to the following: symptomatic disease (fatigue, night sweats, weight loss, fever without infection), threatened end-organ function, progressive bulky disease (spleen >6 cm below costal margin or lymph nodes >10 cm), progressive anemia or thrombocytopenia, symptomatic splenomegaly, rapidly increasing lymphocyte count]
3. At the initial request, the patient must be ECOG performance status 0-2.
4. Patient should not have been previously treated with a BTK inhibitor (e.g. acalabrutinib, ibrutinib, zanubrutinib)
If above criteria are fulfilled, approve x 1 year Dose: 420 mg daily QL: • 3/1 for capsules or 1/1 tablets • If dose is reduced to 140 mg or 280 mg daily, prefer capsules due to cost

Note:

IN FIRST LINE SETTING, ibrutinib improved overall survival compared with chlorambucil in older patients (≥65y) with CLL (2-year OS: 98% with ibrutinib and 85% with chlorambucil; HR 0.16 95% CI, 0.05-0.56; p=0.001). Another study compared ibrutinib + rituximab to fludarabine-based therapy in younger patients and found an improvement in OS (HR 0.168, 95% CI 0.053-0.538; p=0.0003) with few grade 3/4 adverse events in the ibrutinib+rituximab arm. A third study compared ibrutinib to ibrutinib+rituximab and ibrutinib+rituximab+bendamustine in older patients and found similar overall OS for each arm with conclusion that ibrutinib monotherapy is as good as ibrutinib plus rituximab and ibrutinib+rituximab+bendamustine.[1,2,3]

IN PREVIOUSLY TREATED PATIENTS, ibrutinib improved overall survival compared with ofatumumab (12-month OS: 90% vs 81%; HR 0.43; 95% CI 0.24-0.79; p=0.005)[4]. Ibrutinib + bendamustine + rituximab also has been shown to improve OS compared with bendamustine+rituximab.[5]

Dose: 420 mg once daily until progression of disease

REFERENCES:

1. Burger, Jan A., et al. "Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia." *NEJM* 373.25 (2015): 2425-2437.

2. ASH abstract 132 (2018). A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912). http://www.bloodjournal.org/content/132/Suppl_1/LBA-4. (Accessed 3/27/19) NCT02048813

3. Woyach JA et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. NEJM 2018;379(26):2517-2528. NCT01886872 PMID 30501481

4. Byrd, John C., et al. "Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia." *NEJM* 371.3 (2014): 213-223.

5. Fraser G et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. Leukemia. 2018 Oct 12. doi: 10.1038/s41375-018-0276-9. [Epub ahead of print] NCT00611090 PMID 30315239

Mantle Cell Lymphoma
3. Diagnosis of relapsed or refractory mantle cell lymphoma
4. At least one prior rituximab-containing regimen
5. Ibrutinib will be used as single agent

If above criteria are fulfilled, approve x 1 year

Dose: 560 mg daily

QL:

- Do not allow use of capsules (4 x 120 mg) due to significant increase in AWP compared to 1 of the 560 mg tablets.
- If dose reduced to 420 mg daily, tablets or capsules may be used
- If dose is reduced to 140 mg or 280 mg daily, prefer capsules due to cost

Evidence:

Ibrutinib vs temsirolimus in relapsed/refractory mantle cell lymphoma:[1,2,3]

-Ibrutinib improved several QOL parameter compared to temsirolimus as follows.

-Clinically significant increase in FACT-Lymphoma subscale in 62% of ibrutinib patients

(versus 36% in temsirolimus arm)

-Clinically significant increase in FACT-Lymphoma Total score in 66% of ibrutinib patients (versus 48% in temsirolimus arm)

-Time to worsening of FACT-Lymphoma subscale: median not reached for ibrutinib group vs 9.7 mo in temsirolimus group; p<0.0001)

-There was a trend to improved median OS in ibrutinib arm: 30 mo (ibrutinib) vs 23 mo (temsirolimus) (HR 0.74 [95% CI 0.54–1.02]; P = 0.0621)—32% pf temsirolimus patients received subsequent ibrutinib after progression of disease which may have affected results.

Dose: 560 mg once daily until disease progression

Reference:

1. Dreyling M et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet. 2016 Feb 20;387(10020):770-8. doi: 10.1016/S0140-6736(15)00667-4. Epub 2015 Dec 7. PMID 26673811
2. Rule S et al. Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study. Leukemia. 2018 Aug;32(8):1799-1803. doi: 10.1038/s41375-018-0023-2. Epub 2018 Feb 2. PMID 29572505
3. Hess G et al. Health-related quality of life data from a phase 3, international, randomized, open-label, multicenter study in patients with previously treated mantle cell lymphoma treated with ibrutinib versus temsirolimus. Leuk Lymphoma. 2017 Dec;58(12):2824-2832. doi: 10.1080/10428194.2017.1326034. Epub 2017 May 30. PMID 28556689

GVHD: Criteria for new users

1. Must have a diagnosis of CHRONIC graft versus host disease (GVHD) after allogeneic hematopoietic cell transplant

2. Patient had inadequate response to previous treatment of CHRONIC GVHD which included a corticosteroid, a calcineurin inhibitor (cyclosporine or tacrolimus), and one other systemic therapy (options include but are not limited to the following: rituximab, mycophenolate, sirolimus, methotrexate, hydroxychloroquine, imatinib, bortezomib, extracorporeal photopheresis, PUVA photochemotherapy).

If above criteria are fulfilled, approve x 1 year

Dose: 420 mg daily

QL:

- 3/1 for capsules or 30/30 tablets
- If dose is reduced to 140 mg or 280 mg daily, prefer capsules due to cost

Evidence:

Ibrutinib was studied in a single arm trial including patients who had received 1-3 prior therapies for chronic GVHD (cGVHD). Overall response rate was 67% including a 27% complete response rate. Of all responders, 71% maintained response for >20 weeks. Steroid dose in responders was decreased by at least half on average.[1] Response was defined per 2014 NIH response criteria which is based mostly on symptom grading.[2]

References:
1. Miklos D et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood. 2017 Nov 23;130(21):2243-2250. PMID 28924018 NCT02195869
2. Lee SJ et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. Biol Blood Marrow Transplant. 2015 Jun;21(6):984-99. PMID 25796139

Waldenstrom Macroglobulinemia

1. Diagnosis of Waldenstrom macroglobulinemia
2. Indication for treatment (neuropathy, hyperviscosity, organomegaly, amyloidosis, cold agglutinin disease, cryogloblinemia, cytopenias, bulky adenopathy)
3. Ibrutinib will be used in combination with rituximab

If above criteria are fulfilled, approve x 1 year

Dose: 420 mg daily

QL:

- 3/1 for capsules or 30/30 tablets
- If dose is reduced to 140 mg or 280 mg daily, prefer capsules due to cost

Evidence:

Ibrutinib given with rituximab was superior to rituximab alone for progression free survival (30-month PFS: 82% vs 28%). Overall survival was not statistically superior (94% vs 92%), but may have been confounded due to 40% of control patients crossing over to receive ibrutinib. Other benefits included less IgM flare (8% vs 47%), less IgM flare requiring plasmapheresis (0% vs 16%), more improvement of anemia (73% vs 41%), and trends toward improvement in quality of life.

Dose: 420 mg once daily until disease progression

Reference:
1. Dimopoulos MA et al. Phase 3 Trial of Ibrutinib plus Rituximab in Waldenstrom's Macroglobulinemia. N Engl J Med 2018; 378:2399-2410.

Revision History:

Date	What Changed?	Pharmacist's initials

6/10/14	JJ created PA criteria	JJ
10/8/14	JJ changed the ECOG to allow 0 to 2 as per a search looking for all ibrutinib clinical trials in CLL. There were no patients less medically fit than 2s included in the trials. They were excluded. Added a reference.	JJ
3/9/15	JJ added the note after searching PubMed and finding no clinical trials. The PI for Imbruvica has one trial in WM patients that was single armed (no comparisons) and measured the numbers of pts who achieved complete and partial responses.	JJ
6/8/16	I changed the PA criteria to allow 1st line therapy after DCWG 5/24/16. Added references 4-6.	JJ
3/29/2017	I rewrote the criteria.	JJ
8/30/17	I added reference 8. I also added the criteria for the indication for GVHD.	JJ
3/13/18	I deleted the criteria to be “treatment naïve” or “have received ONLY 1 prior therapy” because after reviewing the baseline characteristics of the trial comparing ibrutinib vs ofatumumab in previously treated CLL, over 50% had received >3 prior lines of therapy.	JJohnson
12/14/18	I added the other dosage strengths 70, 280, 420, 560mg.	JJohnson
1/24/19	Updated CLL/SLL criteria; added requirement that for first line treatment, pt must NOT be a candidate for purine-based treatment. Added that previous acalabrutinib is not allowed.	ALM, SK
1/31/19	For CLL/SLL criteria, added that first line treatment is also appropriate for patients with deletion 17p. These patients do not respond well to chemotherapy.	Sk
5/20/19	Criteria reviewed: revised chronic GVHD criteria, simplified CLL criteria based on new data. Added criteria for waldenstrom Macroglobulinemia (new indication)	Sk
11/25/19	Criteria reviewed. Added criteria for mantle cell lymphoma.	Sk
8/21/2020	Criteria reviewed. No change	SK
4/2/21	Applied EBRx criteria to UAS Plan.	JJ
8/19/21	Updated with new capsule/tablet preferences per 8/19/2021 EBRx P&T meeting	SK
10/27/2021	Criteria reviewed. No change	SK

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Icosapent (Vascepa®)

EBRx PA Criteria

FDA-approved for:

Vascepa is an ethyl ester of eicosapentaenoic acid (EPA) indicated:

- as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. Limitations of Use: •The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined. NOT COVERED
- As an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adults with elevated triglyceride levels (>150mg/dL) and
    - Established cardiovascular disease or
    - T2DM + 2 or more additional CV disease risk factors.

Criteria for new users
1. Patient must be ≥45 years old with established cardiovascular disease (coronary artery disease, cerebrovascular or carotid disease, peripheral artery disease) **OR** Patient must be ≥50 years old and with diabetes mellitus (requiring drug treatment) **plus** at least one of these additional risk factors: • Men ≥age 55 or women ≥65 • Hypertension (BP ≥140 mmHg systolic OR ≥90mmHg diastolic), or on antihypertensive medication • HDL-C ≤40mg/dL for men or ≤50mg/dL for women • Hs-CRP>3 mg/L • Renal dysfunction: Creatinine clearance >30 and <60mL/min • Retinopathy, defined as any: non-proliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation; • Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test, an albumin /creatinine ratio ≥2.5 mg/mmol or an albumin excretion r ate on timed collection ≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as albustix or other dipstick evidence of gross proteinuria, an albumin/creatinine ratio ≥25 mg/mmol or an albumin excretion rate on timed collection ≥200 mg/min all on at least two successive occasions;
2. Patient must have a fasting triglyceride level of 200 to 499 mg/dL.
3. Patient must have a LDL cholesterol level of 41 to 100mg/dL.
4. Patient must be receiving a stable dose of a statin (with or without ezetimibe) for at least 4 weeks
Note: Vascepa comes in 0.5g and 1g capsules. The dose is 2g BID with meals.

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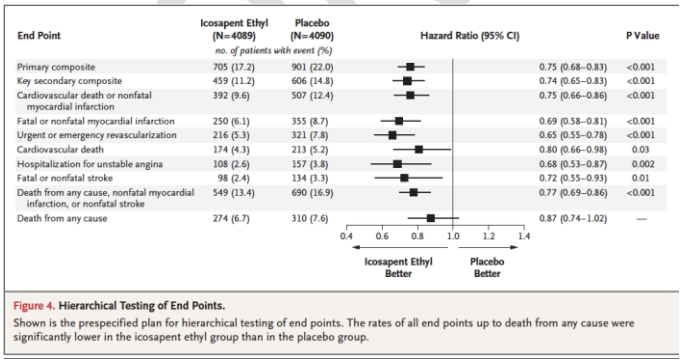
Quantity Limits: For 1g capsules: 120/30d, for 0.5g capsules: 240/30d. The 1g capsules should be used if at all possible due to dose optimization (the 0.5g capsules are more expensive for making a 4g dose than the 1g capsules.)

Revision History:

Date	What changed	Pharmacist's initials
1/15/19	I wrote the criteria.	JJ
4/22/21	Dr. JO called to ask about the data supporting reduction in pancreatitis with Vascepa. My search did not reveal any supporting trials. I then searched FDA and found this: "11. Labeling a disclaimer is included in the labeling that points out the lack of evidence that treatment with Vascepa reduces the risk for pancreatitis in patients with severe hypertriglyceridemia. Given the relative rarity of hypertriglyceridemia-induced pancreatitis, the Division has never required an applicant to demonstrate a statistically significant reduction in the incidence of pancreatitis before granting approval of a TG-lowering drug for the treatment of severe hypertriglyceridemia." The FDA evidently is not going to require that drugs must show this clinical endpoint as long as they include a disclaimer in their package insert. I also provided the reference (#2.). I also updated the FDA-approval to be current and ref #3. To date UAS does not PA this drug.	JJ

References:

1. Bhatt, Deepak L., et al. "Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia." *New England Journal of Medicine* 380.1 (2019): 11-22.



End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—

Figure 4. Hierarchical Testing of End Points.
Shown is the prespecified plan for hierarchical testing of end points. The rates of all end points up to death from any cause were significantly lower in the icosapent ethyl group than in the placebo group.

2. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202057Orig1s000SumR.pdf See page 8 of 9.

3. Vascepa PI. Accessed 4/22/21. file:///Users/johnsonjillt/Downloads/20200723_9c1a2828-1583-4414-ab22-a60480e8e508.pdf

Idelalisib (Zydelig®)

100mg & 150mg tablets

EBRx PA Criteria

FDA approved for:

- Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies. NOT COVERED Data is limited to single arm, non-comparative trial (reference: Gopal AK et al. N Engl J Med 2014;370:1008-18. PMID 24450858)
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies

Criteria
1. The patient must have the diagnosis of relapsed chronic lymphocytic (CLL) or relapsed small lymphocytic leukemia (SLL).
2. Idelalisib will be given concurrently with rituximab
If above criteria are met, approve x 12 months

Dosing for relapsed CLL or SL is 150mg BID until disease progression or unacceptable toxicity.

Idelalisib+rituximab improved overall survival compared to rituximab alone in patients with relapsed CLL. OS at 12 months was 92% vs 80%, HR for death was 0.28; p=0.02. Serious AEs occurred in 40% of idelalisib+rituximab vs 35% in ritux+placebo.

References:

1. Furman RR, Sharman JP, Coutre SE, Cheson BD, et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2014;370:997-1007. PMID 24450857 NCT01539512
2. NCCN guidelines for CLL. http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf Accessed 6/25/19.

Quantity Limits: 60/30d per fill.

Revision History:

Date	What changed	Pharmacist's initials
2/20/15	I wrote the criteria.	JJ
3/1/16	AM and I re-looked at the data for follicular lymphoma. For idelalisib in follicular non-Hodkins lymphoma, to date (3/1/16), there are no comparative data to show idelalisib is superior to any other drug. The National Comprehensive Cancer Network (NCCN) has not established a standard of care nor do the existing trials inform this decision. NCCN suggests clinical trial, local radiation therapy, or bendamustine+rituximab (category 1), or RCHOP, or RCVP, all as category 1 regimens but may not have progression free survival or overall survival superiority data to support their use either. The one single arm trial published in 2014 was the last clinical trial published for idelalisib. The FDA approved the drug under accelerated approval. The manufacturer's package insert also does not include further data to inform the comparative efficacy question. References: 1. http://zydelig.com/include/media/pdf/full-prescribing-information.pdf Accessed 3/1/16. 2. NCCN.org. Non-Hodkin's Lymphoma. Accessed 3/1/16. http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf 3. Gopal AK, Kahl BS, et al. PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma. N Engl J Med 2014;370:1008-18.	JJ
7/18/19	Criteria reviewed. Require use of idelalisib with rituximab. No other significant changes	Sk
1/29/2020	Criteira reviewed. No change.	SK

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Iloprost (Ventavis®)

solution for Inhalation

10 mcg/mL (1mL), 20 mcg/mL (1mL)

EBRx PA Criteria

Ventavis is FDA-approved for: treatment of PAH (WHO Group I) in patients with NYHA class III or IV symptoms to improve exercise tolerance, symptoms, and diminish clinical deterioration.

Criteria	
1. The patient must have the diagnosis of pulmonary artery hypertension (Group 1), WHO functional class IV AND either still be symptomatic despite taking a PDE5 inhibitor (sildenafil),	☐Yes ☐No
OR	
2. The patient must have the diagnosis of PAH Group 5 after treating underlying causes.	☐Yes ☐No

Dosing is 2.5mcg/dose; increase to 5mcg/dose. Administer 6-9 times daily (dosing at intervals >2h while awake according to need and tolerability. Max dose is 45 mcg (5mcg/dose 9 times daily). Not studied in renal impairment. For hepatic impairment, consider changing dosing interval to every 3-4 hours.

Revision History:

Date	What changed	Pharmacist's initials
2/6/15	I wrote the criteria.	JJ

Addendum:

Diagnostic Criteria and WHO categorization of PH						
	All Groups	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 5**
Description	**Elevated PAP**	**Pulmonary arterial hypertension**	**Pulmonary venous hypertension**	**PH due to hypoxemia**	**Chronic thromboembolic PH**	**Miscellaneous or multifactorial PH**

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Estimated prevalence	**Up to 10-20% of the general population**	**15 cases/1,000,000 overall; 6 cases per 1mil for idiopathic PAH**	**>3-4 mil in US**	**20% in COPD pts w/ a prior hospitalization for COPD**	**0.5-2% (up to 3.8%) in survivors of acute PE**	**Unclear**
Diagnostic criteria						
Mean PA pressure, mmHg	**≥25**	**≥25**	**≥25**	**≥25**	**≥25**	**≥25**
PCWP or LVEDP, mmHg		**≤15**	**>15**	**≤15**	**≤15**	**≤15**
PVR, dynes/s/cm		>240		>240	>240	>240

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Imiglucerase (Cerezyme®)

EBRx PA Criteria

Imiglucerase is FDA-approved for: Long term enzyme replacement therapy for patients with type 1 Gaucher disease that results in at least one of the following; anemia, bone disease, hepatomegaly or splenomegaly, and thrombocytopenia

Criteria for new users
1. Patient must have the diagnosis of type 1 Gaucher disease diagnosed by mutation analysis. (**The patient must lack central nervous system involvement**. This is what distinguishes type 1 from types 2 & 3.)
2. The patient must be symptomatic (anemia, bone disease, hepatomegaly, splenomegaly, or thrombocytopenia)
3. The patient is not receiving concurrent substrate-reduciton therapy (eliglustat or miglustat).
If all the criteria are satisfied, the PA is valid for 12 months.

Note: Dose is 30-60 IU/kg q2weeks. Long term outcomes with ERT with imiglucerase at two centers using low-dose (median dose 15-30 U/gh q4w) and high-dose (median dose 80 u/kg q4w) were compared retrospectively. Improvement in hemoglobin, platelet count, and hepatosplenomegaly was not significantly different between cohorts.

For nonneuronopathic (GD1), all the ERTs are approximately equivalent in efficacy. Response to treatment varies from patient to patient, but analysis of data from the Caucher Registry and GD treatment centers demonstrates certain trends for imiglucerase and alglucerase in GD1 disease.

The alternative therpay is substrate-reduction therapy (SRT) (i.e eliglustat, miglustat). Eliglustat is approved for a broader use than miglustat. Miglustat is restricted to adults with GD who are medically unable to receive ERT. Eliglustat was non inferior to imiglucerase for the composite endpoint of decreased hematologic measurements (Hb and plt count) and increased organ volume (spleen and liver)

Quantity Limits: Dose of 60IU/kg q2w.

References:

1. Charrow J, Andersson HC, Kaplan P, et al, “Enzyme Replacement Therapy and Monitoring for Children With Type 1 Gaucher Disease: Consensus Recommendations,” *J Pediatr*, 2004, 144(1):112-20.

2. Barton NW, Brady RO, Dambrosia JM, et al, “Replacement Therapy for Inherited Enzyme Deficiency - Macrophage-Targeted Glucocerebrosidase for Gaucher's Disease,” *N Engl J Med*, 1991, 324(21):1464-70.

3. Whittington R and Goa KL, “Alglucerase: A Review of Its Therapeutic Use in Gaucher's Disease,” *Drugs*, 1992, 44(1):72-93.

4. UpToDate. Gaucher disease: Treatment. Accessed 8/11/2020.

Revision History:

Date	What changed	Pharmacist’s initials
10/19/11	I wrote the criteria for imiglucerase, alglucerase.	JJ
8/11/2020	I revised the criteria with better definitions, required the pt to be symptomatic, and put in a QL for dosing due to no better outcomes with the higher dose. I also wrote that they could not receive combination ERT+SRT.(no data)	JJ
4/1/21	Reviewed. No changes.	JJ

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EBRx PA criteria for

Targeted Immune Modulators

If approved, the PA will be good for 1 year.

Note (8/19/2021): The Emergency Use Authorization (EUA) for bariticinib for treatment of COVID-19 allows use ONLY for hospitalized patients. Therefore, EBRx will not cover this use on the pharmacy benefit. See EUA information at the following link: https://www.fda.gov/media/143823/download

Rheumatoid Arthritis—PA updated 4/22/21JJ

	csDMARD (conventional synthetic)	tsDMARD (targeted synthetic)	boDMARD (biologic originator)	
	Methotrexate Sulfasalazine Leflunomide	Tofacitinib Baricitinib (targets JAK)	Adalimumab Certolizumab Etanercept Golimumab Upadacitinib Sarilumab	Infliximab Abatacept Rituximab* Tocilizumab Anakinra
1. The patient must have the diagnosis of rheumatoid arthritis.				
Early RA (diagnosis less than 6 months ago and still symptomatic):				
1a. If the patient has had the diagnosis of rheumatoid arthritis for 6 months or less, and who are symptomatic with RA symptoms, the patient must reach the optimal dose of methotrexate 25-30 mg weekly and maintain this dose for at least 8 weeks TOGETHER WITH another DMARD (MTX-hydroxychloroquine-sulfasalazine 2-4g/d). (Or else, the patient must have a contraindication to MTX.				
Established RA				
1b. The patient with established RA and with moderate or high disease activity must use combination MTX 25-30mg weekly and another DMARD (MTX-hydroxychloroquine-sulfasalazine 2-4g/d) and maintain the combination for at least 8 weeks, unless MTX is contraindicated. If MTX is contraindicated, other combination DMARD therapy should be used.				

2. For either early RA or established, two different TNF inhibitors must be tried consecutively (not concurrently) for at least 8 weeks each before tofacitinib is a covered drug.
3. Patients with a previously treated lymphoproliferative disorder, rituximab should be used over TNF inhibitor.
Notes: **a. Biologic DMARDs should all be used in combination with DMARD unless contraindicated.** **b. Combination TNFi is not covered.** **c. Combination TNFi and other biologic is not a covered combination.**
***FOR RITUXIMAB**
NOTE: Rituximab is reserved for patients who have responded poorly to TNF blockers and not for csDMARDs.
4. Does the patient have contraindications to other agents (recent history of lymphoma, latent tuberculosis with contraindications to the use of chemoprophylaxis, living in a TB-endemic region, or a previous history of demyelinating disease? (If so, rituximab may be used as 2nd line therapy after csDMARDs.)

***TNF inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, biosimilars (as approved according to a thorough approval process, such as by EMA and/or FDA).**

†The 'certain circumstances', which include history of lymphoma or a demyelinating disease, are detailed in the accompanying text.[1]

‡Tapering is seen as either dose reduction or prolongation of intervals between applications.

§Most data are available for TNF inhibitors, but it is assumed that dose reduction or interval expansion is also pertinent to biological agents with another mode of action.

DMARD, disease-modifying antirheumatic drug; EMA, European Medical Agency; EULAR, European League against Rheumatism; FDA, Food and Drug Administration; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

References:

1. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of RA with synthetic and biological DMARDs: 2013 update. Ann Rheum Dis. 2014;73:492-509.

2. Moreland LW, O'Dell JR, et al. A randomized comparative effectiveness study of triple therapy versus etanercept plus methotrexate in early aggressive RA. TEAR Trial. Arthritis & Rheumatism. 2012;64(9):2824-2835.

3. O'Dell JR, Mikuls TR, et al. Therapies for active RA after methotrexate failure. N Engl J Med. 2013;369:307-18.

4. Van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early RA (Swefot trial): 1-y results of a randomized trial. Lancet. 2009;374:459-66.

5. Van Vollenhoven RF, Geborek P, Forslind K, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early RA: 2 y follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012;379:1712-20.

6. Bathon JM, McMahon DJ. Making rational treatment decisions in RA when methotrexate fails. N Engl J Med. 369;4:384-85.

7. Singh, Jasvinder A., et al. "2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis." *Arthritis & rheumatology* 68.1 (2016): 1-26.

Date	Update	Pharmacist's initials
4/22/14	**RA criteria were updated to require combination DMARD prior to access to biologics**	**JJ**
6/24/18	**I updated the criteria to incorporate the 2015 ACR Guidelines. I added ref 7.**	**JJ**
4/22/21	**I added upadacitinib and sarilumab to the RA criteria. UAS uses MI standard therapy for this PA, not the above criteria.**	**JJ**

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Juvenile Idiopathic Arthritis (previously known as JRA)

↑Etanercept (Enbrel®)-TNFaI, ↑Adalimumab (Humira®)-TNFaI, ↑*Infliximab (Remicade®)-TNFaI --must be used w/ methotrexate,↑anakinra (Kineret),↑infliximab-abda (Renflexis)	
1. Does the patient have the diagnosis of juvenile idiopathic arthritis?	↑Yes ↑No
2. Has the patient received glucocorticoid joint injections and at least 3 months of methotrexate or leflunomide at the maximum tolerated typical dose? OR Has the patient, specifically with enthesitis **(inflammation where tendons or ligaments connect with the bone)**-related arthritis, received glucocorticoid joint injections and an adequate trial of sulfasalazine? OR Has the patient received an adequate trial of NSAIDS and have sacroiliac arthritis?	↑Yes ↑No
Abatacept (Orencia®) Criteria (should apply the above criteria as well as the following:)	
3. Has the JIA patient received more than one TNFaI sequentially and is now seeking to switch therapy due to high disease activity?	↑Yes ↑No
Rituximab (Rituxan®) Criteria (should have fulfilled the above criteria 1-3 and the following:)	
4. Has the JIA patient received more than one TNFaI sequentially, then abatacept, and still have high disease activity, AND test positive for RF?	↑Yes ↑No
*Infliximab must be used with methotrexate due to the recognized potential for MTX to reduce the incidence of neutralizing antibodies to infliximab and consistent with the labeling of infliximab.	
Beukelman T, Patkar NM, Saag KG, Toleson-Rinehart S, et al. 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features. *Arthritis Care & Research*. 2011(April);63(4):465–482.	

Ankylosing Spondylitis

↑Adalimumab (Humira®) ↑Etanercept (Enbrel®) ↑Golimumab (Simponi®)€ ↑Certolizumab (Cimzia®) ↑ Secukinumab (Cosentyx®) ↑Infliximab (Remicade®)—no new starts; only allow if currently receiving.	
1. Does the patient have the diagnosis of active ankylosing spondylitis?	↑Yes ↑No
2. Has the patient failed a trial of 2 NSAIDS? Sequential NSAID trials should be 1 month in length and be optimally dosed.	↑Yes ↑No
Note: Initial PA should be good for 3 months. After physician confirms the patient's positive response, defined as a reduction of the BASDAI‡ to 50% of the pre-treatment value, or a reduction of ≥2 units, together with a reduction of the spinal pain VAS by 2 cm or more, the patient would be eligible for re-approval.	
‡BASDAI is **Bath Ankylosing Spondylitis Disease Activity Index, a scale of** measuring discomfort, pain, and fatigue (1 being no problem and 10 being the worst problem) in response to 6 questions asked of the patient pertaining to the 5 major symptoms of AS, Fatigue, Spinal pain, Arthralgia, Enthesitis, or inflammation of tendons and ligaments, Morning stiffness duration, Morning stiffness severity. To give each symptom equal weighting, the average of the two scores relating to	

morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of ≥4 suggest suboptimal control of disease, and those patients are usually good candidates for a change in medical therapy, may benefit by treatment with biologic therapies.

References:
1. NICE guidelines: Adalimumab, etanercept and infliximab for ankylosing spondylitis. May 2008. http://publications.nice.org.uk/adalimumab-etanercept-and-infliximab-for-ankylosing-spondylitis-ta143/evidence-and-interpretation
2. €DERP. Report on Targeted Immune Modulators Update 3/8/12.

Psoriatic Arthritis

↑Adalimumab (Humira®) ↑Etanercept (Enbrel®) ↑Infliximab (Remicade®) ↑infliximab-abda (Renflexis)↑ Golimumab (Simponi®) ↑Certolizumab (Cimzia®) ↑Abatacept (Orencia) ↑Secukinumab (Cosentyx®)
***Ustekinumab (Stelara)—Please go to the EBD PA criteria "Ustekinumab" for criteria

1. Does the patient have a diagnosis of psoriatic arthritis?	↑Yes ↑No
2. Has the patient failed a trial of 2 NSAIDS? Each trial should be 1 month in length.	↑Yes ↑No
3. Has the patient failed 3 months of a DMARD therapy (examples: methotrexate, sulfasalazine , penicillamine, azathioprine, leflunomide)	↑Yes ↑No

References:
1. DERP. Report on Targeted Immune Modulators Update 3/8/12.
2. Treatment of Psoriatic Arthritis. UpToDate. http://www.uptodate.com/contents/treatment-of-psoriatic-arthritis?source=search_result&search=psoriatic+arthritis&selectedTitle=2%7E105#H18 . Accessed 7/3/12.

Plaque Psoriasis—currently must step through adalimumab and etanercept

TNF inhibitors:	IL-17 inhibitors:	IL-12/23 inhibitors:	IL-23 inhibitor:
↑Adalimumab (Humira®) ↑Etanercept (Enbrel®) ↑Infliximab (Remicade®) ↑infliximab-abda (Renflexis)	↑Secukinumab (Cosentyx®) ↑Ixekinumab (Taltz®) ↑Brodalumab (Siliq®)	*** Ustekinumab (Stelara®)—Please go to EBD PA criteria for "Ustekinumab" for criteria	↑Guselkumab (Tremfya®) ↑Risankizumab (Skyrizi®)

1. Does the patient ALSO HAVE the diagnosis of psoriatic arthritis?	If so, approve the biologic without requiring "fail first therapy".
2. Otherwise, does the patient have a diagnosis of moderate to severe (affecting ≥5% BSA) plaque psoriasis?	↑Yes ↑No
3. Has the patient failed 3 consecutive months of systemic or topical, non-biologic therapy: examples include:	↑Yes ↑No

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• systemic therapy: methotrexate or cyclosporine or acitretin systemic therapy • phototherapy (broadband ultraviolet B (UVB), narrowband UVB, and psoralen with ultraviolet A (PUVA) • topical treatments (calcineurin inhibitors (tacrolimus or pimecrolimus), topical corticosteroids, vitamin D analogs (calcipotriene), topical retinoids (tazarotene))	
If yes to 1., then approve. If yes to 2 & 3 above, approve.	
Approved PA will expire in 12 months.	
References: 1. 2018 American Academy of Dermatology (AAD)Psoriasis Guidelines. [Update is being prepared for 2018.] 2. ICER report 2018, Psoriasis. https://icer-review.org/wp-content/uploads/2017/11/ICER_Psoriasis_Update_Draft_Report_04272018.pdf	

Crohn's Disease

↑Adalimumab (Humira®) ↑Certolizumab pegol (Cimzia®) ↑Infliximab (Remicade®) ↑infliximab-abda (Renflexis®) ↑infliximab-abda (Inflectra®)	
1. Does the patient have a diagnosis of Crohn's disease?	↑Yes ↑No
2. Is the patient corticosteroid-dependent (with CDAI score >220) OR being considered for a second course of systemic corticosteroids w/in 12 months OR Not had a response to at least 4w of either mesalamine (at a dose of ≥2.4g/d) or budesonide (at a dose of ≥6 mg/day)?	↑Yes ↑No
3. If items 1-2 are "yes" and the patient has severe, active Crohns disease (as opposed to fistulizing), then approval of infliximab 5mg/kg IV infusion may be approved. Readministration of 5mg/kg may be approved if disease recurs (and not before 2 weeks after the original dose). In patients not responding within 2 weeks to the initial infusion, NO FURTHER INFLIXIMAB SHOULD BE USED AS THE RESPONSE IS UNLIKELY. Alternatively, adalimumab 80-160mg SC followed by 40mg SC at week 2 may be approved.	
4. If items 1-2 are "yes" and the patient has fistulizing, active Crohn's disease, then additional doses of 5mg/kg should be approved for weeks 2 and 6 after the original infusion. If the patient does not respond after these 3 doses, no additional treatment with infliximab should be given.	
↑Natalizumab (Tysabri) (Patient should satisfy the above criteria as well as the one below.)	
3. Does the patient have a diagnosis of Crohn's disease AND an inadequate response to or was unable to tolerate conventional CD therapies and anti-TNF monoclonal antibody therapy?	↑Yes ↑No
References: 1. Lichtenstein GR, Hanauer SB, Sandborn WJ. ACG Practice Guidelines. Management of Crohn's Disease in Adults. *Am J*	

Gastroenterol. 2009. *Am J Gastroenterol* advance online publication, 6 January 2009; doi: 10.1038/ajg.2008.168.

2. Colombel JF, Sandborn WJ, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362:1383-95.

3. Terdiman JP, Gruss CB, et al. AGA Institute guideline on the use of thiopurines, methotrexate, and anti-TNFalpha biologic drugs for the induction and maintenance of remission in inflammatory CD. Gastroenterology. 2013;145:1459-63.

4. Garnett WR, Yunker N. Treatment of Crohn's Disease with Infliximab. Am J Health Syst Pharm. 2001;58(4).

Note: CDAI is Crohn's Disease Activity Index. >450 is severe. 200-449 is moderate. 150-199 is quiescent disease. <150 is in remission.

Ulcerative Colitis

↑Infliximab (Remicade®)

↑infliximab-abda (Renflexis)

↑infliximab-abda (Inflectra®)

1. Does the patient have the diagnosis of ulcerative colitis?	↑Yes ↑No
2. Has the patient failed at least 3 months of either mesalamine or sulfasalazine or glucocorticoids?	↑Yes ↑No
3. Does the patient have moderate to severe disease (characterized by steroid dependence)?	↑Yes ↑No

General References:

1. Drug Effectiveness Review Project. Targeted Immune Modulators Update 3/8/12.

2. Kornbluth A, Sachar DB, The Practice Parameters Committee of the American College of Gastroenterology. Ulcerative Colitis practice guidelines in adults: ACG, Practice Parameters Committee. *Am J Gastroenterol* 2010; 105:501–523.

Hidradenitis suppurativa

↑Adalimumab (Humira®)

1. The patient must have the diagnosis of moderate-severe hidradenitis suppurativa (HS) as defined by a total abscess and inflammatory-nodule count of at least 3 lesions in at least two distinct anatomic areas. At least one area must be at least Hurley Stage II or III.*

2. The patient must also have had an inadequate response to at least a 90 days continuous duration of an oral antibiotic for the treatment of their HS in the past 180 days.

3. The patient must have tried chlorhexidien gluconate, triclosan, benzoyl peroxide, and dilute bleach in bathwater.

If approved, PA is good for 3 months, then the patient must satisfy continuation criteria.

*Hurley Staging:

- Stage I: abscess formation, single or multiple, without sinus tracts and cicatrization (scarring).
- Stage II: One or more widely separated recurrent abscesses with tract formation and cicatrization (scars).
- Stage III: Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse

involvement.
Continuation Criteria
1. After 3 months of therapy the patient must have at least a 50% reduction from baseline in the total abscess and inflammation-nodule count, and with no increase in the abscess or draining-fistula count.
If approved, PA is good for 12 months.

1. Kimball, Alexa B., et al. "Two phase 3 trials of adalimumab for hidradenitis suppurativa." *New England Journal of Medicine* 375.5 (2016): 422-434.

Noninfectious uveitis (added 9/4/18 JJ)

↑Adalimumab (Humira®),↑etanercept (Enbrel)
1. The patient must have the diagnosis of noninfectious uveitis.
2. The patient must also have had an inadequate response to locally administered ophthalmic corticosteroid drops (prednisolone acetate 1% or difluprednate 0.05%, or periocular inj of glucocorticoid such as triamcinolone or dexamethasone.
3. The patient must have had an inadequate response to systemic glucocorticoid therapy.
4. The patient must have had an inadequate response to cyclosporine and methotrexate, combined.
If approved, PA is good for 12 months.
Continuation Criteria
1. After 3 months of therapy the patient must have at least a 50% reduction from baseline in the total abscess and inflammation-nodule count, and with no increase in the abscess or draining-fistula count.
If approved, PA is good for 12 months.

Ref for uveitis:

1. UpToDate, “Uveitis: Treatment”, accessed 9/4/18.

2. Jaffe, Glenn J., et al. "Adalimumab in patients with active noninfectious uveitis." *New England Journal of Medicine* 375.10 (2016): 932-943.

General References:

1. Drug Effectiveness Review Project. Targeted Immune Modulators Update 3/8/12.

2. Kornbluth A, Sachar DB, The Practice Parameters Committee of the American College of Gastroenterology. Ulcerative Colitis practice guidelines in adults: ACG, Practice Parameters Committee. *Am J Gastroenterol* 2010; 105:501–523.

Date	What Changed?	Pharmacist’s Initials
7/5/12	Complete revision. If needed, please see the previous version of Immune Modulator criteria in “Old	JJ

	Criteria" on the EBRx, EBD PA Criteria Folder	
7/30/12	Added a 1 year approval; reapproval duration. Added under UC the requirement for the diagnosis of UC.	JJ
3/4/14	Changed the CD approval allowing those with severe, active CD to get access to either infliximab or adalimumab as induction therapy. It also allows access to infliximab for active, fistulizing CD. Maintenance therapy should be encouraged with azathioprine or 6MP (standard of care (SOC)) as there are no comparative trials for maintenance therapy using SOC vs infliximab or vs adalimumab and due to TNFs high costs and the likelihood a high number of people would achieve maintenance therapy with SOC, the SOC should be used for maintenance therapy.	JJ
12/4/14	I put in a note for those seeking approval for ustekinumab (Stelara) for both plaque psoriasis and for psoriatic arthritis to please see the individual criteria for this drug (not within the immune modulator criteria).	JJ
5/13/15	I added certolizumab (Cimzia) to ankylosing spondylitis and psoriatic arthritis.	JJ
2/23/17	I added hidradenitis suppurativa as an approved indication for adalimumab with the criteria for initial and continuation.	JJ
2/20/18	I added infliximab-abda (Renflexis) to the criteria where Remicade also is.	JJ
7/25/18	Added baricitinib (Olumiant) to RA tsDMARD list.	ALM
9/4/18	I added adalimumab and etanercept as a covered drug with criteria for noninfectious uveitis.	JJ
6/3/19	I added risankizumab to the plaque psoriasis section; must step through adalimumab and etanercept	JJ
5/13/21	Added note that for plaque psoriasis, the use of topical or systemic agents must be for 3 consecutive months	CP
8/19/21	Added note that baricitinib is not covered for treatment of COVID as use is only covered for hospitalized patients on oxygen/vented/ECMO.	SK

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Interferon Beta-1a (Rebif®)

EBRx PA Criteria

FDA-approved for:

- Multiple sclerosis, relapsing: treatment of relapsing MS including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

Criteria for new users
1. The patient must have the diagnosis of relapsing multiple sclerosis

Rebif (subcutaneous)	Avonex (intramuscular)
Note: DOSES: For target dose of 44mcg: Initially: 8.8mcg 3 times/w for 2 w, then Titration: 22 mcg 3 times/w for 2 w, then Finally: 44mcg 3 times/w For target dose of 22mcg: Initially: 4.4 mcg 3 times/w for 2 w, then Titration: 11 mcg 3 tim3s/w for 2 w, then Finally: 22 mcg 3 times/w	Note: DOSES: For target dose of 30mcg once weekly: Initial 7.5mcg (week 1), then increase dose in increments of 7.5mcg QW (weeks 2-4) up to 30mcg QW.

Revision History:

Date	What changed	Pharmacist's initials
5/5/14	JJ wrote PA. (Previously, there was a PA with the same criteria in an Excel sheet that included Rebif. This is simply more explicit.)	JJ
10/18/2019	I reviewed the criteria. No changes	JJ
4/07/2021	I reviewed the criteria. Criteria are the same. I provided Avonex dosing. I applied EBRx criteria to UAS Plan. EBRx previously did not cover Avonex, however UAS covers it and the criteria are the same as for Rebif.	JJ

Interferon Beta-1b (Betaseron®)

EBRx PA Criteria

FDA-approved for: relapsing-remitting multiple sclerosis (RRMS)

Criteria for new users
1. The patient must have the diagnosis of RRMS.

Note: Target dose is 0.25mg QOD.

Initially: 0.0625 mg QOD; gradually increase dose by 0.0625 mg q2w until target dose is reached, then maintain.

Quantity Limits:

Revision History:

Date	What changed	Pharmacist's initials
5/20/14	JJ wrote PA.	JJ
9/18/19	I updated the PA and removed failure of Rebif as a criterium.	JJ

References:

4. AAN. Practice Guideline: Disease-modifying Therapies for Adults with multiple sclerosis. American Academy of Neurology 4/24/2018. https://www.aan.com/Guidelines/Home/GetGuidelineContent/900

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Ipilimumab (Yervoy®)

50 mg and 200 mg vials

EBRx PA Criteria

FDA-approved for:

- **Melanoma**
  - Unresectable or metastatic melanoma in adults and pediatric patients (12 years and older)
  - Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy
- **Renal Cell Carcinoma (RCC)**
  - Intermediate or poor risk RCC previously untreated advanced RCC, in combination with nivolumab
- **Colorectal cancer**
  - in combination with nivolumab: adult and pediatric (age 12 and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan[a] NOT COVERED: data is limited to a single arm trial
- **Hepatocellular Carcinoma (HCC)**
  - Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib, in combination with nivolumab.[a] NOT COVERED: data is limited to a single arm trial with response rate data only
- **Non-Small Cell Lung Cancer (NSCLC)**
  - Treatment of adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with nivolumab.
  - Treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy.

a=This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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Melanoma, metastatic
2. Diagnosis of unresectable or metastatic melanoma.
3. If the patient has received no prior therapy, ipilimumab will be used in combination with nivolumab
4. If the patient has received prior therapy for advanced/metastatic, tumor is progressing.
5. The patient must be ECOG performance status 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity) at initiation
6. Patient does not have diagnosis of ocular/uveal melanoma.
Denial criteria: Access is denied for adjuvant treatment of melanoma after complete resection of stage III disease. (In this setting, nivolumab is superior to ipilimumab for recurrence free survival and associated with less toxicity. Nivolumab and pembrolizumab are preferred and covered by EBRx)
If criteria fulfilled, approve ipilimumab for 4 months (maximum of 4 doses total).
Criteria for continuation
Continuation not allowed if 4 doses already given. If doses were delayed due to toxicity or other reason and reapproval is needed, approve for 1 month if no disease progression and no unacceptable toxicity.
Notes: -Not covered for first line use as monotherapy, due to other checkpoint inhibitors having superior efficacy (see nivolumab or pembrolizumab) -Ipilimumab/Nivolumab comes extremely close to statistically improving overall survival compared to nivolumab alone in the 5-year update of the CHECKMATE 067 trial. Due to consistency of results compared to initial release of data and strong trend to improving overall survival, EBRx recommends coverage. However, note that toxicity is also increased in the ipi/nivo arm compared to nivolumab alone (grade 3-5 toxicity incidence: 59% vs 23%).[1,2] -Ipilimumab does have activity after nivolumab or pembrolizumab though this is based on a retrospective review[3] -Ipilimumab showed improved survival vs. placebo/vaccine in patients previously treated with chemotherapy. Median OS was 10 mo for ipilimumab vs. 6.4 mo in placebo/vaccine group. Vaccine had no effect on efficacy and should be considered as placebo for the purpose of interpreting study results.[4] Dosing: 3 mg/kg IV every 3 weeks x 4 doses MAX

REFERENCES:

1. Hodi F, VAnna C, Rene G et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (Checkmate 067): 4-year outcomes of a multicenter, randomized, phase 3 trial. Lancet Oncol 2018; 19:1480-92.

2. Larkin J et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019 Oct 17;381(16):1535-1546.
3. PMID 31562797 NCT01844505
4. Zimmer L et al. Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. Eur J Cancer. 2017 Apr;75:47-55.
5. Hodi FS et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010 Aug 19;363(8):711-23. NCT00094653

Renal Cell Carcinoma (RCC)

1. Diagnosis of advanced RCC with no prior systemic therapy
2. Ipilimumab will be used in combination with nivolumab
3. Tumor must have clear cell component
4. The patient must have IMDC intermediate or poor risk disease indicated by 1 or more of the following being present:
   - Less than 1 year from time of diagnosis to systemic therapy
   - Performance status <80% (Karnofsky—see guide below)
   - Hemoglobin < lower limit of normal (LLN)

If criteria fulfilled, approve ipilimumab for 4 months (maximum of 4 doses total).

Criteria for continuation

Continuation not allowed if 4 doses already given. If doses were delayed due to toxicity or other reason and reapproval is needed, approve for 2 months if no disease progression and no unacceptable toxicity.

Notes:

FIRST LINE SETTING:

-In intermediate/poor risk tumors with clear cell component, nivo/ipi was superior to sunitinib alone (median OS not reached for nivo/ipi and 26 mo for sunitinib; HR 0.63 99.8% CI 0.44-0.89). Improvement in OS was accompanied by clinically meaningful improvement in QOL.[1]

-Nivo/ipi does not appear superior to sunitinib in FAVORABLE risk patients and is not FDA approved for this population and should not be used at this time.[1]

-Dose: Nivolumab 3 mg/kg every 3 weeks PLUS ipilimumab 1 mg/kg every 3 weeks x 4 doses; THEN nivolumab monotherapy continues at 240 mg every 2 weeks or 480 mg every 4 weeks IV infusion until disease progression or unacceptable toxicity

REFERENCES:

Non-Small Cell Lung Cancer (NSCLC)
Patient meets criteria for use of nivolumab (Opdivo) for first-line treatment (no prior therapy for advanced/metastatic disease) of NSCLC.

Karnofsky Score (KS)	Definition
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Revision History:

Date	Notes	Pharmacist's initials
12/31/14	I wrote the criteria.	JJ
1/27/2016	I changed the criteria after the DCWG meeting on 1/25/16. Specifically, access will be denied for previous or concurrent nivolumab; access will also be denied for adjuvant use for stage III complete tumor resection.	JJ
2/26/19	Melanoma: use for second line only due to pembro/nivo being superior in first line setting with fewer toxicities; updated	Sk

	continuation criteria Renal cell: allow use in combination with nivo for untreated, intermediate/poor risk patients for max of 4 doses only	
8/7/19	Criteria reviewed. No change.	SK
6/5/2020	Added new indication for HCC (ipi + nivo). (not covered)	SK
7/22/2020	Added new indications for NSCLC (ipi + nivo)—covered	SK

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Istradefylline (Nourianz®)

EBRx PA Criteria

is FDA-approved for: Parkinson's Disease "off" episodes

Criteria for new users
1. The patient must have the diagnosis of Parkinson's disease and be experiencing "off" episodes.
2. The patient must be routinely receiving levodopa/carbidopa as a concurrent medication with istradefylline.

Note: In the trials, the 20mg daily dose seemed to outperform the 40mg dose. Also, the effect of istradefylline in reducing "off" episodes was more effective in patients with lower levodopa doses.

Quantity Limits: 1/1

References:

1. Mizuno, Yoshikuni, Tomoyoshi Kondo, and Japanese Istradefylline Study Group. "Adenosine A2A receptor antagonist istradefylline reduces daily OFF time in Parkinson's disease." Movement Disorders 28.8 (2013): 1138-1141.

2. Kondo, Tomoyoshi, Yoshikuni Mizuno, and Japanese Istradefylline Study Group. "A long-term study of istradefylline safety and efficacy in patients with Parkinson disease." Clinical neuropharmacology 38.2 (2015): 41-46.

3. LeWitt, Peter A., et al. "Adenosine A2A receptor antagonist istradefylline (KW- 6002) reduces "off" time in Parkinson's disease: a double- blind, randomized, multicenter clinical trial (6002- US- 005)." Annals of neurology 63.3 (2008): 295-302.

4. Jankovic, Joseph. "Are adenosine antagonists, such as istradefylline, caffeine, and chocolate, useful in the treatment of Parkinson's disease?." Annals of neurology 63.3 (2008): 267-269.

Revision History:

Date	What changed	Pharmacist's initials
10/28/2019	I wrote the criteria. I also placed this drug on the revisit list for 2/2020 to look for more data on the possibly waning of therapeutic effect.	JJ
2/14/2020	Reviewed PA, added the note.	JJ

Itraconazole

Capsules, Solution 10mg/mL

EBRx PA Criteria

FDA-approved for:

- Aspergillosis, invasive (salvage therapy); solution dose: 200mg BID 6-12w (sometimes longer)
- Blastomycosis; 200mg TID X3d, then 200mg BID for 6-12m
- Esophageal Candidiasis; 200mg QD for 14-21d
- Oropharyngeal Candidiasis: 100-200mg QD for up to 28d
- [there are several off-label uses for which there are supportive data]

Criteria for new users
1. The patient must have the diagnosis of a fungal infection listed above; nail onychomycosis is not a covered diagnosis.
2. To get the solution, the patient must be unable to tolerate itraconazole capsules.

Revision History:

Date	What changed	Pharmacist's initials
1/19/10	Criteria written	JJ
11/8/2019	I updated the criteria and required intolerability of taking the capsules is a criteria for getting the much more costly solution. I am also seeking with P&T to archive the PA Criteria for the capsules.	JJ
8/12/2020	I updated the criteria to clarify the capsules require PA and that onychomycosis is not a covered diagnosis (and in fact oral terbinafine is first line before itraconazole). There are a lot of drug interactions.	JJ
3/10/2021	Criteria reviewed. No changes	JJ

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Ivabradine (Corlanor®)

5mg (scored), and 7.5mg tablets

EBRx PA Criteria

FDA-approved: to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with LV EF≤35%, who are in sinus rhythm with resting HR ≥70 bpm and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use.

HEART FAILURE INDICATION
Criteria (MUST HAVE ALL OF THE FOLLOWING):
1. diagnosis of stable, symptomatic HF, AND
2. left ventricular ejection fraction ≤35%, AND
3. sinus rhythm, AND
4. resting heart rate >75 beats per minute*, AND
5. Either on maximally tolerated doses of B-blockers or have a contraindication to B-blocker use, AND
6. must be given in combination with standard therapy including beta-blocker therapy, ACE inhibitor or ARB, and an aldosterone antagonist, or when beta-blocker therapy is contraindicated or not tolerated.

***SHIFT (2010) and SHIFT subgroup analysis(2012) showed that if HR was <77bpm, there was no difference on 1` endpoint. If HR was >77bpm, there was a reduction in the 1` endpoint. This is why EBRx PA criteria chose 75bmp rather than the FDA-approval criteria of 70. 70 bpm came from the SHIFT inclusion criteria; this is not the same as what yielded the results.**

Criteria (AND MUST HAVE NONE OF THE FOLLOWING):
1. acute decompensated heart failure, OR
2. blood pressure 90/50, OR
3. sick sinus syndrome, sino-atrial block, or 3rd degree AV block, unless functional pacemaker is present, OR
4. severe hepatic impairment (Child-Pugh C), OR
5. pacemaker dependence (operative for 40% or more of the day, OR
6. use of strong CYP3A4 inhibitors, OR
7. atrial fibrillation
Dose is 5mg BID or 2.5mg BID (in pts w/ a hx of conduction defects or with hemodynamic

compromise due to bradycardia. Max dose is 7.5mg BID.

OFF LABEL USE: POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS)
1. Diagnosis of POTS including documentation of either heart rate increase of ≥30 beats per minute or sustained HR ≥120 bpm within 10 minutes of sustained orthostasis. (other symptoms include palpitations, presyncope, syncope, or profound fatigue)
2. Must NOT have acute decompensated heart failure, BP <90/50mmHg, have the diagnosis of sick sinus syndrome or sinoatrial block or 3rd degree AV block unless a functioning pacemaker is present, have a resting HR of <60 bpm prior to therapy, have severe hepatic impairment, be pacemaker dependent, or plan to use ivabradine with potent CYP 3A4 inhibitors.
Dose is 5mg BID or 2.5mg BID (in pts w/ a hx of conduction defects or with hemodynamic compromise due to bradycardia. Max dose is 7.5mg BID.

OFF LABEL USE: INAPPROPRIATE SINUS TACHYCARDIA (IST)
1. Diagnosis of IST including documentation of sustained heart rate of >100 bpm with all other causes excluded.
2. Patient must have failed maximally tolerated doses of verapamil.
3. Patient must have failed maximally tolerated doses of metoprolol succinate (200mg XL daily)
Dose is 5mg BID or 2.5mg BID (in pts w/ a hx of conduction defects or with hemodynamic compromise due to bradycardia. Max dose is 7.5mg BID.

Quantity Limits: 60/30

References:

1. Swedberg K, Komajda M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; 376: 875–85

2. Bohm M, Borer J, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol* (2013) 102:11–22.

3. Fox K, Ford I, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 372: 807–16

4. Fox K, Ford I, et al. Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure. N Engl J Med 2014; 371: 1091-9.

5. Cappato et al. Clinical Efficacy of Ivabradine in Patients with inappropriate Sinus Tachycardia: A prospective, Randomized, Placebo-Controlled, Double-blind, crossover evaluation. JACC 2012, 60 (15): 1323-9.

6. Ptaszynski P, Kaczmarek K, Ruta J, et al. Metoprolol succinate vs. ivabradine in the treatment of inappropriate sinus tachycardia in patients unresponsive to previous pharmacological therapy. Europace 2013. 15:116-121. Doci 10.1093/europace/eus204

7. Calo L, Rebecchi M, Sette A, et al. Efficacy of Ivabradine administration in patients affected by inappropriate sinus tachycardia

Heart Rhythm 2010; 7 (9): 1318-1322

8. Sutton R, Salukhe T, et al. Ivabradine in treatment of sinus tachycardia mediated vasovagal syncope. Europace 2014; 16: 248-288. Doi: 10.1093/eruopace/eut226

Revision History:

Date	What changed	Pharmacist's initials
6/18/15	I wrote the criteria w/ the help of M Estes. Beta blocker therapy must be reflected in the current or else there must be a documented contraindication. Otherwise, Corlanor should be denied.	JJ
9/1/15	I added the off label criteria.	JJ
8/12/2020	I reviewed the criteria. No changes made	JJ
3/10/2021	I reviewed the criteria. No changes.	JJ

CONFIDENTIAL

Ivacaftor (Kalydeco®)

150mg tablets

EBRx PA Criteria

FDA-approved for: the treatment of CF in patients >6m of age who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data. If phenotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the mutation followed by verification with bidirectional sequencing when recommended by the mutation test instructions for use.

Initial approval criteria:
1. The patient must have a diagnosis of cystic fibrosis with gene positive testing for one of the following CFTR genotypes (a gating mutation included in the data showing clinical benefit): G551D, G178R, S1251N, S1255P, R117H, G1244E, G1349D, G178R, G551D, G551S, R117H, S1251N, S1255P, S549N, S549R, G1069R*, R1070Q*. AND be older than 6 months old. OR The patient must have no F508 deletion but HAVE a residual function mutation. (Res Fxn mutations: A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R1070W, R117C, R347H, R352H, R352Q, R74W, S945L, S977F, 2789+5G—A, 3272-26A…G, 3849+10kbC…T, 711+3A…G, AND be under age 6 years old.
2. The patient must be currently demonstrating compliance with the evidence-based standard of care for inhaled therapies for cystic fibrosis.[1] (Or the patient must have experienced intolerance to dornase alfa &/OR bronchospasm or irritability with inhaled hypertonic saline and therefore cannot use it.—This must be documented in the medical record and represented to the call pharmacists.)
3. The patient must have had transaminases (ALT and AST) drawn prior to beginning the drug and plan to be monitored every 3 months during the 1st year of treatment and then annually thereafter. [Ivacaftor should be interrupted if ALT or AST is greater than 5xs ULN and benefits/risks should be reconsidered.]
4. The patient must be a nonsmoker.

***Quantity limit of 62/31 days; normal dose is 150 mg BID**

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Continuation criteria:
6. The patient must currently be demonstrating adherence with the evidence-based standard of care for inhaled therapies for cystic fibrosis.[1] (or the patient must have experienced intolerance to dornase alfa &/OR bronchospasm or irritability with inhaled hypertonic saline and therefore cannot use it).
7. The patient must have had transaminases (ALT and AST) drawn in the past 6 months and be lower than 5 times the ULN.
8. The patient must be a nonsmoker.
9. The patient must demonstrate a clinical benefit with ivacaftor as shown by lung function (FEV1), weight gain, or reduction in CF exacerbations or CF hospitalizations as shown in chart notes.
10. The patient must demonstrate adherence (1 fill/1 month) with therapy as determined by refill history or reported by physician.

*Quantity limit of 62/31 days; normal dose is 150 mg BID

References:

1. Mogayzel PJ, Naureckas ET, Robinson KA, Mueller G, et al. cystic Fibrosis Pulmonary Guidelines: Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013;187(7):680-689.
2. Ramsey, B et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation. N Engl J Med 2011; 365: 1663-72
3. UpToDate: Cystic Fibrosis: Treatment with CFTR Modulators. Accessed 11/22/19.

Revision Summary

Date	Notes	Pharmacist's initials
3/6/13	Criteria created	JB
3/6/13	JJ added standard of care criteria and transaminase monitoring requirement	JJ
6/30/14	JJ added other gene mutations to be allowed.	JJ
12/30/14	JJ inserted the requirement that CF patients on ivacaftor must be tobacco free; introduced continuation criteria; and changed the language for demonstrating adherence to evidence-based SOC therapies. Also added reference for current CF guidelines.	JJ
10/14/15	I clarified the continuation therapy, defined "compliance" as a fill of	JJ

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	ivacaftor and the standard of care medications every month, and corrected the way the key should be answered for continuation criteria to maintain access to the drug.	
07/26/2017	Coverage updated to ONLY include genotypes with clinical efficacy determined by a mean change in baseline CFQ – R scores ≥ 4 and a minimum change in CFQ – R scores ≥ 4 for each subgroup. Genotypes that only had in-vitro data or did not meet the MCID criteria in clinical trials were excluded.	JK
12/16/19	I updated the criteria to be consistent with the CF recs per UpToDate.	JJ

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Ivermectin (Sklice®)

EBRx PA Criteria

FDA-approved for: treatment of Pediculosis capitis (head lice) infestation in adults and children >6 months old

Criteria for new users
1. The patient must have had a 2 courses of treatment with permethrins and spinosad (Natroba) in the past 30 days..

"It is concluded that both 1% permethrin and 0.5% ivermectin have comparable efficacies in managing pediculosis capitis infestation, but permethrin was found to be more effective in treatment…the efficacies of 1% permethrin lotion are almost comparable with 0.5% ivermectin shampoo. But, on subsequent follow up visits, 1% permethrin shampoo was found to be superior in treating pediculosis capitis"(2)***ivermectin had lack of efficacy at 4 weeks in 10% of subjects that initially responded versus permethrin 0% seen in initial responders, may suggest rapid resistance development to ivermectin***

2015 AAP AAP Updates Treatments for Head Lice: "in areas where resistance to permethrin or pyrethrins has been demonstrated or for a patient with a documented infestation that has failed to respond to appropriately administered therapy with permethrin or pyrethrins. Spinosad and topical ivermectin are newer preparations that might prove helpful in difficult cases" (1)

"Spinosad, which did not require nit combing, was significantly more effective than permethrin in 2 studies reflecting actual-use conditions, and most spinosad-treated participants required only 1 application"(4)

AWP (12/16/19)

$ 3.52 per gram, $411.84 per tube (only available in 117 g tube)

Cost of comparator: Spinosad($288/120 mL bottle)

References

1. AAP. (2015). Head lice clinical report. Accessed 11/22/19 at https://pediatrics.aappublications.org/content/pediatrics/early/2015/04/21/peds.2015-0746.full.pdf
2. Monisha. B.M. (2018). Comparison of efficiency of 1% permethrin lotion vs. 0.5% ivermectin shampoo in the treatment of Pediculosis capitis. Accessed 11/25/19 at http://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20183158
3. Lexicomp. Ivermectin alpha/monograph. Accessed 11/25/19

4. Popescu, C.M. (2012). Efficacy and Safety of Spinosad Cream Rinse for Head Lice. *Arch Dermatol.* 2012;148(9):1065-1069. Accessed 11/25/19 https://jamanetwork-com.libproxy.uams.edu/journals/jamadermatology/fullarticle/1359503 Revision History:

Revision History:

Date	What changed	Pharmacist's initials
11/25/19	Added efficacy/guideline data; New user criteria addition: 2 treatment cycles permethrin and 1 treatment Spinosad (Natroba) within 30 days	CS/JJ

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Immune Globulins

EBRx PA Criteria

Immune globulin gamma (IGG)-KLHW (Xembify)*

Hyqvia Kit (IGG/hyaluronidase, recombinant)

Bivigam

Flebogamma

Gammagard*

Gammaked

Gammaplex*

Gamunex-C

Hizentra*

Octagam

Privigen

Garimune NF

Gammagard S/D

Gammagard S/D less IgA

FDA-approved for: Indicated for treatment of Primary Humoral Immunodeficiency (PI) in patients 2 years of age or older. This includes but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

***FDA-approved for SC injection.**

Criteria for new users
1. The patient must be ≥2y old.
2. The patient must have the diagnosis of congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, or severe combined immunodeficiencies.

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Revision History:

Date	What changed	Pharmacist's initials
5/6/15	I wrote the PA with DK's guidance/intention.	JJ
12/16/19	I updated the criteria.	JJ

IVIG given by IV infusion is not covered under the pharmacy plan but is covered under the medical plan with no PA required.

IVIG given subcutaneously is covered under the pharmacy plan but a PA is required.

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Ixazomib (Ninlaro®)

2.3 mg, 3 mg, 4 mg capsules

EBRx PA Criteria

FDA-approved for:

Treatment of multiple myeloma (in combination with lenalidomide and dexamethasone) in patients who have received at least one prior therapy.

Criteria for new users
1. The patient must have the diagnosis of relapsed and/or refractory multiple myeloma.
2. Multiple myeloma must be progressing at first request.
3. The patient must have received at least one prior therapy for multiple myeloma.
4. The patient must be receiving concurrent lenalidomide and dexamethasone
5. The patient must be ECOG performance status 0, 1, or 2 at first request.
If above criteria are met, approve for 1 year.
Quantity Limits: 3 tablets per 28 days.

Criteria for continuation
1. There must be evidence from the pharmacy profile or other document that the patient has been receiving lenalidomide and dexamethasone concurrently with ixazomib in order to continue.
If above criterion met, approve for 1 year.
Note: Dose: 4 mg once weekly on days 1, 8, and 15 of a 28-day cycle (in combination with lenalidomide and dexamethasone) until disease progression or unacceptable toxicity. Not covered: maintenance therapy in patients who have undergone autologous transplant. In the TOURMALINE-MM3 study, progression free survival (PFS) was improved with ixazomib compared with placebo, but there was no overall survival (OS) benefit demonstrated to date. Lenalidomide (Revlimid) and bortezomib (Velcade) are alternative options for maintenance therapy.[1] In the TOURMALINE-MM1 trial, ixazomib/lenalidomide/dexamethasone improved PFS compared with lenalidomide/dexamethasone in patients with relapsed and/or refractory multiple myeloma, but overall survival data was immature.[2] However, there was improved OS in a

Chinese study[3]. Note: 12% of population received prior lenalidomide and according to subgroup analysis (although numbers were small), PFS and response rate benefits were still seen in this subgroup.[4] QOL was maintained in ixazomib group (but not improved compared to control group).[5]

References:

1. Dimopoulos MA et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2019 Jan 19;393(10168):253-264. PMID 30545780 NCT02181413
2. Moreau P et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Apr 28;374(17):1621-34. PMID 27119237 NCT01564537
3. Hou J et al. Randomized, double-blind, placebo-controlled phase III study of ixazomib plus lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma: China Continuation study. J Hematol Oncol. 2017 Jul 6;10(1):137. PMID 28683766 NCT01564537
4. Mateos MV et al. Impact of prior therapy on the efficacy and safety of oral ixazomib-lenalidomide-dexamethasone vs. placebo-lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma in TOURMALINE-MM1. Haematologica. 2017 Oct;102(10):1767-1775. PMID 28751562 NCT01564537
5. Leleu X et al Patient-reported health-related quality of life from the phase III TOURMALINE-MM1 study of ixazomib-lenalidomide-dexamethasone versus placebo-lenalidomide-dexamethasone in relapsed/refractory multiple myeloma. Am J Hematol. 2018 May 4. doi: 10.1002/ajh.25134. [Epub ahead of print] PMID 29726031 NCT01564537

Revision History:

Date	What changed	Pharmacist's initials
4/30/18	I wrote the PA criteria.	JJ
5/20/19	Criteria reviewed. No significant changes. Emphasized that myeloma should be progressing in order to be approved (ixazomib is not covered for maintenance therapy yet).	SK
10/31/19	Criteria reviewed. No changes. Added QOL report reference.	SK
8/21/2020	Criteria reviewed. No change.	SK

Long-acting Beta-agonists

Fax: 877-540-9036

Phone: 866-564-8258

PATIENT INFORMATION		
Last Name:	First Name:	ID Number:
Date of Birth:		

1. Does the patient have a diagnosis of asthma that is at least step 3 severity and have supporting documentation (PFTs or symptom scores)? **<u>Symptom scores</u> consistent with ***<u>at least</u>* Step 3 severity are as follows:** (fulfillment of 1 of the following indicates Step 3 severity) ☐ **Daily symptoms** ☐ **>1x/week nightly awakenings due to asthma symptoms** ☐ **Daily use of SABA** ☐ **Some limitation with normal activity due to asthma symptoms** **<u>PFT's</u>:** ☐ **FEV1 <80% or FEV1/FVC reduced 5% or more**	☐ Yes ☐ No
2. Has the patient been on a trial of at least three months of a single agent inhaled corticosteroid and the asthma symptoms are not adequately controlled?	☐ Yes ☐ No

PRESCRIBER INFORMATION		
Prescriber	Speciality:	
Address:	City State	
Ph #	Fax#	
Today's Date:		I certify that the above therapy is medically necessary and all the above information is accurate to the best of my knowledge. **Physician's Signature:**

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Lacosamide (Vimpat®)

50mg, 100mg, 150mg, 200mg tablets and 10mg/mL oral solution

EBRx Prior Authorization Criteria

1. Does the patient have a diagnosis of focal, partial-onset seizures?	**☐ Yes ☐ No**
If "yes", approve for 12 months. If "no", then deny coverage.	

References:

1. Wechsler RT, Li G, French J, et al. Conversion ot lacosamide monotherapy in the treatment of focal epilepsy: results from a historical-controlled multicenter, DB study. *Epilepsia*. 2014;55(7):1088-98.

Revision history:

Date	Notes	Pharmacist's initials
8/18/2009	Criteria written	JJ
5/15/2012	Revision hx added	JJ
10/28/15	I revised the criteria to allow for lacosamide monotx for focal epilepsy, partial-onset seizures. I also expanded the PA duration to be good for 12 months.	JJ

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Lanreotide (Somatuline Depot®)

120 mg/0.5 mL, 60 mg/0.2 mL, 90 mg/0.3 mL prefilled syringes for SQ injection

EBRx PA Criteria

FDA approved for:

- the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy
- the treatment of patients with unresectable, well- or moderately- differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival
- the treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy

Acromegaly
6. The patient has a diagnosis of acromegaly
2. The patient had an inadequate response to or has a contraindication to surgery and/or radiotherapy
If all criteria fulfilled, approve for 12 months.
Initial Somatuline Depot dosing is 90 mg given via deep subcutaneous injection every 4 weeks for 3 months. The dose is then adjusted according to growth hormone levels, insulin-like growth factor-1 levels, and clinical symptoms.

Neuroendocrine Tumors
1. The patient has a diagnosis unresectable, locally advanced, or metastatic gastroenteropancreatic neuroendocrine tumor (GEP-NET; pancreatic, small or large intestine, appendix, rectum, anal canal, anus)
2. Tumor is well or moderately differentiated
3. Somatostatin-receptor scintigraphy is grade 2 or higher (e.g. positive OctreoScan)
If all criteria fulfilled, approve for 12 months.

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Dose is 120 mcg SQ every 4 weeks given until disease progression or unacceptable toxicity.

Lanreotide markedly improved progression free survival over placebo in this patient population (2-year PFS: 65% vs 33%). Overall survival was confounded by high rate (~85%) of crossover from placebo to active treatment.

References:

1. Caplin ME et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014 Jul 17;371(3):224-33. PMID 25014687 NCT00353496

2. Caplin ME et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. Endocr Relat Cancer. 2016 Mar;23(3):191-9. PMID 26743120

Carcinoid Syndrome
1. Diagnosis of carcinoid syndrome with presence of symptoms (e.g. flushing, diarrhea)
2. Diagnosis of neuroendocrine or carcinoid tumor
3. Somatostatin-receptor scintigraphy is grade 2 or higher (e.g. positive OctreoScan)
If all criteria fulfilled, approve for 12 months.

Dose is 120 mcg SQ every 4 weeks given until disease progression or unacceptable toxicity.

Lanreotide improves symptoms in patients with carcinoid syndrome to a greater extent than placebo.

Reference:

1. Fisher GA Jr et al. Patient-Reported Symptom Control of Diarrhea and Flushing in Patients with Neuroendocrine Tumors Treated with Lanreotide Depot/Autogel: Results from a Randomized, Placebo-Controlled, Double-Blind and 32-Week Open-Label Study. Oncologist. 2018 Jan;23(1):16-24. doi: 10.1634/theoncologist.2017-0284. Epub 2017 Oct 16. PMID 29038234

Reference: Package Insert. Somatuline Depot. Ipsen. August 2007.

Revision History:

Date	Notes	Pharmacist's initials
3/12/08	Criteria written	SV/JJ
5/15/12	Revision hx added	JJ
8/26/19	Criteria reviewed. Added coverage for neuroendocrine tumor indications	SK
1/29/2020	Criteria reviewed. Listed additional FDA indication for carcinoid syndrome (covered with criteria).	sk

Lapatanib (Tykerb®)

250 mg tablets

EBRx PA criteria

FDA approved for:

- With capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress human epidermal growth factor receptor 2 (HER2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
    - Limitations of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with lapatinib in combination with capecitabine.
- With letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.
    - NOT COVERED: In patients with untreated HER2+, HR+ metastatic breast cancer, lapatinib+letrozole improved progression free survival compared to letrozole alone (median 8 mo vs 3 mo), but an overall survival benefit has not yet been demonstrated. In a similar patient population, trastuzumab+anastrozole improved overall survival compared with anastrozole alone (median 29 mo vs 17 mo) in an analysis that excluded patients who crossed over. Therefore, trastuzumab will be preferred over lapatinib when HER2+ therapy is to be given with an aromatase inhibitor.
        - References:
            - Schwartzberg LS et al. Lapatinib plus letrozole as first-line therapy for HER-2+ hormone receptor-positive metastatic breast cancer. Oncologist. 2010;15(2):122-9. PMID 20156908
            - Kaufman B et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol. 2009 Nov 20;27(33):5529-37. PMID 19786670

Criteria for new users
1. Diagnosis of HER2 or HER2/neu positive breast cancer
2. Breast cancer is locally advanced or metastatic
3. Left ventricular ejection fraction is normal at first request
4. Patient has undergone prior therapy with trastuzumab, an anthracycline and a taxane for

treatment of metastatic breast cancer
5. Lapatinib will be used in combination with capecitabine or trastuzumab
6. No prior tucatinib (Tukysa)
If above criteria are met, approve x 1 year

Doses:

In combination with capecitabine: 1250 mg once daily

In combination with trastuzumab: 1000 mg once daily

EBRx will not cover lapatinib in patients whose disease has progression on prior tucatinib. Efficacy has not been established in this setting.

References:

1. Cameron D et al. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. Oncologist. 2010;15(9):924-34. PMID 20736298
2. Blackwell KL et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012 Jul 20;30(21):2585-92. PMID 22689807 NCT00320385
3. Tykerb package insert. Novartis. 12/2018. Accessed 6/18/19. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/tykerb.pdf

Guideline:

NCCN guidelines for breast cancer. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Quantity Limits: 150 tablets/30 days

Revision history:

Date	Notes	Pharmacist's initials
6/19/2007	Insurance board voted T3PA, criteria written	JJ
5/15/12	Revision hx added	JJ
6/17/19	Criteria reviewed. Allow Lapatinib to be used with trastuzumab. New indication of HR+, HER2+ breast cancer not covered.	SK
5/27/20	Added that no prior tucatinib is allowed.	SK

Lenalidomide (Revlimid®)

2.5mg, 5mg, 10mg, 15mg, 20mg, 25mg capsules

EBRx PA Criteria

FDA approved for:

- Multiple myeloma, in combination with dexamethasone
- Multiple myeloma, as maintenance following autologous hematopoietic stem cell transplantation (auto-HSCT)
- Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities
- Mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib NOT COVERED:
    - Lenalidomide was compared to investigator's choice of therapy (rituximab, gemcitabine, fludarabine, clorambucil, or cytarabine) in patients with relapsed/refractory MCL and were ineligible for intensive chemotherapy or stem-cell transplant. Progression free survival was improved in the lenalidomide group (median 9 mo vs 5 mo). Overall survival was numerically improved in the lenalidomide group (28 mo vs 21 mo), but this change was not statistically significant. Of note, crossover to lenalidomide from the control arm WAS allowed. However, the OS analysis was adjusted for crossover and found no statistical difference. Will not recommend coverage at this time.
    - REFERENCES:
      Trněný, Marek, et al. "Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial." *The Lancet Oncology* 17.3 (2016): 319-331. PMID 2689978 NCT00875667
      Arcaini L et al. Prospective subgroup analyses of the randomized MCL-002 (SPRINT) study: lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma. Br J Haematol. 2018 Jan;180(2):224-235. PMID 29193019 NCT00875667
- Previously treated follicular lymphoma, in combination with a rituximab product
- Previously treated marginal zone lymphoma, in combination with a rituximab product NOT COVERED
    - The AUGMENT study enrolled patients with marginal zone lymphoma (MZL) and follicular lymphoma. Patients were required to have been treated with at least 1 prior therapy, and patients were treated with either lenalidomide+rituximab or placebo+rituximab. Each regimen was given for 12 cycles only. Median f/u was 28.3 mo. In the MZL subgroup, progression free survival was not different between groups (median 20.2 vs 25.2 months; HR, 1.00; 95% CI 0.47 to 2.13). Overall survival in the MZL subgroup (n=63) also did not differ between treatment groups (HR 2.89, 95% CI 0.56-14.92; rate of OS at 2 years: 82% vs 94%).

FDA-approved indication not listed in the lenalidomide package insert:

- In combination with tafasitamab (Monjuvi) for treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).
    - NOT COVERED This indication is supported by a single arm trial reporting response rate of 55% and median duration of response of 21.7 months. No overall survival or quality of life improvement has been reported to date.
        - Reference: Salles, G., Duell, J., Barca, E. G., Tournilhac, O., Jurczak, W., Liberati, A. M., & Kalakonda, N. (2020). Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. The Lancet Oncology.

Limitations of use: Lenalidomide is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia outside of controlled clinical trials.

Multiple Myeloma (treatment)
6. Diagnosis of active (not smoldering) multiple myeloma (see definition below)
7. Lenalidomide will be used in combination with dexamethasone with or without a third agent
8. Thromboembolic prophylaxis will be used (aspirin or anticoagulation) [Note: See black box warning. Thromboprophylaxis is required if lenalidomide is used in combination with dexamethasone or chemotherapy]
If criteria fulfilled, approve for 12 months. **QL: 21/28 days** Note: there is no multiple myeloma treatment indication that requires continuous dosing (e.g. 25 mg daily x 28 days). Do not approve continuous dosing.

Dose: The usual starting dose with normal renal function is 25 mg daily x 21 days, then take 7 days off (28-day cycle).

Some protocols use 25 mg daily x 14 days, then take 7 days off (21-day cycle).

Definition of active (non-smoldering) myeloma:

- Bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma

  AND at least 1 of the following:

  - Corrected calcium >1 mg/dL higher than the ULN or >11 mg/dL
  - Creatinine >2 mg/dL or CrCl <40 ml/min
  - Hemoglobin <10 g/dL or hemoglobin >2 g/dL below the LLN
  - One or more lytic bone lesions on imaging
  - Bone marrow plasma cells ≥60%
  - Serum free light chains kappa/lambda ratio ≥100 (if kappa disease) or ≤0.01 (if lambda disease)
  - >1 focal lesion on MRI studies ≥5 mm

-For treatment of active multiple myeloma, lenalidomide is effective in all lines of treatment. It is approved by EBRx in combination with dexamethasone, elotuzumab, ixazomib, bortezomib, carfilzomib, and daratumumab.

Multiple Myeloma (maintenance)
1. Diagnosis of active (not smoldering) multiple myeloma
2. Patient has undergone induction therapy followed by autologous stem cell transplant **OR** patient is ineligible for transplant and has undergone induction therapy only
3. The requesting provider has discussed with the patient the increased risk of secondary malignancies associated with long-term use of lenalidomide.
If criteria fulfilled, approve for 12 months. Note: there is no indication that requires 25 mg daily x 28 days. Do not approve this dose.
Dose: FDA-approved dosing is 10 mg daily continuously and may increase to 15 mg daily if tolerated. Alternative dosing: 10 mg daily x 21d, then take 7 days off. Maintenance therapy should continue at least 2 years. FDA approved dosing allows treatment until disease progression or unacceptable toxicity.

Evidence:

-After autologous stem cell transplant, lenalidomide maintenance therapy improves progression free survival (PFS) and a meta-analysis showed an improvement in overall survival (OS). Median OS was not reached in the lenalidomide maintenance group and was 86 months in the placebo or observation group (HR, 0.75; 95% CI, 0.63 to 0.90; P = 0.001)[1]. Trials show mixed results whether lenalidomide maintenance is beneficial for high-risk patients[2].

-After induction therapy (in patients not eligible for stem cell transplant): Lenalidomide maintenance consistently improves PFS, but OS benefit is less clear. However, a meta-analysis indicates that lenalidomide maintenance given after induction therapy improves OS (at four years: rate of OS was 69 versus 60 percent, HR 0.69; 95% CI 0.54-0.88)[3].

-Secondary malignancies (AML, MDS, solids tumors, and non-melanoma skin cancers) are associated with lenalidomide therapy. Rates of secondary malignancies was 6% with lenalidomide maintenance and 3% with placebo after stem cell transplant[1]. Patients should be educated on this risk.

REFERENCES:

1. McCarthy PL et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. J Clin Oncol. 2017;35(29):3279. PMID 28742454

2. Mateos MV et al. Management of multiple myeloma in the newly diagnosed patient. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):498-507. PMID 29222298

3. Palumbo A et al. Continuous Therapy Versus Fixed Duration of Therapy in Patients With Newly Diagnosed Multiple Myeloma.J Clin Oncol. 2015 Oct;33(30):3459-66. PMID 26282661

Anemia of Myelodysplastic Syndrome (MDS)
1. Diagnosis of MDS
2. Presence of 5q deletion [may be denoted as 5q-, 5q minus, or del(5q)]
3. IPSS risk category is low or intermediate-1 (see below)
4. Presence of transfusion-dependent anemia (defined in trials as no 8 consecutive weeks without RBC transfusions within the 16 weeks before randomization)
5. If EPO level ≤500 mU/ml, patient has failed prior treatment with an erythropoietin stimulating agent. [failure to reduce frequency of PRBC transfusion]

6. Absolute neutrophil count (ANC) is >500/mcL and platelet count is >25,000/mcL
7. Dose will be 10 mg daily (or appropriate renal dose) x 21 days, then take 1 week off [as done in MDS-004 study. Continuous dosing without a break is associated with more dose reductions and toxicity. See note below]
If criteria fulfilled, approve for 12 months.
Lenalidomide is not approved for MDS without 5q- or if IPSS risk category is INT-2 or high risk
Dose: FDA approved initial dose is 10 mg daily (without breaks), but dose used in main study was 10 mg daily x 21 days then take one week off. May take 2-4 months of therapy to see response. Evidence: In the MDS-004 study[1], lenalidomide induced transfusion independence for ≥ 26 consecutive weeks in 56.1% (10 mg daily 21/28 days) and 42.6% (5 mg daily 28/28 days) of patients compared with 5.9% of patients on placebo. Most patients responded in cycles 1 or 2 but some took 4 cycles of therapy to respond. There was also a clinically significant improvement in quality of life in the lenalidomide groups compared with placebo. 50% of patients received prior erythropoietin stimulating agent (ESA). Survival between groups was not statistically different, but may be confounded due to crossover allowed by protocol. For MDS patients with symptomatic anemia, NCCN (version 2.2019) recommends lenalidomide for patients with 5q- with or without 1 additional cytogenetic abnormality (except those involving chromosome 7).[2] ESMO 2014 guideline recommends that MDS patients with 5q- be first treated with an ESA if epo level is <500 mcU/ml[3]. Note that first author of ESMO guideline is also the first author of the MDS-004 study. A review article in Blood also recommends that ESA be used first in the same population.[4] Although responses to ESAs in 5q- patients appear to be lower than responses seen with lenalidomide, ESAs and lenalidomide have not been compared head to head. In light of ESMO and the Blood review article's recommendations, will recommend failure of ESA before access is granted to lenalidomide if EPO <500 mcU/ml due to lower cost of ESA. IPSS risk scoring and categories:

	Score Value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%)[b]	<5	5-10	—	11-20	21-30
Karyotype[c]	Good	Intermediate	Poor	—	—
Cytopenia[d]	0/1	2/3	—	—	—

[c]Karyotype:

-good=normal, -Y alone, del(5q) alone, del(20q) alone

-intermediate=other abnormalities (including t(8;21), inv 16, t(15;17)

-poor=complex (≥3 abnormalities) or chromosome 7 anomalies

[d]Refers to # of cell lines that are low: ANC <1,800/mcL, platelets <100k/mcl, Hb <10 g/dL

IPSS Risk category (% IPSS pop.)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
LOW (33)	0	5.7	9.4
INT-1 (38)	0.5-1.0	3.5	3.3
INT-2 (22)	1.5-2.0	1.1	1.1
HIGH (7)	≥2.5	0.4	0.2

REFERENCES:

1. Fenaux et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. Blood 2011 118:3765-3776. PMID 21753188 NCT00179621
2. Myelodysplastic Syndromes NCCN Guidelines Version 2.2019. Accessed at https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. April 25, 2019.
3. Fenaux et al. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Accessed at https://www.esmo.org/Guidelines/Haematological-Malignancies/Myelodysplastic-Syndromes. April 25, 2019.
4. Platzbecker U. Treatment of MDS. Blood 2019 133(10):1096-1107. PMID 30670446

Previously Treated Follicular Lymphoma
1. Diagnosis of grade 1, 2, or 3a follicular lymphoma
2. Patient has been treated with at least one prior systemic therapy
3. Documented relapsed, refractory, or progressive disease after prior systemic therapy
4. Lenalidomide will be given concomitantly with rituximab.
If criteria fulfilled, approve for 12 months. **NOTE: maximum duration of therapy for this indication is 12 cycles (28 days/cycle). If 12 cycles were not completed in the initial 1 year approval period, use judgment for whether a limited renewal should be approved. **QL: 21/28 days** Note: there is no follicular lymphoma indication that requires continuous dosing (e.g. 25 mg daily

x 28 days). Do not approve continuous dosing.
Dose: 20 mg daily x 21 days, then take 7 days off (28-day cycle). Treatment is continued up to 12 cycles MAXIMUM. Dose may be adjusted or delayed due to toxicity. <u>Evidence:</u> The AUGMENT study enrolled patients with grade 1-3a follicular lymphoma and marginal zone lymphoma. Patients were required to have been treated with at least 1 prior therapy. Lenalidomide+rituximab was compared to placebo+rituximab, and each regimen was given for 12 cycles only. Median f/u was 28.3 mo. In the follicular lymphoma subgroup, len+ritux improved progression free survival (median 39.4 vs 13.9 months, HR, 0.4; 95% CI 0.29 to 0.56). Overall survival was also improved (medians not reached, HR 0.45, 95% CI 0.22-0.92; rate of OS at 2 years: 95% vs 86%). Reference: Leonard JP et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2019 May 10;37(14):1188-1199. PMID 30897038

Date	Notes	Pharmacist's initials
	Criteria were established	CP
5/15/2012	Revision history added	JJ
9/11/13	Mantel cell lymphoma was not added as a covered type of cancer. The dropout rate in the trial was 45%; they measured only overall and complete response rate in phase 1 & 2 trials. Need more data. No OS or QOL data yet.	JJ
5/20/19	Criteria reviewed. Revised criteria for multiple myeloma active treatment and maintenance. For MDS require EPO before Revlimid if patient has epo level <500.	SK
9/9/19	Reviewed newer follicular lymphoma indication at call center's request. When lenalidomide is used in combination with rituximab, an improvement is seen in overall survival vs rituximab alone with a large difference in progression free survival. Will formally review at next P&T meeting.	SK

9/23/19	Reviewed all criteria. No further data have been released for mantle cell lymphoma diagnosis. Added criteria for follicular lymphoma. Marginal zone lymphoma will not be covered per 9/23/19 EBRx P&T meeting. (see data above)	SK
10/7/2020	Added new indication for lymphoma in combination with Monjuvi (tafasitamab). Not covered per 9/2020 P&T review	SK
10/19/2020	Criteria reviewed. No changes	SK

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Lenvatinib (Lenvima®)

4mg, 10mg capsules

EBRx PA criteria

FDA approved for:

- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC) Covered for age >65 year old only
- In combination with everolimus, for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior antiangiogenic therapy
- First-line treatment of unresectable hepatocellular carcinoma
- In combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation (accelerated approval).
    - NOT COVERED Data for this indication is limited to a single arm, non-comparing trial. Therefore, EBRx will not cover at this time.

Differentiated Thyroid Cancer
1. The patient has a diagnosis of differentiated thyroid cancer (such as papillary, poorly differentiated, follicular, Hurthle cell). [anaplastic and medullary thyroid cancers are not covered]
2. Thyroid cancer is progressing
3. Thyroid cancer is radioactive iodine refractory or resistant
4. The patient is >65 years old
5. Lenvatinib will be used as single agent
6. The patient has adequately controlled blood pressure (<150/90)
If all criteria are met, approve for 12 months.
Dosing: 24 mg once daily CrCl <30ml/min or Child-Pugh class C severe hepatic impairment: 14mg daily Lenvatinib was compared to placebo in an age unrestricted patient population. In the overall population, overall survival (OS) was not improved. Crossover was allowed but a post hoc crossover analysis still did not find a significant difference in OS. However, in patients >65 years

old, lenvatinib did improved overall survival (median not reached in lenvatinib group versus 18.4 mo placebo) in the older patient group only. The original study stratified patients by age.

References:

1. Schlumberger M et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015 Feb 12;372(7):621-30. PMID 25671254 NCT01321554Brose MS et al.
2. Effect of Age on the Efficacy and Safety of Lenvatinib in Radioiodine-Refractory Differentiated Thyroid Cancer in the Phase III SELECT Trial. J Clin Oncol. 2017 Aug 10;35(23):2692-2699. PMID 28613956 NCT01321554

Renal Cell Carcinoma
1. The patient has a diagnosis of progressive advanced or metastatic clear-cell renal cell carcinoma.
2. Lenvatinib will be given in combination with everolimus.*
3. The patient has previously been treated with a VEGF-targeted treatment for advanced disease (such as sunitinib, pazopanib, bevacizumab, cabozantinib, axitinib)
4. The patient has previously been treated with immunotherapy for advanced disease (such as nivolumab, pembrolizumab)
5. The patient has an ECOG status of 0 or 1.
6. The patient has adequately controlled blood pressure (<150/90)
If above criteria are met, approve for 12 months.
Dosing: 18mg once daily in combination with everolimus 5 mg daily CrCl <30ml/min or Child-Pugh class C severe hepatic impairment: 10mg daily Toxic side effects, first: 14mg daily Toxic side effects, second: 10mg daily Toxic side effects, third: 8mg daily Lenvatinib+everolimus improved overall survival compared with everolimus alone. Prior antiangiogenic therapy was required in the study and prior immunotherapy was allowed. We will require prior immunotherapy due to cost advantage of nivolumab versus the combination of lenvatinib+everolimus. If patient received ipilimumab/nivolumab OR pembrolizumab+axitinib in the first line setting, the immunotherapy criterion would be fulfilled. Reference: 1. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomized, phase 2, open-label, multicenter trial.

Lancet Oncol 2015;16:1473-82.

***Monotherapy with lenvatinib is not covered on this plan.**

Hepatocellular Carcinoma
1. The patient has a diagnosis of unresectable hepatocellular carcinoma (HCC).
2. Lenvatinib will be used as single agent
3. The patient's Child Pugh liver function score is A
4. The patient has an ECOG status of 0 or 1.
5. The patient has adequately controlled blood pressure (<150/90)
If above criteria are met, approve for 12 months.
Dosing: ≥60 kg: 12mg once daily <60 kg: 8 mg once daily Lenvatinib was compared to sorafenib in this patient population. Lenvatinib had improved progression free survival (7.4 mo vs 3.7 mo) and response rate (24% vs 9%), but overall survival was non-inferior (median 13.6 mo vs 12.3 mo). Cost of lenvatinib is slightly cheaper than sorafenib so will cover for now. Reference: Kudo M et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial.Lancet. 2018 Mar 24;391(10126):1163-1173. PMID 29433850 NCT01761266

Notes: Lenvima is available as packs of capsules. Each Rx should be limited to 30-day supply.

10mg (30 each)
14mg--- 10 & 4mg (60 each)
18mg---10mg and 2-4mg (15ea, 90ea)
20mg--- 2-10mg (60 ea)
24mg---2-10mg and 4mg (90 ea)

8mg---2-4mg (10ea, 60ea)

Date	What changed	PharmD Initials
8.19.2016	PA criteria written	GBB
12/29/2016		JJ
6/17/19	Criteria reviewed. Added new covered indications (thyroid cancer and HCC)	SK
6/16/2020	Criteria reviewed. Added new endometrial cancer indication (not covered) Added that cost of lenvatinib for hepatocellular carcinoma is slightly cheaper than sorafenib. No change to criteria	SK

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Linaclotide (Linzess®)

EBRx PA Criteria

1. The patient must have a diagnosis of IBS with constipation OR a diagnosis of chronic idiopathic constipation after a complete GI workup for other causes and meet the Rome II criteria: • less than 3 spontaneous bowel movements (SBMs) per week (occurring without the use of a laxative, enema, or suppository within the previous 24 hours) • AND having had one or more of the following signs or symptoms during more than 25% of bowel movements for at least 12 weeks within the previous 12 months: straining, lumpy or hard stools, or a sensation of incomplete evacuation • AND Does not meet criteria for IBS
2. The patient must have tried and failed miralax or be planning to take it concurrently with linaclotide.
3. There must have been a recent attempt to completely stop all opioid medications.
4. The patient must have tried and failed dietary modifications including eating more roughage.
5. The prescriber of linaclotide must state they have queried the AR PMP to assess the patient's current opioid use.
6. There must be no overlapping days supply of linaclotide with any of the following: lubiprostone,,plecanatide, naloxegol, or methylnaltrexone.
"Yes" to allow PA to be approved for 1y. QL approval for a 31 days supply.

References: Lembo AJ, Schneier HA, Shiff SJ, et al. Two Randomized Trials of Linaclotide for Chronic Constipation. N Engl J Med 2011;365:527-36.

Revision History:

Date	Notes	Pharmacist's initials
4/23/2013	PA criteria written	JJ
9/11/13	I added the website for Arkansas Prescription Monitoring Program. Querying this system was put forth by Dr. Golden as part of this PA criteria. (and for lubipristone (Amitiza).	JJ
9/26/13	I removed the requirement for call center pharmacists to query the	JJ

	AR PMP for this purpose. Per the Health Dept's general counsel, we cannot do this.	
9/27/16	I inserted the requirement for the prescriber to have queried the AR PMP to assess current opioid use.	JJ
6/12/17	I included CIC as a covered diagnosis due to inadvertent exclusion of that diagnosis. I also inserted no therapeutic duplication by inserting #6. I also added the Rome II criteria requiring parameters for CIC.	JJ

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Liraglutide (Victoza®)

EBRx PA Criteria

FDA-approved for:

- Treatment of T2DM; and for risk reduction of major CV events in adults with T2DM and established CV disease.
- Obesity and select overweight patients—NOT A COVERED INDICATION

Criteria for new users
1. Patient must have the diagnosis of type 2 diabetes mellitus.
2. Patient must have a documented Hb A1C in the previous 3 months of >7.0%.
3. Patient must be receiving metformin at 1000mg twice daily for the past 4 out of 5 months. Pharmacist should look back to be sure this occurred. OR The patient must have a contraindication to metformin that must be documented by the pharmacist.
4. No duplication of therapy with exenatide or other GLP-1 agonists (dulaglutide, albiglutide, semaglutide, exenatide) or with SGLT2 inhibitor therapy.

Criteria for continuation
1. The patient should have liraglutide on the profile as having filled for 10 of the 12 previous months.
2. The patient should have metformin on the profile as having filled for 10 of the 12 previous months.

Note: a. Metformin must be titrated slowly upward. Metformin 500mg BID is the initial dose.

References:

1. Marso, Steven P., et al. "Liraglutide and cardiovascular outcomes in type 2 diabetes." *New England Journal of Medicine* 375.4 (2016): 311-322.

2. Palmer, Suetonia C., et al. "Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials." *bmj* 372 (2021).

Revision History:

Date	What changed	Pharmacist's initials
7/13/15	I reformatted the proposal from 4/1/2011 to address individual drugs. The 4 of 5 month time period is to allow the HbA1C to correct while taking the prerequisite drug prior to allowing access to exenatide or liraglutide (or any GLP-1 agonist).	JJ

6/22/16	Due to the LEADER results, we removed some of the stipulations for receiving liraglutide. Also added the reference.	JJ
10/28/19	I reviewed the PA. I added reference 1, and the criteria 5. I also added the continuation criteria to ascertain adherence to both metformin and liraglutide.	JJ
10/28/2020	Reviewed. No changes.	JJ
3/29/2021	I provided explanation for 5a. and 5b. Deleted explanation about exenatide (not relevant)	JJ
4/22/21	Removed these criteria: 5a. Patient must be age 50+ with at least one CV coexisting condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage $\geq$3, or chronic heart failure. OR 5b. Patient must be age 60+ with at least 1 CV risk factor (microalbuminuria/proteinuria, HTN and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction). (select criteria consistent with the LEADER population in the liraglutide CVOT) per the contract.	JJ
4/26/21	Per EBRx P&T meeting 4/22, we removed criteria all together on SGLT2 inhibitors, but left criteria on GLP1a. We also decided to disallow concurrent SGLT2i and GLP1a therapy due to uncertain benefit with the combination. I also added ref 2.	JJ
3/28/22	I updated the use per the FDA indication, risk reduction in patients with established CV disease.	JJ

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Lubiprostone (Amitiza®)

EBRx PA Criteria

1. The patient must have a diagnosis of IBS with constipation OR a diagnosis of chronic idiopathic constipation after a complete GI workup for other causes OR be currently taking opiates and have opiate-induced constipation.
2. The patient must have tried and failed miralax or be planning to take it concurrently with lubiprostone.
3. There must have been a recent attempt to completely stop all opioid medications.
4. The patient must have tried and failed dietary modifications including eating more roughage.
5. The prescriber of lubiprostone must state they have queried the AR PMP to assess the patient's current opioid use.
6. . There must be no overlapping days supply of lubiprostone with any of the following: plecanatide, linaclotide, naloxegol, or methylnaltrexone.
"Yes" to allow PA to be approved for 1y. QL approval for a 31 days supply.

Revision History:

Date	Notes	Pharmacist initials
4/23/13	PA criteria written	JJ
9/11/13	I added the website for Arkansas Prescription Monitoring Program. Querying this system was put forth by Dr. Golden as part of this PA criteria.	JJ
9/26/13	I removed the AR PMP requirement. It cannot be queried for this purpose by call center pharmacists per the Health Dept's General Counsel	JJ
9/27/16	I inserted the requirement for the prescriber to have queried the AR PMP to assess current opioid use.	JJ
6/12/17	I included the diagnosis of CIC as an approvable diagnosis due to an inadvertent omission of the diagnosis previously. I also included the item to prevent therapeutic duplication with other similar agents shown in #6.	JJ
4/2/18	I added the indication of having opiate-induced constipation and currently taking opiates.	JJ
2/19/19	I reviewed the criteria.	JJ

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Lumacaftor-ivacaftor (Orkambi®)

Tablets: 200/125mg tablets, 100mg/125mg tablets

Packets: 100mg/125mg, 150mg/188mg

EBRx PA Criteria

Initial approval criteria:
5. The patient must have a diagnosis of cystic fibrosis with gene positive testing for being HOMOZYGOUS for the F508del mutation in the CFTR gene.
6. The patient must be between the ages of 2 years and age 12.
7. The patient must be currently demonstrating compliance with the evidence-based standard of care for inhaled therapies for cystic fibrosis.[1] (Or the patient must have experienced intolerance to dornase alfa &/OR bronchospasm or irritability with inhaled hypertonic saline and therefore cannot use it.—This must be documented in the medical record and represented to the call pharmacists.)
8. The patient must have had transaminases (ALT and AST) drawn prior to beginning the drug and be monitored every 3 months during the 1st year of treatment and then annually thereafter. [Ivacaftor should be interrupted if ALT or AST is greater than 5xs ULN and benefits/risks should be reconsidered.]
9. The patient must be a nonsmoker

***Quantity limit of 4/1 days; normal dose is 400mg/250 mg BID (2tabs BID)**

Deny if taking Kalydeco or Symdeko. There can be no therapeutic duplication with the drugs.

Continuation criteria to be determined after 6 months of being on Orkambi:
11. The patient must be currently demonstrating compliance with the evidence-based standard of care for inhaled therapies for cystic fibrosis.[1] (or the patient must have experienced intolerance to dornase alfa &/OR bronchospasm or irritability with inhaled hypertonic saline and therefore cannot use it).
12. The patient must have had transaminases (ALT and AST) drawn within the past 3 months and be less than 5 times the ULN. (if the patient has been taking Orkambi for 1 year, transaminases must be drawn only annually.)

13. The patient must continue to be a nonsmoker.
14. For continuation, the patient must demonstrate a clinical benefit with lumacaftor-ivacaftor as shown by lung function (FEV1), weight gain, or reduction in CF exacerbations or CF hospitalizations
15. The member must demonstrate adherence (6 fills out of 6 fills) with therapy as determined by refill history or reported by physician.

***Quantity limit of 4/1 days; normal dose is 400mg/250 mg BID (2tabs BID)**

If yes, **approve by GPID for 24 weeks for the requested formulation and strength with the following quantity limits:**

For patients age 2 to 5 years old:

- **Orkambi 100-125 mg granule packets (GPID 36937): #2 packets per day**
- **Orkambi 150-188 mg granule packets (GPID 42848): #2 packets per day**

For patients age 6 years and older:

- **Orkambi 100-125 mg tablets (GPID 42366): #4 tablets per day**
- **Orkambi 200-125 mg tablets (GPID 39008): #4 tablets per day**

References:

4. Mogayzel PJ, Naureckas ET, Robinson KA, Mueller G, et al. cystic Fibrosis Pulmonary Guidelines: Chronic medications for maintence of lung health. Am J Respir Crit Care Med. 2013;187(7):680-689.
5. Ramsey, B et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation. N Engl J Med 2011; 365: 1663-72
6. Orkambi (lumacaftor/ivacaftor) [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; July 2015.
7. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med 2015; 373:220.
8. Lexicomp. Orkambi. Accessed 12/10/18.

Date	Notes	Pharmacist
8/28/15	Criteria created	JJ
10/14/15	I changed the initial approval to 6months because the trial lasted only 24 w. The extrapolated 48w rate of pulmonary exacerbations reflects assumption.	JJ
10/14/15	I improved the question for #2 continuation criteria to better reflect that we are trying to ascertain normal LFTs in the correct time frame. Also, I defined compliance in #6continuation criteria. I also changed to key	JJ

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	for continuation criteria so if they answer yes to 1,2,4,& 5 and answer no to 3, they would be given access for 1 year.	
12/10/18	I updated the PA to include coverage down to age 2; also I included the packets.	JJ
12/16/19	I updated the criteria to cover only ages 2-12 with F508 del homozygotes. The recommendations state that for pts >12, they should receive Trikafta. Younger than age 12 should receive Orkambi or Symdeko.	JJ

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Lurasidone (Latuda®)

tablets

EBRx PA Criteria

FDA-approved for:

- Bipolar depression (monotherapy or adjunct to lithium or divalproex)
- Schizophrenia

Criteria for new users with Bipolar Depression
1. The patient must have the diagnosis of bipolar depression.
OR
Criteria for new users with Schizophrenia
1. The patient must have the diagnosis of schizophrenia.
2. The patient must have a QTc interval of >490ms as shown by EKG.
3. The patient must not be taking any QT prolonging drug other than the antipsychotic drug; if concurrent use, the prescriber must provide an EKG showing prolonged QTc while only taking the generic antipsychotic drug.

Note: The maximum dose for bipolar depression is 120mg daily; for schizophrenia the max dose is 160mg daily.

Revision History:

Date	What changed	Pharmacist's initials
1/29/2020	I wrote the criteria.	JJ

References:

1. Daisy Ng-Mak, Rachel Halpern, Krithika Rajagopalan & Antony Loebel (2019) Hospitalization risk in bipolar disorder patients treated with lurasidone versus other atypical antipsychotics, Current Medical Research and Opinion, 35:2, 211-219
2. Huhn, Maximilian, et al. "Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis." *The Lancet* 394.10202 (2019): 939-951.
3. Ziad Ali, Cunyet Tegin, Rif S. El-Mallakh. (2020) Evaluating lurasidone as a treatment option for bipolar disorder. *Expert Opinion on Pharmacotherapy* 21:3, pages 253-260.
4. Latuda package insert. [www.latuda.com/LatudaPrescribingInformation.pdf] Accessed 1/28/2020

Lutetium Lu 177 (Lutathera®)

370 MBq/ml (10 mCi/ml) vial [one vial contains equivalent of 200 mCi)

EBRx PA Criteria

FDA-approved for:

Treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

Criteria for new users
1. Diagnosis of midgut gastroenteropancreatic neuroendocrine tumor (GEP-NET) [e.g. neuroendocrine tumor or carcinoid tumor of the jejunum, ileum, appendix, right colon, or small intestine (not otherwise specified).
2. Tumor is unresectable
3. Somatostatin-receptor scintigraphy of tumor is grade 2 or higher (e.g. positive OctreoScan)
4. Tumor Ki67 index is 20% or less
5. Tumor has progressed (gotten larger) on a somatostatin analogue (lanreotide or octreotide)
6. Karnofsky performance status is at least 60.
If all criteria met, approve for 6 months. Treatment duration is limited to 4 doses TOTAL.

Note:

Lutathera was compared to high-dose octreotide in the above population. A ***trend*** to improved overall survival was demonstrated (median OS not reached in Lutathera arm vs 27.4 mo in the control arm; HR 0.52 95% CI 0.32-0.84, p=0.0068). The prespecified p-value threshold for significance at the time of analysis was 0.002, so statistical significance was not achieved. However, due to clinically significant delays in deterioration of global health (28.8 mo vs 6.1 mo) and physical functioning (25.2 mo vs 11.5 mo), EBRx will cover midgut NETs as defined in criteria.[1-4]

Note: The FDA approved indication also includes foregut and hindgut GEP-NETs, and off label use of Lutathera for thymic, bronchial, and pheochromocytomas may be requested. However, due to lack of randomized trials showing improvement in quality of life or overall survival in tumors of these primary sites, EBRx does not recommend coverage at this time.

References:

1. Strosberg J et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017 Jan 12;376(2):125-135. doi: 10.1056/NEJMoa1607427. PMID 28076709

2. Strosberg J et al. Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With 177Lu-Dotatate in the Phase III NETTER-1 Trial. J Clin Oncol. 2018 Sep 1;36(25):2578-2584. Epub 2018 Jun 7. PMID 29878866
3. FDA Review of Lutathera. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208700Orig1s000MultidisciplineR.pdf. Accessed 1/13/2020.
4. Lutathera PI. https://s3-eu-west-1.amazonaws.com/s3-lutathera/wp-content/uploads/2018/07/12100815/LUTATHERA_lutetium_Lu_177_dotatate_FDA_Prescribing_Information.pdf

NCCN guidelines: NCCN Guidelines Version 1.2019 Neuroendocrine and Adrenal Tumors.
https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf.

Revision History:

Date	What changed	Pharmacist's initials
2/24/2020	Reviewed at DCWG 2/3/2020 and criteria written.	SK
3/29/2021	Criteria reviewed. No change.	SK

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Macitentan (Opsumit®)

10mg oral tablets

EBRx PA Criteria

Macitentan (Opsumit) is FDA-approved for: the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to delay disease progression.

Criteria	
1. The patient must have the diagnosis of PAH (Group I) and either be taking a CCB and still having symptoms, or have failed a CCB.	☐Yes ☐No
2. The patient must have tried and failed a PDE5inhibitor (like sildenafil)	☐Yes ☐No
Dosing: 10mg QD. Max dose is 10mg QD.	

Quantity Limits: 1 tabs/1 day (30 tabs/30).

Revision History:

Date	What changed	Pharmacist's initials
2-6-15	I wrote the criteria.	JJ

Addendum:

Diagnostic Criteria and WHO categorization of PH						
	All Groups	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 5**
Description	**Elevated PAP**	**Pulmonary arterial hypertension**	**Pulmonary venous hypertension**	**PH due to hypoxemia**	**Chronic thromboembolic PH**	**Miscellaneous or multifactorial PH**
Estimated prevalence	**Up to 10-20% of the general population**	**15 cases/1,000,000 overall; 6 cases per 1mil for idiopathic PAH**	**>3-4 mil in US**	**20% in COPD pts w/ a prior hospitalization for COPD**	**0.5-2% (up to 3.8%) in survivors of acute PE**	**Unclear**
Diagnostic						

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criteria						
Mean PA pressure, mmHg	**≥25**	**≥25**	**≥25**	**≥25**	**≥25**	**≥25**
PCWP or LVEDP, mmHg		**≤15**	**>15**	**≤15**	**≤15**	**≤15**
PVR, dynes/s/cm		>240		>240	>240	>240

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Mepolizumab (Nucala®)

EBRx PA Criteria

Asthma, eosinophilic type
1. The prescriber must be a pulmonologist or allergist.
2. The patient must be age ≥ 6 and have demonstrated an eosinophil count of >150 cells/microliter in the past 6 weeks or >300 cells/microliter in the past year.
3. The patient must have an inadequate response to standard controller despite proper adherence.
4. There must be no concurrent asthma biologic agent use. (No overlapping days supply)
5. Does the patient have FEV1 >80% at the time he/she is requesting the first prior authorization[3]?
Patients must be 12 or older (no published data in younger) with the diagnosis of asthma not controlled by continued inhaled corticosteroids. They (arbitrarily) should have 75% ICS adherence rate.
Note: Nucala® (mepolizumab) is FDA approved as add-on therapy to optimal asthma therapy. Currently there is not peer-reviewed published literature to support its use as monotherapy in asthma and therefore will not be covered in this manner.
DOSE is 100mg SC in a physician office q4w.
If approved for coverage, PA is good for 3 months. Re-authorization for a PA will require the patient to be compliant with optimal asthma drug therapy as per the current NHLBI Asthma guidelines. Subsequent requests for PA require that the past 3 of 4 months have a paid claim for a LABA/ICS either separately or as a combination product. If this is not the case, the PA should be denied.
Eosinophilic granulomatosis with polyangiitis (EGPA)
1. The patient must be at least 18 years of age or older

2. The patient must have a diagnosis eosinophilic granulomatosis with polyangiitis for at least 6 months. Defined as:
• History or presence of asthma AND
• Blood eosinophil level of 10% or an absolute eosinophil count of more than 1000 cells/mm^3 AND
• Presence of 2+ criteria below typical of EGPA:
  • A biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation;
  • Neuropathy, mono or poly (motor deficit or nerve conduction abnormality);
  • Pulmonary infiltrates, non-fixed;
  • Sino-nasal abnormality;
  • Cardiomyopathy (established by echocardiography or mri);
  • Glomerulonephritis (hematuria, red cell casts, proteinuria);
  • Alveolar hemorrhage (by bronchoalveolar lavage);
  • Palpable purpura;
  • Antineutrophil cytoplasmic antibody (anca) positive (mpo or pr3)

3. History of **relapsing OR refractory disease**
4. The patient must have tried azathioprine, methotrexate, leflunomide, OR mycophenolate

REDACTED

OR have a contraindication to these therapies.
5. Patients MUST NOT have diagnosis of granulomatosis with polyangiitis (aka Wegener's granulomatosis) **or** microscopic polyangiitis **or** have had organ-threatening or life-threatening EGPA 3 months prior.
-If criteria 1-5 fulfilled for EGPA, drug approved for 300 mg q4weeks. (only formulated in 100 mg strengths, so 3 injections given per dose) -Asthma patients should should have 75% ICS adherence rate. It is prudent to follow less costly standard treatment prior to access to asthma biologics.

References:

1. Ortega, HG, et al. "Mepolizumab treatment in patients with severe eosinophilic asthma" New England Journal of Medicine 2014 September 25:371(13):1198-207. MENSA
2. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189-97. SIRIUS.
3. Wechsler, Michael E., et al. "Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis." *New England Journal of Medicine* 376.20 (2017): 1921-1932.

Date	What Changed?	Pharmacist's initials
3/14/2016	Criteria written	JJ
4/5/16	I spoke with CJ from GSK after communicating with EB at the DUEC meeting 4/4/16. He said the requirement for a positive skin test or with in vitro reactivity to a perennial aeroallergen is part of Xolair and not Nucala. I told him I would look into it. ICER's link to mepolizumab was not working for me to see at the time. Subsequently, I found mepolizumab did not have the requirement for either and so I removed it from our PA criteria. I added: "Subsequent requests for PA require that the past 3 of 4 months have a paid claim for a LABA/ICS either separately or as a combination product. If this is not the case, the PA should be denied."	JJ
12/20/17	Updated PA to include dx of eosinophilic Eosinophilic granulomatosis with polyangiitis (EGPA). Per #4 under EGPA, it is not known which first line therapy is superior, therefore, it seems reasonable to step through the less costly alternative before gaining access to MEP.	JK
12/8/2020	I lowered the age for use in asthma to >6y per FDA label.	JJ

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Meropenem/vaborbactam (Vabomere)

2g vial for IV

EBRx PA criteria

Note: Vabomere is **excluded** from **pharmacy benefits**. This is a **MEDICAL PA** document. Also note dosing is based on components of meropenem + vaborbactam. (Vabomere 4 grams = 2 grams mero + 2 grams vaborbactam).

FDA approved: complicated UTI including pyelonephritis in pts 18+ (12/8/17)

Dosing:

- **4 grams** (meropenem 2 grams and vaborbactam 2 grams) **q8h (for pts with eGFR ≥ 50 mL/min/1.73m^2)** by IV infusion over 3 hours for **up to 14 days.**
- **Renal Adjustment:**

eGFR[a] (mL/min/ 1.73m^2)	Recommended Dosage Regimen for VABOMERE (meropenem and vaborbactam) [b, c, d]	Dosing Interval
30 to 49	VABOMERE 2 grams (meropenem 1 gram and vaborbactam 1 gram)	Every 8 hours
15 to 29	VABOMERE 2 grams (meropenem 1 gram and vaborbactam 1 gram)	Every 12 hours
Less than 15	VABOMERE 1 gram (meropenem 0.5 grams and vaborbactam 0.5 grams)	Every 12 hours

PA Coverage Criteria:

1)

- The patient must have a diagnosis of complicated bacterial UTI or pyelonephritis caused by a bacteria susceptible to Vabomere AND
- The bacteria must be an Enterobacteriaceae in the presence of betalactamases/extended spectrum beta-lactamses (ESBL) of the following groups: KPC, SME, TEM, SHV, CTX-M, CMY, or ACT. AND
- The patient must have failed a trial of, be intolerant to, or the bacteria shown resistance to pip/tazo (Zosyn) or meropenem.

OR

2)

- The patient must have a diagnosis of complicated bacterial UTI or pyelonephritis caused by a bacteria susceptible to Vabomere AND
- The necessity of Vabomere is accompanied by a documented recommendation by an ID specialist.

3) The bacteria CAN NOT produce metallo-beta lactamses or oxacillinases with carbapenemase activity.

If either criteria 1 or 2 is fulfilled **AND** the bacteria does not fulfill criteria 3, approve **medical PA** for maximum of 14 day supply based on pts eGFR.

Revision History:

Date	Notes	Pharmacist's initials
12/8/17	Criteria were written	JK
2/20/18	I reviewed JK's criteria.	JJ

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Midazolam 5mg/intranasal spray (Nayzilam®)

EBRx PA Criteria

FDA-approved for: acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from patient's usual seizure pattern in patients with epilepsy ≥ 12 y/o.

Criteria for new users
1. The patient must have a diagnosis of seizure disorder.
2. The prescriber must be a neurologist.
3. The patient must have on the profile a concurrent antiseizure medication.
If all 3 of the above are true, approve for 6 months.

Criteria for continuation
1. For repeat fills, the patient must show adequate adherence to the concurrent antiepileptic medication as shown on the drug profile over the preceeding months.
If the continuation criterium is fulfilled, may approve for 12 months.

Quantity Limits: **QL of 6 units (3 packages of 2) per 30 days will be the limit.**

Note: The maximum limit is 5 sprays per month, however, they are packaged in cartons of 2's. Therefore, the pharmacy is not likely to break a package so a QL of 6 doses per 30 days will suffice.

References:

1. Detyniecki, Kamil, et al. "Safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters—a randomized, double-blind, placebo-controlled trial." *Epilepsia* (2019).
2. Wheless, James W., et al. "Safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters: An open-label extension trial." *Epilepsia* 60.9 (2019): 1809-1819.
3. Package Insert: Nayzilam.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211321s000lbl.pdf

Revision History:

Date	What changed	Pharmacist's initials
10/28/19	I wrote the criteria.	JJ
10/28/2020	Reviewed criteria. No changes.	JJ

CONFIDENTIAL

Nab-paclitaxel (Abraxane®)

100 mg vial

EBRx PA Criteria

FDA-approved for:

- Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
  - Not covered: Abraxane in the second line setting of advanced breast cancer has not been shown to significantly improve outcomes and increases risk for neuropathy Reference: Gradishar WJ et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005 Nov 1;23(31):7794-803. Epub 2005 Sep 19. PMID 16172456

- Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
  - The registration study for this indication compared Abraxane/carboplatin to paclitaxel/carboplatin and found no difference in overall survival with slight decrease in neuropathy (3% vs 12%).
    - Reference: Socinski MA et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol. 2012 Jun 10;30(17):2055-62. doi: 10.1200/JCO.2011.39.5848. Epub 2012 Apr 30. PMID 22547591
  - For NSCLC, Abraxane is covered only in combination with atezolizumab (see “other indications”) for non-squamous tumors only.
  - If request is for Abraxane in combination with pembrolizumab (Keytruda), the recommended alternative is conventional paclitaxel (Taxol).

- Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine NOT COVERED Abraxane + gemcitabine statistically improved overall survival compared with gemcitabine alone (median 8.7 mo vs 6.6 mo). EBRx does not believe this difference to be clinically significant.
  Reference: Goldstein D et al. J Natl Cancer Inst. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. 2015 Jan 31;107(2). pii: dju413. doi: 10.1093/jnci/dju413. Print 2015 Feb. PMID 25638248 NCT00844649

Other indications (both listed in atezolizumab package insert and covered by EBRx):

- In combination with atezolizumab for the treatment of adult patients with unresectable locally advanced or metastatic triple negative breast cancer whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA approved test.
- In combination with atezolizumab and carboplatin for the first-line treatment of adult patients

with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations

Metastatic Triple Negative Breast Cancer
1. Diagnosis of metastatic triple negative breast cancer
2. Nab-paclitaxel will be used in combination with atezolizumab (Tecentriq)
3. Patient meets criteria for atezolizumab for treatment of metastatic triple negative breast cancer
If above criteria are fulfilled, approve x 1 year (duration of therapy: until disease progression or unacceptable toxicity)
Note: See atezolizumab (Tecentriq) criteria for data summaries regarding criteria. Dose: Triple negative breast cancer (with atezolizumab): 100 mg/m2 IV on days 1, 8, and 15 of a 28-day cycle. Continue until disease progression or unacceptable toxicity.

Metastatic Non-Small Cell Lung Cancer
1. Diagnosis of metastatic non-small cell lung cancer
2. Nab-paclitaxel will be used in combination with atezolizumab (Tecentriq) and carboplatin
3. Patient meets criteria for atezolizumab for treatment of non-small cell lung cancer
If above criteria are fulfilled, approve x 6 months (maximum duration of therapy: 6 cycles)
Note: See atezolizumab (Tecentriq) criteria for data summaries regarding criteria. Dose: Metastatic non-small cell lung cancer (with atezolizumab and carboplatin): 100 mg/m2 on days 1, 8, and 15 of a 21-day cycles. Continue x 4-6 cycles.

Revision History:

Date	Notes	Pharmacist's initials
12/4/19	Drug reviewed at DCWG. Criteria written	sk

Naloxegol (Movantik®)

12.5mg & 25mg tablets

EBRx PA Criteria

FDA-approved for: opioid-induced constipation in adults with chronic noncancer pain

Criteria for new users
1. The patient must NOT have cancer-induced pain.
2. The patient must have chronic non-cancer pain.
3. The patient **must be receiving opioid medication of at least 30mg of oral morphine equivalent**.[1]
4. The patient must have tried and failed dietary modifications including eating more roughage.
5. The patient must have tried and failed miralax and senna and bisacodyl or be planning to take them concurrently with naloxegol.
6. The prescriber of naloxegol must state they have queried the AR PMP to assess the patient's current opioid use.
If yes to all of the above, the PA may be approved for 1 year. QL is 1/1 for a 31 days supply.

Quantity Limits: 1/1

Revision History:

Date	What changed	Pharmacist's initials
2/8/17	I wrote the criteria.	JJ
2/19/19	I reviewed the criteria and added references 2-5 below.	JJ
9/17/19	I reviewed the criteria and made no changes.	JJ

References:

1. Chey, William D., et al. "Naloxegol for opioid-induced constipation in patients with noncancer pain." *New England Journal of Medicine* 370.25 (2014): 2387-2396.

2. Crockett, Seth D., et al. "American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation." *Gastroenterology*, vol. 156, no. 1, 2019, pp. 218–226., doi:10.1053/j.gastro.2018.07.016.

3. Ford, Alexander C., Darren M. Brenner, and Philip S. Schoenfeld. "Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis." *The American journal of gastroenterology* 108.10 (2013): 1566-1574.

4. Sridharan, K., & Sivaramakrishnan, G. (2018). Drugs for Treating Opioid-Induced Constipation: A Mixed Treatment Comparison Network Meta-analysis of Randomized Controlled Clinical Trials. *Journal of Pain and Symptom Management,55*(2). doi:10.1016/j.jpainsymman.2017.08.022

5. Shah, Eric D, et al. “Efficacy and Tolerability of Guanylate Cyclase-C Agonists for Irritable Bowel Syndrome with Constipation and Chronic Idiopathic Constipation: A Systematic Review and Meta-Analysis.” *The American Journal of Gastroenterology*, vol. 113, no. 3, 2018, pp. 329–338., doi:10.1038/ajg.2017.495.

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Naloxone (Narcan®)

nasal spray 4mg/0.1mL

EBRx PA Criteria

FDA-approved for: opioid overdose (initial treatment of an opioid-associated life-threatening emergency).

Criteria for new users
1. The patient (under whom the Rx is being billed) must have an opiate medication on the current profile.

Note: The drug is NOT COVERED for “expedited partner” treatment.
This PA is good for ONLY ONE FILL. The DUEC wishes for the patient to be forced to request another prescription from their physician so that the physician knows the drug was consumed and there was need for opiate reversal (someone overdosed).

Quantity Limits: 1.

Revision History:

Date	What changed	Pharmacist’s initials
2/3/16	I wrote the criteria per the DUEC recommendations/wishes.	JJ
3/10/21	Criteria reviewed. No changes	JJ

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Naltrexone (Vivitrol®)

380mg IM

(generic) 50mg tablet (not PA'd)

EBRx PA Criteria

FDA-approved for:

- Treatment of alcohol use disorder.
- For the blockade of the effects of exogenously administered opioids.

  Note: Limitation of use: Oral naltrexone tablets have not been shown to be more effective than placebo for opioid use disorder due to poor patient adherence.

Criteria for new users
1. The patient must have a diagnosis of alcohol dependence or opioid use disorder.
2. The patient must currently be abstinent from alcohol for at least 7 days.
3. The patient must not be currently in acute opioid withdrawal or on an opioid analgesic or physiologically dependent on opioids.
4. The patient must be enrolled in alcohol or opioid use disorder counseling.
If all 4 above are true, approve a quantity limit of #1 kit per month for 12 months.

Note:

Alcohol use disorder dosing:

- oral 50mg daily (max 1000mg/day); alternative dosing 50mg weekdays then 100mg Saturday; 100mg QOD, 150mg q3d.
- IM 380mg q4w

Opioid use disorder dosing:

- 25mg X1, then 50mg QD. Alternative dosing 50mg weekdays with 100mg Saturday; 100mg QOD, 150mg q3d.

Quantity Limits: 1 IM per month.

References:

1. Bisaga, Adam, et al. "Outpatient transition to extended-release injectable naltrexone for patients with opioid use disorder: A phase 3 randomized trial." *Drug and alcohol dependence* 187 (2018): 171-178.

Revision History:

Date	What changed	Pharmacist's initials
10/28/2020	I wrote the criteria.	JJ

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Natalizumab (Tysabri®)

MEDICAL PA

EBRx PA Criteria

FDA-approved for:

- relapsing multiple sclerosis,
- Crohns disease

Relapsing Multiple Sclerosis **Criteria for new users**
7. Patient must have the diagnosis of relapsing MS with highly active disease as indicated by the prescriber (high frequency of relapses, MRI changes).
8. Patient must be at low risk for progressive multifocal leukoencephalopathy (PML) including those who are antibody positive as long as the anti-JCV antibody index is below 0.9.
9. No concurrent therapy with immunosuppressive drugs
10. No concurrent therapy with other RRMS drug therapies.

Crohn's Disease **Criteria for new users**
1. Patient must have the diagnosis of severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and TNF-alpha inhibitors.
2. Patient must have on their profile or in their medical record that they have tried a TNF-alpha inhibitor.
3. The patient must be considered low risk per the prescriber for PML.

Note: Dose is 300mg IV infusion q4W for either indication

Quantity Limits: 300mg IV infusion q28d

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Revision History:

Date	What changed	Pharmacist's initials
9/18/19	I wrote the criteria.	JJ
10/28/2020	I updated the criteria.	JJ

References:

5. Lexicomp. Natalizumab. Accessed 9/18/19.
6. UpToDate. DMT for RRMS. Accessed 9/18/19.
7. AAN. Practice Guideline: Disease-modifying Therapies for Adults with multiple sclerosis. American Academy of Neurology 4/24/2018. https://www.aan.com/Guidelines/Home/GetGuidelineContent/900
8. Sandborn, William J., et al. "Natalizumab induction and maintenance therapy for Crohn's disease." *New England Journal of Medicine* 353.18 (2005): 1912-1925.

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Nilotinib (Tasigna®)

EBRx PA Criteria

FDA-approved for:

- Adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- Adult patients with chronic phase (CP) and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib.
- Pediatric patients greater than or equal to 1 year of age with Ph+ CML-CP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.

Criteria for new users
4. Ph+ chronic myeloid leukemia (CML) in chronic phase, accelerated/advanced phase, or blast crisis with resistance*, intolerance, or contraindication to imatinib AND dasatinib (note: Ph+ may also be denoted as t(9;22) or BCR/ABL)
*Resistance to CML therapy is generally defined as any of the following: j. Inadequate response (defined as one of the following): i. After 3 months of therapy: Lack of complete hematologic response (Platelets <450 x10^9/L; leukocyte count <10 x 10^9/L) ii. After 3 months of therapy: Cytogenetic analysis shows >95% Ph+ metaphases iii. After 6 months of therapy: BCR-ABL1 (IS) >10% by quantitative PCR (qPCR) iv. After 6 months of therapy: Cytogenetic analysis shows >35% Ph+ metaphases v. After 12 months of therapy: BCR-ABL1 (IS) >1% by quantitative PCR (qPCR) vi. After 12 months of therapy: Cytogenetic analysis shows >0% Ph+ metaphases k. Progression of disease after a cytogenetic/hematologic response was achieved l. Documentation of mutation associated with drug resistance (typically checked after failure of first-line therapy—see below)
If criteria 1 is fulfilled, approve for 6 months
Criteria for continuation
Review of fill history indicates compliance with therapy
No progression of disease
No unacceptable toxicity
If continuation criteria fulfilled, approve for 1 year

Note about EBRx coverage: EBRx prefers imatinib for treatment of all phases of CML. Dasatinib is preferred after imatinib therapy because no drug has been shown to be superior to dasatinib in the second line setting. Also, dasatinib comes with a cost advantage and impending patent expiration. Nilotinib may be covered if the patient experiences resistance or intolerance to

imatinib and dasatinib. NCCN guidelines suggest using a non-imatinib agent for first line therapy for intermediate/high risk patients (risk determined by Sokal or Hasford methods) based on quicker time to response. Although quicker time to response has been associated with improved outcomes, non-imatinib agents have not been shown to improve overall survival compared to imatinib in the first line setting. Therefore, EBRx recommends that non-imatinib agents be denied access for first line use unless there is documentation of resistance or intolerance to a trial of imatinib.

Notes:

General CML information:

2. Cytogenetic monitoring: Chromosomes are examined directly for BCR-ABL chromosomal translocation. Number of cells in metaphase are examined. The number of metaphase cells that contain BCR-ABL are divided by total number of metaphase cells to get a percentage. Test requires bone marrow aspirate.
3. Molecular monitoring: Transcripts for BCR-ABL mRNA are quantified via real time PCR. "IS" denotes that the result is obtained via a standardized method. Test requires peripheral blood sample.
4. Cytogenetic and molecular monitoring are both valid. Since cytogenetic monitoring requires bone marrow biopsy, molecular monitoring may be preferred.
5. Analysis of BCR-ABL mutations is typically not done until failure of first-line therapy for chronic phase CML but may be checked sooner in advanced phase. If a mutation is documented that predicts resistance to imatinib or other therapy, an alternative agent should be used. NCCN has guide for treatment options according to which mutation is identified.

Mutation	Treatment recommendation
Y253H, E255K/V, or F359V/C/I	Dasatinib
F317L/V/I/C, T315A, or V299L	Nilotinib
E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H	Bosutinib
T315I	Ponatinib, omacetaxine, stem cell transplant, clinical trial

Notes regarding EBRx criteria:

10. Above criteria for resistance/failure of imatinib were obtained from NCCN guidelines Early Treatment Response Milestones page CML-3 in version 1.2019 and guideline published by European LeukemiaNet (ELN).[1] ELN proposes more restrictive resistance/failure definitions for second line therapy, however, NCCN has no specific guidelines. Therefore, will leave resistance/failure definitions as listed above for simplicity.
11. Nilotinib in the first line setting was shown to induce quicker responses as compared to imatinib. Though quicker responses have been associated with improved outcomes, no overall survival benefit has been demonstrated in the primary study.[2,3] Imatinib will be

preferred until more data is available.

12. After failure of first line therapy, there are no randomized trials showing one TKI to be superior to another.

Adult nilotinib dosing:

300-400 mg BID

Pediatric dasatinib dosing:

230 mg/m^2 BID rounded to nearest 50 mg (max 400 mg bid)

REFERENCE:

10. Baccarani M et al. Blood. 2013 Aug 8;122(6):872-84. PMID 23803709
11. Hochhaus A et al. Leukemia. 2016 May;30(5):1044-54. NCT00471497
12. Kantarjian HM et al. Lancet Oncol. 2011 Sep;12(9):841-51. NCT00471497

Quantity limits: 28-day supply max

Revision History:

Date	Notes	Pharmacist's initials
2/19/08	Insurance Board approved coverage at T2PA	JJ
3/13/08	Criteria were written	JJ/SV
	PA approval was changed from "good for 1 year" to "approve for 6 months".	JJ
5/15/12	Revision Hx added; NCCN reference added.	JJ
7/25/2012	Changed QL to accommodate the maximum doses.	JJ
8/28/2012	Added #1, approval for newly diagnosed chronic-CML. Deleted requirement to fail imatinib based on reference #3.	BA/JJ/JB
3/4/19	Updated criteria to require imatinib and dasatinib CML per 2/2019 P&T meeting. Added general information about CML monitoring and rationale for criteria.	SK
8/7/19	Criteria reviewed. No change.	SK
8/20/2020	Criteria reviewed. No change.	SK

Nimodipine

(generic oral compounded solution or suspension)

EBRx PA Criteria

FDA-approved for: subarachnoid hemorrhage: for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in adult patients with SAH from ruptured intracranial berry aneurysms regardless of their postictus neurological condition.

Criteria for new users
1. Diagnosis of subarachnoid hemorrhage in the past 30 days.

Note: The dose is 20-90mg q4h for 21 days.
If approved, the PA is good for 1 month.

References:

1. Lexicomp. Nimodipine. Accessed 1/14/21.

Revision History:

Date	What changed	Pharmacist's initials
2/20/18	I wrote the criteria.	JJ
1/14/21	I reviewed the criteria. References added.	JJ

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Nitisinone (Nityr®)

Nitisinone (Nityr) 2, 5, 10mg tablet

Orfadin 2, 5, 10, 20mg capsule

Generic 2, 5, 10mg capsule

Orfadin 4mg/mL (90mL) suspension

[Capsules and suspension 4mg/mL (90mL) suspension are not covered due to tablets being lower cost and the package insert has instructions for making a suspension from tablets.)

FDA-approved for: treatment of hereditary tyrosinemia type 1 (HT-1) as an adjunct to dietary restriction of tyrosine and phenylalanine

Criteria for new users
1. Must be diagnosed with HT-1 by the presence of succinylacetone
2. Must have evidence of liver disease
• If criteria are satisfied, PA is good for **TABLET FORMULATION** for 6 months; prescriber will need to provide new patient weight q6m until adult age. At adulthood, the PA can be recorded as valid for 1 year.
• **Nitisinone (Orfadin) capsules and suspension are excluded.**

Note: **A diet low or absent phenylalanine, tyrosine, methionine, and restriction of natural protein results in decreased tyrosine levels. However, this approach does not stop the production of succinylacetone, prevent the progression of liver or renal disease, or reduce the risk of developing hepatocellular carcinoma or neurologic abnormalities. Use of nitisinone has also NOT shown to reduce the progression of these outcomes.**

Quantity Limits: 2mg/kg/day is the maximum dose.

Revision History:

Date	What changed	Pharmacist's initials
10/26/16	I wrote the criteria.	JJ
12/14/16	I added for EBD the requirement for swallowing criteria so that those age 7 and under can have access to suspension unless they are currently taking tabs or caps.	JJ
2/20/18	Updated coverage to tablets from capsules and suspension. Capsule and suspension formulations are now EXCLUDED after today's IB meeting.	JJ
4/1/21	Criteria reviewed. No change	JJ

Nivolumab (Opdivo®)

EBRx PA Criteria

FDA-approved for:

- **Melanoma** (link to **metastatic** melanoma criteria) (link to **adjuvant** criteria)
  - Unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab
  - Patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection in the adjuvant setting
- **Non-Small Cell Lung Cancer (NSCLC)** (link to criteria)
  - Adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab.
  - Adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
  - Metastatic NSCLC and progression on or after platinum based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.
- **Small Cell Lung Cancer (SCLC)** NOT COVERED:
  - Metastatic (or extensive stage) SCLC with progression after platinum-based chemotherapy and at least one other line of therapy[a].
  - Registration trial was single arm trial with no comparison arm.[1]
  - Nivolumab was compared to nivolumab/ipilimumab and no overall survival difference was demonstrated.[2]
  - A randomized study of nivolumab vs. topotecan or amrubicin (Checkmate-331; NCT02481830) found no improvement in overall survival.[3,4,5] However, toxicity may be less. Peer reviewed full study not published as of 11/16/2020. Will monitor for full publication to assess potential toxicity benefit.
  - Second-line nivolumab would NOT be used in patients who progressed on or after atezolizumab- or durvalumab-containing therapy. EBRx does not cover any immunotherapy for non-first line treatment of SCLC.
  - References:

1. Antonia SJ et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016 Jul;17(7):883-895. PMID 27269741

2. Ready NE et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. J Thorac Oncol. 2019 Oct 17. pii: S1556-0864(19)33531-2. doi: 10.1016/j.jtho.2019.10.004. [Epub ahead of print] PMID 31629915 NCT01928394
3. https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-announces-phase-3-checkmate-331-study-doe (Accessed 8/8/19)
4. https://www.targetedonc.com/news/overall-survival-not-improved-with-nivolumab-in-sclc (Accessed 8/8/19)
5. Reck M et al. Efficacy and Safety of nivolumab (nivo) monotherapy versus chemotherapy (chemo) in recurrent small cell lung cancer (SCLC): Results from CheckMate 331. https://academic.oup.com/annonc/article/29/suppl_10/mdy511.004/5238042. Accessed 8/8/19.

- **Malignant Pleural Mesothelioma** (link to criteria)
    - Adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab
- **Renal Cell Carcinoma (RCC)** (link to criteria)
    - Advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy (VEGF inh, ex: sunitinib, pazopanib)
    - Intermediate or poor risk RCC previously untreated advanced RCC, in combination with ipilimumab
- **Classical Hodgkin lymphoma (CHL)** (link to criteria)
    - CHL that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin[a]
    - CHL that has relapsed or progressed after 3 or more lines of systemic therapy that includes autologous HSCT[a]
- **Head and Neck Cancer** (link to criteria)
    - Squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy
- **Urothelial carcinoma**
    - Locally advanced or metastatic disease with progression during or following platinum-containing chemotherapy[a] NOT COVERED: lack of comparative data
    - Locally advanced or metastatic disease with progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy[b] NOT COVERED: lack of comparative data
- **Colorectal cancer**
    - Adult and pediatric (age 12 and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan as

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a single agent or in combination with ipilimumab[a] NOT COVERED: lack of comparative data

- **Hepatocellular Carcinoma (HCC)**
    - Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab[a] NOT COVERED: lack of comparative data; EBRx does not cover any immunotherapy for HCC
    - Note: In untreated patients with advanced HCC, a randomized trial comparing nivolumab to sorafenib did not find an improvement in overall survival. Full study has not been published as of 2/10/2020. Link to press release: https://www.targetedonc.com/news/phase-iii-checkmate-459-trial-in-unresectable-hcc-misses-primary-endpoint (accessed 2/10/2020) [CHECKMATE-459, NCT02576509]
- **Esophageal squamous cell carcinoma** (link to criteria)
    - Treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy.

a=This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Melanoma, metastatic (new users)
1. Diagnosis of unresectable or metastatic melanoma.
2. The patient must be ECOG performance status 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity) at initiation
3. Patient does not have diagnosis of ocular/uveal melanoma.
4. No prior treatment for unresectable/metastatic melanoma.
5. Nivolumab will be used as single agent OR in combination with ipilimumab
If above criteria fulfilled, approve for 12 months
Criteria for continuation
1. No disease progression
2. No unacceptable toxicity
If both continuation criteria are fulfilled, approve for 12 months.

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Notes:

-Two trials support use of nivolumab in the first line setting in BRAF mutated and non-mutated melanoma. One showed improvement in overall survival vs chemo in untreated BRAF unmutated patients (37.5m vs 11.2 m[a]) and another showed improvement in overall survival vs. ipilimumab in untreated patients with or without BRAF mutation (36.9m vs. 19.9 mo[b]). Nivolumab also studied in second line setting after ipilimumab and showed better response rates vs chemo. Survival not improved in overall population per clinical trials.gov (NCT01721746), so EBRx will not cover in the second line setting.

-Ocular/uveal melanoma behaves differently and is treated differently from cutaneous melanoma.

-Nivolumab+ipilimumab has been shown to improve overall survival vs ipilimumab alone. Ipilimumab/nivolumab also comes extremely close to statistically improving overall survival compared to nivolumab alone in the 5-year update of the CHECKMATE 067 trial. Due to consistency of results compared to initial release of data and strong trend to improving overall survival, EBRx recommends coverage. However, note that toxicity is also increased in the ipi/nivo arm compared to nivolumab alone (grade 3-5 toxicity incidence: 59% vs 23%).[b,c] NCCN guidelines for cutaneous melanoma (version 2.2019) recommend nivolumab monotherapy as a preferred regimen for this indication. Nivolumab+ipilimumab has a category 1 recommendation but is non-preferred and should be considered for a very fit patient population.

Melanoma, adjuvant (new users)
1. Diagnosis of stage IIIB, IIIC, or IV melanoma (i.e. with metastasis to regional lymph nodes or distant metastases) that has been surgically resected
2. The patient must be ECOG performance status 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity) at initiation
3. Patient does not have diagnosis of ocular/uveal melanoma.
If all criteria fulfilled, approve for 12 months. NOTE: maximum treatment duration is 1 year. Do not approve more than 1 year TOTAL.

Note:

The endpoint to the trial showed a hazard ratio for disease ***recurrence or death*** of 0.65 (97.56%CI 0.51 to 0.83, P<0.001. (This is similar to PFS and Death evaluated together, when independently ***there may be no difference in survival because they did not evaluate it independently***). In this trial, the grade 3 or 4 AE rates were 14.4% Nivolumab vs 45.9% Ipilimumab, thus meeting EBRx's threshold for improving QOL due to being less toxic after 18 mo of follow-up.

REFERENCE:

Weber J et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. NEJM 2017 1826-1835 [CHECKMATE-238] NCT02388906 PMID 28891423

Non-Small Cell Lung Cancer (NSCLC)

1. **If previously treated, all of the following criteria must be met:**
   - Diagnosis of metastatic NSCLC (squamous or non-squamous)
   - Progression of disease after 1 prior platinum-containing doublet regimen (cisplatin or carboplatin plus another agent).
   - ECOG performance status is 0 (fully active), 1 (ambulatory but restricted in physically strenuous activity), or 2 (Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours) at initiation.
   - The tumor must be EGFR negative. **(Few EGFR+ patients were in the trials comparing PD-1 immunotherapies with docetaxel; however, two such trials did report on this subgroup. ICER's meta-analysis suggests there is a difference in OS for PD-1 immunotherapy. Compared with docetaxel, PD-1 OS was different in EGFR- and EGFR+ patients. Their analysis suggests there is little if any benefit with PD-1 immunotherapy compared to docetaxel in EGFR+ patients treated after progression on TKI therapy and prior to treatment with a platinum doublet. As such, there are reasons to be concerned that PD-1 immunotherapy could be inferior to a platinum doublet, which is more efficacious than docetaxel monotherapy).**[1]
2. **If no prior therapy for metastatic disease AND PD-L1 is ≥1%, all of the following criteria must be met:**
   - Nivolumab will be given with ipilimumab with or without 2 cycles of platinum-doublet chemotherapy
   - Tumor is EGFR and ALk negative
3. **If no prior therapy for metastatic disease AND PD-L1 <1%, all of the following criteria must be met:**
   - Nivolumab will be given with ipilimumab and 2 cycles of platinum-doublet chemotherapy
   - Tumor is EGFR and ALK negative

If all criteria fulfilled from either 1, 2, or 3, approve for 12 months

Criteria for continuation

No disease progression

No unacceptable toxicity

If both continuation criteria are fulfilled, approve for 12 months. Ipilimumab and nivolumab are continued until disease progression or unacceptable toxicity

Notes:

SECOND-LINE SETTING:

-CHECKMATE 017/CHECKMATE 057 showed pooled median OS was 11.1m nivolumab vs 8m docetaxel (a difference of 3.1m); HR 0.72, 95% CI 0.62, 0.84 at 2-year f/u.[2]

FIRST-LINE SETTING (nivolumab+ipilimumab):

-In patients with any level of PD-L1, nivolumab + ipilimumab was compared with platinum-doublet

chemotherapy.

-In patients with PD-L1 ≥1%, nivolumab + ipilimumab improved overall survival compared with platinum-doublet chemotherapy (median 17.1 mo vs 14.9 mo; HR 0.79; rate of survival at 3-yr was 33% vs 22%).

-In patients with PD-L1 <1%, this regimen did not statistically improve overall survival (median 15.2 mo vs 12.2 mo; HR 0.78, 95% CI 0.6-1.02). To achieve statistical significance for this *interim* analysis, p value must have been <0.023. Actual P-value was 0.035).[4,5] FDA approved this regimen for PD-L1 ≥1% only.

FIRST-LINE SETTING (nivolumab+ipilimumab+2 cycles of chemo):

-In patients with PD-L1 of any level, nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy improved overall survival compared to platinum-doublet chemotherapy (median 15.6 mo vs 10.9 mo; HR 0.66; rate of survival at 1-yr 63% vs 47%.[6,7]

REFERENCES:

1. ICER review re: use for EGFR negative tumors: https://icer-review.org/wp-content/uploads/2016/08/MWCEPAC_NSCLC_Evidence_Report_Plus_Supplement_101716.pdf
2. Horn L et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). J Clin Oncol. 2017 Dec 10;35(35):3924-3933. [CHECKMATE-017 and 057; NCT01642004 and NCT01673867]
3. Carbone DP et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med. 2017 Jun 22;376(25):2415-2426. CHECKMATE 026, NCT02041533
4. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2019;381(21):2020-2031. doi:10.1056/NEJMoa1910231. PMID 31562796. NCT02477826
5. Ramalingam SS et al. Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: Three-year update from CheckMate 227 Part 1. J Clin Oncol 38: 2020 (suppl; abstr 9500). https://meetinglibrary.asco.org/record/184651/abstract. Accessed 7/9/2020. NCT02477826
6. Opdivo PI. https://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed 7/9/2020.
7. Reck M et al. Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA. https://meetinglibrary.asco.org/record/184688/abstract. NCT03215706

Malignant Pleural Mesothelioma
1. Diagnosis of unresectable malignant pleural mesothelioma
2. No prior therapy for unresectable malignant pleural mesothelioma
3. Nivolumab will be used in combination wit ipilimumab
4. No active autoimmune disease, interstitial lung disease, or systemic immunosuppression
5. No active, untreated brain metastasis
6. ECOG performance status of 0 or 1
If all criteria are met, approve for 12 months. May renew approval if no progression of disease.
Note: Ipilimumab + Nivolumab were compared to standard, platinum-based chemotherapy in the above patient population. Ipilimumab/Nivolumab improved overall survival compared to chemotherapy (median 18.1 mo vs 14.1 mo; HR 0.74 95% CI 0.61-0.89)

Renal Cell Carcinoma (RCC)
FIRST LINE TREATMENT CRITERIA (no prior systemic therapy; must be used in combination
6. Diagnosis of advanced RCC 7. Tumor must have clear cell component 8. The patient must have IMDC intermediate or poor risk disease indicated by 1 or more of the following being present: • Less than 1 year from time of diagnosis to systemic therapy • Performance status <80% (Karnofsky) • Hemoglobin < lower limit of normal (LLN) • calcium > upper limit of normal (ULN) • Neutrophil > ULN • Platelets > ULN
CRITERIA FOR PREVIOUSLY-TREATED PATIENTS
1. Diagnosis of advanced/metastatic RCC 2. Patient has received at least one prior antiangiogenic therapy (e.g. VEGF inhibitors: sunitinib, pazopanib, cabozantinib, sorafenib, axitinib, bevacizumab, lenvatinib) 3. Patient must have Karnofsky performance status of >70%
DENIAL CRITERIA (for any line of therapy)
1. Deny access if patient has active brain metastases unless adequately treated as shown by the patient being neurologically stable for at least 2 weeks without the use of steroids or on stable or decreasing dose of ≤ 10mg daily prednisone (or equivalent).
2. Deny access if receiving therapy for an autoimmune disease or taking an immunosuppressant (>10mg daily prednisone equivalent.
3. Deny access if prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD-137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co stimulation or checkpoint pathways).
If criteria fulfilled, approve for 6 months (any line of therapy)
Criteria for continuation (for any line of therapy)
1. No disease progression
2. No unacceptable toxicity
If both continuation criteria are fulfilled, approve for 12 months.

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Notes:

FIRST LINE SETTING:

-In intermediate/poor risk tumors with clear cell component, nivo/ipi was superior to sunitinib alone (median OS not reached for nivo/ipi and 26 mo for sunitnib; HR 0.63 99.8% CI 0.44-0.89). Improvement in OS was accompanied by clinically meaningful improvement in QOL.[1,2]

-Nivo/ipi does not appear superior to sunitinib in FAVORABLE risk patients and is not FDA approved and should not be used at this time.[1]

-Dose: Nivolumab 3 mg/kg every 3 weeks PLUS ipilimumab 1 mg/kg every 3 weeks x 4 doses; THEN nivolumab monotherapy continues at 240 mg every 2 weeks or 480 mg every 4 weeks IV infusion until disease progression or unacceptable toxicity

PREVIOUSLY TREATED:

-Nivolumab improved overall survival vs everolimus in patients previously treated with one or two antiangiogenic agents (median OS 25 mo vs 19.6 mo)[2]

Head and Neck Cancer (squamous cell carcinoma only)
1. Diagnosis of recurrent or metastatic squamous cell carcinoma of the head and neck that progressed within 6 months after treatment with platinum-based chemotherapy.
2. Patient does NOT have nasopharyngeal cancer
3. The patient must be ECOG performance status 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity).
DENIAL CRITERIA
1. Deny access if patient has active brain metastases unless adequately treated as shown by the patient being neurologically stable for at least 2 weeks without the use of steroids or on stable or decreasing dose of ≤ 10mg daily prednisone (or equivalent).
2. Deny access if receiving therapy for an autoimmune disease or taking an immunosuppressant (>10mg daily prednisone equivalent.
3. Deny access if the presence of human immunodeficiency virus (HIV), hepatitis B virus infection, or hepatitis C virus infection.
4. Deny access if prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD-137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co stimulation or checkpoint pathways).
If all criteria fulfilled, approve for 12 months
Criteria for continuation
1. No disease progression

2. No unacceptable toxicity
If both continuation criteria are fulfilled, approve for 6 months.
Note: -OS benefit vs single agent systemic therapy (methotrexate, docetaxel, cetuximab) was 7.5 mo for nivolumab vs 5.1 months with standard therapy. At 1 year, 36% of patients were alive in nivolumab group vs 17% in control group. Severe adverse events occurred in fewer nivolumab patients vs chemotherapy (13% vs 35%). -Nivolumab has not been well studied for treatment of nasopharyngeal tumors. These tumors behave differently from other head and neck cancers and were excluded from reference trial. -Dose: 240 mg every 2 weeks or 480 mg every 4 weeks IV infusion. Continue until disease progression

Classical Hodgkin Lymphoma (relapsed/refractory)
1. Diagnosis of Classical Hodgkin Lymphoma
2. Classical Hodgkin Lymphoma has relapsed or progressed after autologous hematopoietic stem cell
3. No prior PD-L1 or PD-1 inhibitor
4. Nivolumab will be used as single agent
If above criteria fulfilled, approve x 12 months
Note: -Classical Hodgkin Lymphoma includes the following subtypes: nodular sclerosis, mixed cellularity, lymphocyte-predominant, and lymphocyte-rich, which are all treated similarly. - Nodular lymphocyte-predominant Hodgkin lymphoma is NOT a type of classical Hodgkin lymphoma and is not covered under this criteria
Notes: An indirect comparison found that nivolumab was superior for overall survival compared to brentuximab and best supportive care (median overall survival 100 mo vs 48 mo vs 25 mo, respectively) in patients who had undergone previous autologous hematopoietic stem cell transplant. REFERENCES:

Esophageal Squamous Cell Carcinoma (ESCC)
1. Diagnosis of advanced/metastatic esophageal squamous cell carcinoma (not adenocarcinoma)
2. Previously treated with fluoropyrimidine- and platinum-based chemotherapy (treatment must have contained a fluoropyrimidine (fluorouracil or capecitabine) AND a platinum agent (oxaliplatin,
3. No prior PD-L1 or PD-1 inhibitor
4. Nivolumab will be used as single agent

If above criteria fulfilled, approve x 12 months
Notes: In the above population, nivolumab was compared to investigator's choice of either paclitaxel or docetaxel. Overall survival was improved in the nivolumab group (median 10.9 mo vs 8.4 mo; HR 0.77) with fewer grade 3/4 adverse events in the nivolumab group (18% vs 63%). Serious grade 3/4 adverse events were also reduced in the nivolumab group (10% vs 20%). Quality of life parameters were also significantly improved in the nivolumab group. REFERENCE: Kato K et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial Lancet Oncol. 2019;20(11):1506-1517. doi:10.1016/S1470-2045(19)30626-6. PMID 31582355, NCT02569242

Revision History:

Date	What changed?	PharmD initials
2/20/2015	I wrote the criteria	JJ
3/4/15	FDA approved the indication NSCLC while on or after platinum CTX. The OS was 3.2m beneficial. The ASCO states a meaningful outcome over what already exists would provide a benefit of 3.25-4m of OS better than the comparator.	JJ
3/10/15	DCWG discussed. There are no peer-reviewed, published data to support the NSCLC indication or the melanoma indication after ipilimumab. There is however an article supporting 1st line treatment of melanoma in BRAF – patients. OS benefit over dacarbazine.	JJ
6/1/15	I changed PA criteria to allow NSCLC coverage due to a NEJM article that showed improved survival (median OS was 9.2m nivolumab vs 6m docetaxel) and 12 month survival was 42%N vs 24%D. SAEs were 7%N vs 24%D; treatment-related AEs leading to withdrawal were 3%N vs 10%D.	JJ
1/26/2016	I changed the PA criteria after the DCWG meeting 1/25/16. Please see references under individual criteria indications.	JJ
2/13/17	• I revised the NSCLC criteria to reflect coverage of nivolumab for 2nd line therapy but not as monotherapy for 1st line therapy. Since CheckMate-026 showed nivolumab failed to meet the primary endpoint of superior PFS compared to chemotherapy. In pts w/ >5% PD-L1 expression, the median PFS was 4.2m with Opdivo and 5.9m with platinum-based doublet chemotherapy (stratified HR=1.15 995%Ci: 0.91, 1.45, p=0.25). Overall survival was 14.4m for Opdivo vs 13.2m for chemotherapy (HR=1.02 (95%Ci: 0.80, 1.3) **Although the press release emerged 10/9/16, the peer reviewed publication still has not been published.** • I removed an FDA-approved indication for melanoma because the FDA did. Of note, we never covered this FDA-approved indication: (unresectable or	JJ

	metastatic melanoma and disease progression following ipilumumab and (if BRAF V600 mutation positive) a BRAF inhibitor.—**NOT a covered use)**	
2/13/17	I updated PA criteria after DCWG meeting on 1/18/2017 to include coverage for Head and Neck CA	GBB
1/28/19	1. New FDA indication listed: SCLC (not covered) 2. Melanoma (metastatic): expanded to cover BRAF unmutated pt (first line therapy only), added exclusion of ocular melanoma, updated notes and references 3. Melanoma (adjuvant): Added exclusion for ocular melanoma; added emphasis of duration of 1 year only. 4. NSCLC: updated formatting, notes, references (no change in criteria) 5. RCC: Add new indication (in combo with ipi): cover per criteria 6. Head and Neck: added that patient should NOT have nasopharyngeal cancer	Sk
6/17/19	Focused review: cover relapsed/refractory Hodgkin lymphoma as above	Sk
8/26/2019	All indications reviewed. Updated FDA approved indications. Changed approval period from 6 mo to 12 mo for all indications. Metastatic melanoma: added criterion to clarify that nivo will be covered as monotherapy only.	SK
10/28/19	Criteria reviewed. Update to allow use of nivolumab in combination with ipilimumab for first-line treatment of metastatic melanoma.	Sk
2/24/2020	Criteria reviewed. No changes to any criteria and no addition of new criteria **[Note: metastatic melanoma: watch for BRAFi/IO sequencing trials (NCT02631447 and NCT02224781).]**	Sk
6/5/2020	Added new FDA indication for use of nivolumab with ipilimumab for treatment of hepatocellular carcinoma (not covered)	SK
7/7/2020	Added new indications: esophageal squamous cell carcinoma (covered) and in combination with ipilimumab for non small cell lung cancer (covered)	SK
11/19/2020	Added new indication for mesothelioma (covered); other criteria reviewed (no change)	SK
2/10/2021	Under NSCLC criteria 2 and 3, changed from “If no prior therapy for advanced/metastatic disease” to “If no prior therapy for metastatic disease.”	SK

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Nusinersen (Spinraza®)

12 mg/5 mL

EBRx PA Criteria

is FDA-approved for: treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

Criteria for new users
6. The patient must be 12 years or younger at initial request.[4]
• The patient **must have** a diagnosis of Spinal Muscular Atrophy with all of the following criteria:[1,4] including genetic documentation of homozygous deletion or mutation in **SMN1 gene.** • Onset of clinical signs/symptoms consist with SMA at ≤ 48 months of age.[1,4] • Disease duration of ≤ 7 years.[4]
7. For infantile SMA, then they must also have 2 copies of the SMN2 gene[1], and no more than 3 copies of SMN. (Patients with 4 or more copies of SMN2 are likely to not develop the most severe forms of SMA and it may be reasonable to wait and monitor for signs of disease progression.)
8. No prior use of Zolgensma. (There are not data to support subsequent Spinraza use (benefit or detriment) in patients who were administered Zolgensma.)
9. Prescriber must be a neuromuscular specialist.
10. At the initial request, the patient must have NO HISTORY of the ability to walk independently (defined as the ability to walk ≥15 feet unaided.
If patient meets criteria above approve medical PA for 1 year. Medication is excluded from pharmacy.

Dosing: Intrathecal: **Loading dose**: 12 mg once q14 days for 3 doses; then the 4th dose is 12 mg administered once 30 days after the third dose. **Maintenance:** 12 mg once q4 months. Year 1 maximum doses is 6 doses. Year 2 and beyond, maximum doses are 3 per year.

Criteria for CONTINUATION.
11. The patient must have begun Spinraza treatment before age 12.[4]
7. The patient must have achieved sitting independently and be maintaining the ability to do so.
If patient meets criteria above approve medical PA for 1 year. Medication is excluded from pharmacy.

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Revision History:

Date	What changed	Pharmacist's initials
12/20/17	I wrote the criteria. Current approval is only for pediatric population described above. SMA has 5 types; this drug is for SMA1.	JK
3/11/19	I changed the age of symptom onset per the CHERISH trial. Those patients also had meaningful clinical improvement. I also added references 3&4. The meaningful improvement was estimated to be a 3 point change in HFMSE following 6 months of treatment. I also changed the disease duration to <7 years because CHERISH showed improvement in older patients. I did not include in the criteria a HFMSE score because this is used for research purposes and, to my knowledge, not used clinically.	JJ
7/22/19	I updated the criteria for the medical benefit after the 5/24/19 ICER update.	JJ

Ref:

1. Finkel, Richard S., et al. "Nusinersen versus sham control in infantile-onset spinal muscular atrophy." *New England Journal of Medicine* 377.18 (2017): 1723-1732. ENDEAR

2. ICER SMA Draft Evidence Report. Accessed 1/17/19.

3. Swoboda, Kathryn J., et al. "SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy." *PLos one* 5.8 (2010): e12140.[estimated meaningful endpoint of HMFSE to be 3 points]

4. Mercuri, Eugenio, et al. "Nusinersen versus sham control in later-onset spinal muscular atrophy." *New England Journal of Medicine* 378.7 (2018): 625-635. CHERISH

5. ICER Report. Spinraza and Zolgensma for SMA. https://icer-review.org/wp-content/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf

CONFIDENTIAL

Obinutuzumab (Gazyva®)

1000 mg/40 ml vial

EBRx PA Criteria

FDA Approved Indications:

- Treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) in combination with chlorambucil.
- in combination with bendamustine followed by obinutuzumab monotherapy for treatment of follicular lymphoma in patients who relapsed after, or are refractory to, a rituximab-containing regimen
- In combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adults with previously untreated stage II bulky, III or IV follicular lymphoma
    - NOT COVERED: Obinutuzumab + chemotherapy was compared to rituximab + chemotherapy. A slight benefit in progression free survival was demonstrated but no benefit has been demonstration for overall survival or quality of life yet.
    - Reference: Hiddemann W et al. Immunochemotherapy With Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety. J Clin Oncol. 2018 Aug 10;36(23):2395-2404. NCT01332968 PMID 29856692

Note: obinutuzumab is also FDA approved in combination with venetoclax for untreated CLL/SLL. This indication is listed in the venetoclax package insert and not in the obinutuzumab package insert, and is not covered by EBRx. The approval for first line use of venetoclax in combination with obinutuzumab was based on a study that enrolled older patients or patients with comorbidities. Progression free survival (PFS) was improved with obinutuzumab+venetoclax compared with obinutuzumab + chlorambucil (24-month rate of PFS 88% vs 64%). At 4 years, the rate of PFS remained improved with obinutuzumab/venetoclax (74% vs 35%). At a median follow up of 52 mo, the median OS has was not reached in either arm (HR, 0.85; 95% CI, 0.54-1.35; P = 0.4929), and the 4-year OS rate was 85% for the venetoclax arm and 83% for the control arm. Quality of life was not improved to a greater extent than the control group. See ibrutinib (Imbruvica) which does have overall survival data reported in the first-line setting.

References:

- Fischer K et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med. 2019 Jun 6;380(23):2225-2236. doi: 10.1056/NEJMoa1815281. Epub 2019 Jun 4. PMID 31166681 NCT02242942
- Al-Sawaf O et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2020 Sep;21(9):1188-1200. doi: 10.1016/S1470-2045(20)30443-5. PMID: 32888452.
- Al-Sawaf O et al. Rapid Improvement of Patient-Reported Outcomes with Venetoclax Plus Obinutuzumab in Patients with Previously Untreated CLL and Coexisting

Conditions: A Prospective Analysis from the CLL14 Trial. https://ash.confex.com/ash/2019/webprogram/Paper126542.html. Accessed 1/21/2020.

- 4-year follow up data (press release only; data presented at European Hematology Association 2021 Virtual Congress): https://www.cancernetwork.com/view/three-year-follow-up-continues-to-support-fixed-dose-venetoclax-obinutuzumab-in-treatment-na-ve-cll. Accessed 9/28/2021.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) in combination with chlorambucil (first line)
1. The patient must have previously untreated CD20-positive CLL.
2. The patient must be planning to use concomitant chlorambucil.*
3. The patient must have Binet stage C or symptomatic disease
4. The patient must have an Absolute Neutrophil Count ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L.
5. The patient must have a life expectancy of >6 months.
If the above criteria are met, approve coverage for 6 months. At this time, continuation of treatment beyond 6 cycles has not been studied and will not be approved. However, if the start of a cycle had to be delayed, and the schedule adjusted accordingly, a PA may be extended to account for that and allow the entire 6 cycles to be administered.
Dosing: Dosing is done in cycles of 28 days for a total of 6 cycles. Cycle 1: 100mg on day 1, followed by 900mg on day 2, followed by 1,000mg weekly for 2 doses (days 8 and 15). Cycles 2 through 6: 1,000mg on day 1 every 28 days for 5 doses.
Evidence: Obinutuzumab+chlorambucil (OC) or rituximab+chlorambucil (RC) was compared to chlorambucil (C) alone in CLL patients with coexisting conditions. Progression free survival was improved with OC and RC compared to chlorambucil. Treatment with OC prolonged overall survival compared with chlorambucil. RC did not improve overall survival compared with chlorambucil alone. There was no difference in overall survival between OC and RC. References: Goede V et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014 Mar 20;370(12):1101-10. PMID 24401022 NCT01010061

***Monotherapy with obinutuzumab is not covered on this plan.**

FOLLICULAR LYMPHOMA (relapsed/refractory, in combination with bendamustine)
1. The patient must have the diagnosis of CD20-positive follicular lymphoma refractory to rituximab (defined as failure to respond to or progression during any previous rituximab-containing regimen or progression w/in 6 months of the last rituximab dose).
2. The patient must be planning to use concomitant bendamustine.
3. The patient must have an Absolute Neutrophil Count ≥1.5 x 10^9/L and platelets ≥100 x 10^9/L.
4. The patient must have a life expectancy of >6 months.
5. The patient must be ECOG performance status 0-2 at initial request.
If the above criteria are met, approve coverage for 12 months. Obinutuzumab maintenance should be limited to 2 years (see dosing below).
Dosing: Dosing is given in cycles of 28 days for a total of 6 cycles. Cycle 1: 1000mg IV obinutuzumab on days 1, 8, & 15 PLUS bendamustine 90mg/m2/day IV on days 1 & 2. Cycles 2-6: 1000mg IV obinutuzumab on day 1 every 28 days for 5 doses PLUS bendamustine 90mg/m2/day IV on days 1 & 2 . After combination therapy is complete (6-8 cycles), obinutuzumab may be given every 2 months for up to 2 years beginning ~2 months after the last induction phase obinutuzumab dose
Evidence: Obinutuzumab+bendamustine was compared to bendamustine alone in patients with relapsed/refractory follicular lymphoma. Overall survival was improved in the obinutuzumab+bendamustine group and time to deterioration of HRQOL was prolonged in the obinutuzumab/bendamustine group compared with bendamustine alone (8.0 mo vs 4.6 mo). References: 1. Sehn LH et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016 Aug;17(8):1081-1093. PMID 27345636 NCT01059630 2. Cheson BD et al. Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. J Clin Oncol. 2018 Aug 1;36(22):2259-2266. PMID 29584548 NCT01059630 3. Cheson BD et al. Health-related quality of life and symptoms in patients with rituximab-refractory indolent non-Hodgkin lymphoma treated in the phase III GADOLIN study with obinutuzumab plus bendamustine versus bendamustine alone. Ann Hematol. 2017 Feb;96(2):253-259. PMID 27900446. NCT01059630

Date	What changed	PharmD Initials
8.17.2016	PA criteria written	GBB
2/27/17	I updated the criteria. Added ref #4.	JJ
3/8/17	I added ref #5. I also changed the criteria to cover follicular lymphoma due to an improvement in HRQOL, specifically time to deterioration from 8m (combo) vs 4.6m (on monotherapy bendamustine)	JJ
7/18/19	Criteria reviewed, will not cover new indication of untreated CLL (in combination with venetoclax) or new indication of untreated follicular lymphoma.	SK
7/7/2020	Criteria reviewed. Looked for opportunity to prefer rituximab over obinutuzumab but don't think it would be justified for any covered indications.	SK
9/28/2021	Criteria reviewed. Added new info for first line use in combination with venetoclax—substantial PFS benefit, but no OS benefit at this time. No change to criteria.	SK

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Ocrelizumab (Ocrevus®)

EBRx PA Criteria

Ocrevus is a CD20-directed cytolytic antibody **indicated** for the treatment of patients with **relapsing or primary progressive forms of multiple sclerosis.**

Primary Progressive Multiple Sclerosis (PPMS)
1) The patient has a diagnosis of **Primary Progressive Multiple Sclerosis (PPMS) AND**
2) Their most recent Expanded Disability Status Scale (Range 0-10, higher scores = greater disability) (EDSS) score is 3.0 to 6.5 when prescription is requested. **AND**
3) The patient's duration of MS symptoms must be < 15 years in patients with an **EDSS score of > 5.0** at the most recent screening; **OR** A duration of MS symptoms of < 10 years in patients with an **EDSS score of 5.0 or less during their most recent screening. AND**
4) A score on the pyramidal functions component of the Functional Systems Scale (see next page and ref#3 for link) of at least 2 (range, 0 to 6, with higher scores indicating greater disability). **AND**
5) The patient must be both age ≥ 51y AND without gadolinium-enhancing lesions. (If not, rituximab is the alternative treatment.)
OR
6) The patient has a diagnosis of **Primary Progressive Multiple Sclerosis (PPMS) AND**
7) The patient has failed treatment for PPMS with rituximab characterized by confirmed disease progression (CDP).
If the patient fulfills all criteria (1-5) **OR** all criteria in 6-7, then ocrelizumab will be approved for 1y (max of 1200mg/y. Dosing Regimen per package insert: • Start dose: 300 mg IV, followed two weeks later by a second 300 mg IV infusion. • Subsequent doses: 600 mg IV every 6 months (beginning 6 months after the first 300 mg dose). • After the two initial 300 mg starting doses, doses must be separated by at least 5 months.
Patients should be denied access if currently taking other MS disease modifying agents (Rituximab, Zinbryta, Copaxone, Glatopa, Interferon, Plegridy, Tecfidera, Gilenya, Aubagio, Lemtrada, Tysabri, or Mavenclad).

References:

1) Hawker, Kathleen, et al. "Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial." *Annals of neurology* 66.4 (2009): 460-471.
2) Montalban, Xavier, et al. "Ocrelizumab versus placebo in primary progressive multiple sclerosis." *N Eng J Med* 376.3 (2017): 209-220.

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3) Ocrelizumab FDA package insert.
4) Kurtzke, John F. "Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS)." *Neurology* 33.11 (1983): 1444-1444. http://www.neurology.org/content/33/11/1444.full.pdf+html
5) 1. He, Dian, et al. "Rituximab for relapsing-remitting multiple sclerosis." *Cochrane Database Syst Rev*12 (2011).
6) Hauser, Stephen L., et al. "B-cell depletion with rituximab in RRMS." *NEngJMed.* 358.7 (2008): 676-688. HERMES Trial Group; phase 2 trial. [NCT00097188]
7) 3. ICER. Disease-modifying therapies for RRMS and PPMS: Effectiveness and Value. 3/6/17, prepared by California Technology Assessment Forum. https://icer-review.org/announcements/final-ms-report/
8) NCT02746744. Rituximab Versus Fumarate in Newly Diagnosed Multiple Sclerosis. (RIFUND-MS). Rituximab, dimethyl fumarate or placebo. Population: N = 200, ages 18-40, both sexes. Diagnosis of RRMS or one demyelinating episode with ≥2 asymptomatic high-intensity lesions compatible with MS diagnosis No previous MS tx other than with interferon or glatiramer acetate, <5 years disease duration, ≥1 relapse, ≥ 2 T2 lesions or >Gd+ lesions in previous year, EDSS score 0-5.5. Primary outcomes: RR of relapse during study period. Est. Completion Date 8/2021.

Kurtzke Functional Systems Scores (FSS)
❑Pyramidal Functions:
0 – Normal
1 - Abnormal signs without disability
2 - Minimal disability
3 - Mild to moderate paraparesis or hemiparesis (detectable weakness but most function sustained for short periods, fatigue a problem); severe monoparesis (almost no function)
4 - Marked paraparesis or hemiparesis (function is difficult), moderate quadriparesis (function is decreased but can be sustained for short periods); or monoplegia
5 - Paraplegia, hemiplegia, or marked quadriparesis
6 - Quadriplegia
9 - (Unknown)

Revision History:

Date	Changes	Pharmacist
07/19/17	Document Created.	JK
8/6/17	**For PPMS:** I added reference 1 pertaining to rituximab's utility in PPMS in the subgroup <51yo or w/ GAD-enhancing lesions. We chose to prefer rituximab over ocrelizumab in PPMS due to reference 1, however, if the patient is ≥51yo AND without GAD-enhancing lesions, we would allow ocrelizumab. **For RRMS:** Although rituximab lacks the FDA indication for RRMS, we recommend coverage of rituximab for RRMS.[5-8]	JJ
12/17/2020	I added Mavenclad to the list of medications that should not be taken concurrently.	JJ

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Olaparib (Lynparza®)

100 and 150 mg tablets

EBRx PA Criteria

FDA-approved for:

Ovarian cancer, advanced (BRCA-mutated): Tablets, capsules: Treatment of deleterious or suspected deleterious g*BRCA*m advanced ovarian cancer in patients who have been treated with 3 or more prior lines of chemotherapy NOT COVERED Data leading to FDA approval are limited to single arm non comparative trial. A randomized study (SOLO3) has reported a progression free survival benefit with olaparib compared to chemo, however, an overall survival, quality of life, or toxicity benefit has been demonstrated to date. (reference: Penson RT et al. J Clin Oncol. 2020;38(11):1164-1174. doi:10.1200/JCO.19.02745. PMID 32073956 NCT02282020)

Ovarian cancer, advanced (HRD-positive), first-line maintenance therapy: in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either a deleterious or suspected deleterious BRCA mutation and/or genomic instability NOT COVERED
Benefit compared to placebo is limited to progression free survival only without overall survival or quality of life benefit. (reference: Ray-Coquard et al. NEJM 2019 381(25):2416-2428. PMID 31851799 NCT02477644)

Ovarian cancer, advanced (BRCA-mutated), first-line maintenance therapy: Tablets: First-line maintenance treatment of deleterious or suspected deleterious g*BRCA*m or somatic *BRCA*-mutated (s*BRCA*m) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer in adult patients who are in complete or partial response to first-line platinum-based chemotherapy. NOT COVERED Data is limited to progression free survival benefit at this time. Benefit compared to placebo is limited to progression free survival only without overall survival or quality of life benefit. (reference: Moore K et al. N Engl J Med. 2018;379(26):2495-2505. PMID 30345884 NCT01844986)

Ovarian cancer, recurrence maintenance therapy: Tablets: Maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who are in complete or partial response to platinum-based chemotherapy. COVERAGE LIMITED TO BRCA MUTATION POSITIVE PATIENTS ONLY

Breast cancer, metastatic (BRCA-mutated, HER2-negative): Tablets: Treatment of deleterious or suspected deleterious germline BRCA-mutated (g*BRCA*m), HER2-negative metastatic breast cancer in patients who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting; patients with hormone receptor-positive disease should have received a prior endocrine therapy (or be considered inappropriate for endocrine therapy) SEE CRITERIA

Pancreatic Cancer: maintenance treatment of adults with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. NOT COVERED Use in this population improved progression free survival by 3.6 months compared with placebo (7.4 mo vs 3.8 mo). An overall survival benefit has not been demonstrated to date. No differences in quality

of life compared to placebo. References: Golan T et al. N Engl J Med 2019; 381:317-327. PMID 31157963/ NCT02184195; Hall MJ et al. J Clin Oncol 38, 2020 (suppl 4; abstr 648) https://meetinglibrary.asco.org/record/182333/abstract.

Prostate Cancer: for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. SEE CRITERIA

BREAST CANCER: Criteria for new users
1. Diagnosis of unresectable or metastatic breast cancer
2. Disease is progressing or has recurred after previous therapy
3. Germline BRCA mutation is documented
4. Tumor is HER2 negative
5. Patient has received a taxane (docetaxel, paclitaxel) and an anthracycline (epirubicin, doxorubicin) in the neoadjuvant, adjuvant, or metastatic setting unless contraindicated.
6. If platinum-based chemotherapy was previously given (e.g. cisplatin, carboplatin), tumor did not progress during platinum-based therapy
7. If tumor is hormone receptor (e.g. estrogen and/or progesterone receptor) positive, patient has received at least one hormonal therapy for treatment of metastatic disease (e.g. tamoxifen, letrozole, anastrozole, exemestane, fulvestrant)
8. No prior PARP inhibitor (e.g. talazoparib, olaparib, rucaparib)
If all criteria fulfilled, approve for 12 months
Notes: Olaparib was compared to physician's choice of chemotherapy (vinorelbine, capecitabine, or eribulin) in the above patient population. Olaparib improved progression free survival (median 7 vs 4.2 mo). Overall survival was not statistically different between groups (median 19.3 vs 17.1; HR 0.9, 95% CI 0.66-1.23). However, there were fewer grade 3-5 adverse events in the olaparib group (36.6% vs 50.5%). There was also a longer delay in time to deterioration (TTD) of the EORTC QLQ-C30 global health status (median TTD not reached in olaparib group versus 15.3 mo in chemo group). Note: 8.2% of chemotherapy patients received a subsequent PARP inhibitor. See other notes at end of document. -Dose: 300 mg bid. Treatment is continued until relapse, progression of disease, or unacceptable toxicity. -Dose adjustments are recommended for renal impairment (200 mg bid for CrCl 31-50 ml/min) and toxicity (200-250 mg bid)

References:

1. Robson M et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017 Aug 10;377(6):523-533. NCT02000622 PMID 28578601
2. Robson ME et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol. 2019 Apr 1;30(4):558-566. PMID 30689707 NCT02000622
3. Robson M, Ruddy KJ, Im SA, et al. Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial. Eur J Cancer. 2019;120:20-30. doi:10.1016/j.ejca.2019.06.023 PMID 31446213 NCT02000622

OVARIAN CANCER: Criteria for new users

1. Diagnosis of RECURRENT epithelial ovarian, fallopian tube or primary peritoneal cancer
2. Deleterious or suspected deleterious BRCA mutation positive
3. Patient has completed platinum-based chemotherapy for treatment of recurrent disease and has achieved a partial or complete response.

If all 3 criteria fulfilled, approve for 12 months

Note:

-For RECURRENT ovarian cancer, olaparib has been shown to improve progression free survival (vs placebo) when given as maintenance therapy after a complete or partial response after chemotherapy[1,2].

-Overall survival has not been shown to be improved in overall populations in clinical trials which included patients with BRCA mutated and unmuted tumors. However, evidence shows improvement in overall survival in the subgroup of patients with a BRCA mutation.

-A post-hoc analysis of BRCA-mutated patients from NCT00753545, showed that, when study sites which enrolled patients who used a PARP inhibitor after the trial were excluded, overall survival was improved (POST HOC, HR 0.52 (95%CI 0.28-0.97), median OS was 34.9m olaparib vs 26.6m placebo.

-A follow up analysis of the SOLO2 trial[1,4] found an improvement in overall survival in BRCA-mutated patients as assessed by Myriad's assay. Median 52.4 mo vs 37.4 mo; HR 0.71, 95% CI 0.52-0.97; p=0.0306)

-Based on the above data, EBRx will restrict use to this very specific population (BRCA mutated, RECURRENT ovarian cancer for maintenance tx after response to chemotherapy).

-Dose: 300 mg bid. Treatment is continued until relapse, progression of disease, or unacceptable toxicity.

-Dose adjustments are recommended for renal impairment (200 mg bid for CrCl 31-50 ml/min) and toxicity (200-250 mg bid)

References:

1. Pujade-Lauraine, Eric, et al. "Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial." The Lancet Oncology 18.9 (2017): 1274-1284.
2. Ledermann, Jonathan A., et al. "Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial." The lancet oncology 17.11 (2016): 1579-1589. NCT00753545
3. Matulonis UA et al. Olaparib maintenance therapy in patients with platinum-sensitive, relapsed serous ovarian cancer and a BRCA mutation: Overall survival adjusted for postprogression poly(adenosine diphosphate ribose) polymerase inhibitor therapy. Cancer. 2016 Jun 15;122(12):1844-52. https://onlinelibrary.wiley.com/doi/epdf/10.1002/cncr.29995
4. Poveda A et al. Final overall survival (OS) results from SOLO2/ENGOT-ov21: A phase III trial assessing maintenance olaparib in patients (pts) with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation.J Clin Oncol 38: 2020 (suppl; abstr 6002). https://meetinglibrary.asco.org/record/185419/abstract.

PROSTATE CANCER: Criteria for new users

1. Diagnosis of castration resistant prostate cancer (mCRPC). Note: Castration-resistant prostate cancer (CRPC) is defined as progression of disease (rising PSA or increase in tumor size on imaging) when testosterone level is <50 ng/dl (due to LHRH agonist/antagonist OR orchiectomy).
2. Presence of metastatic disease
3. Disease progression on abiraterone OR enzalutamide
4. Alteration in at least 1 of the following 15 genes:
   BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L

If all criteria fulfilled, approve for 12 months

Note:

-The population described in the criteria were randomized to either olaparib or physician's choice of enzalutamide or abiraterone. The median overall survival at interim analysis was 17.5 months in the olaparib group and 14.3 months in the control group (HR, 0.67; 95% CI, 0.49 to 0.93). This improvement occurred despite 82% of control group crossing over to olaparib treatment. Also, at 6 months, more patients in the olaparib group were free of pain progression (85% vs 75%).

-Dose: 300 mg bid. Treatment is continued until progression of disease or unacceptable toxicity.

Reference:

de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020;382(22):2091-2102. doi:10.1056/NEJMoa1911440. PMID 32343890 NCT02987543

Quantity Limits:

100 mg tablets: 120 tablets/30 days

150 mg tablets: 120 tablets/30 days

Revision History:

Date	What changed	Pharmacist's initials
1/28/19	Wrote criteria	sk
1/29/19	I inserted the median OS from the post hoc analysis.	JJ
8/26/19	All criteria reviewed. Added criteria for breast cancer indication.	SK
1/29/2020	Reviewed new pancreatic cancer indication (not covered, see above)	SK
2/10/2020	Criteria reviewed. No changes made.	SK
6/24/2020	All criteria reviewed. Added new study results for relapsed ovarian maintenance indication. Added coverage for prostate cancer.	SK
8/4/2020	Edits to evidence summary for ovarian cancer. No change to criteria.	SK

FOR BREAST CANCER INDICATION: Differences between study inclusion/exclusion criteria and EBRx criteria with rationale

-Study required previous treatment with hormonal therapy in the adjuvant or metastatic setting. EBRx will require prior treatment with hormonal therapy for metastatic disease to push for use of less expensive therapies first.

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Omalizumab (Xolair®)

EBRx PA Criteria

ASTHMA

2. The patient must be age 6y or older.
2. The patient must have a diagnosis of moderate or severe persistent asthma with either a positive skin test or with in vitro reactivity to a perennial aeroallergen.
3. The patient must have a total serum IgE level ≥30 IU/mL.
3. The patient must be adherent to prescribed asthma controller medications and must have filled inhaled corticosteroids/LABA combination for a minimum of the past 3 of 4 months prior to this request.
4. The patient must NOT be dependent on systemic steroids to prevent serious asthma exacerbations[2].
5. The patient's FEV1 must NOT be better than 80% of the predicted value at the time he/she is requesting the first prior authorization[3].
Xolair failed to show a benefit in patients with FEV1 >80% at initiation. Xolair also failed to reduce exacerbations requiring maintenance systemic steroids.
Note: Xolair® (omalizumab) is FDA approved as add-on therapy to optimal asthma therapy. Currently there is not peer-reviewed published literature to support its use as monotherapy in asthma and therefore will not be covered in this manner.
DOSE is 150-375mg SC q2 or 4w as determined by serum total IgE level measured before the start of therapy. (See chart in the package insert.)
If approved for coverage, PA is good for 3 months. Re-authorization for a PA will require the patient to be compliant with optimal asthma drug therapy as per the current NHLBI Asthma guidelines[4].

CHRONIC IDIOPATHIC URTICARIA

For omalizumab to be covered for CIU, the following criteria must be met: **1. The patient must be 12 years or older.** **2. The patient must have a diagnosis of chronic idiopathic pruritis with the presence of itch AND hives for >8 consecutive weeks despite current use of H1 antihistamine treatment during this time period.** **3. The patient must have tried: cetirizine 10mg daily, levocetirizine 5mg daily, fexofenadine 180mg daily, loratadine 10mg daily, or desloratadine 5mg daily for 2 weeks.** **4. The patient must also avoid non-steroidal anti-inflammatory drugs and any other relevant triggers.** **5. Dose elevation of desloratadine or levocetirizine should be advanced to 4X the labeled**

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dose. **6. A second, different antihistamine should be added if dose escalation does not help.** **7. Montelukast 10mg daily must be tried for at least 4weeks.** **8. If still not controlled, first generation antihistamines hydroxyzine 100mg-200mg, or doxepin 100-150mg, must be tried at bedtime.**
The dose is not to exceed 300mg q4w. Usual dose is 150-300mg every 4 weeks regardless of IgE or body weight.
IF ALL OF THE ABOVE MEASURES HAVE BEEN TRIED, A PA MAY BE APPROVED FOR OMALIZUMAB FOR 12 MONTHS.

References:

1. Xolair PI.

2. NHLBI Asthma Guidelines.

3. Humbert M, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy: INNOVATE. Allergy 2005: 60: 309–316.

4. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria. NEJM 2013; 368:924-935.

5. THIS GUIDELINE WAS PRODUCED BY HIGHLY CONFLICTED EDITORS: Bernstein JA, Lang DM, Khan DA. The diagnosis and management of acute and chronic urticarial: 2014 update. J Allergy Clin Immunol. 2014;133(5):1270-1277.

Notes:

[1]Per the PI: Considering the risk of anaphylaxis and malignancy seen in Xolair-treated patients ≥12 years old and the modest efficacy of Xolair in the pivotal pediatric study, the risk-benefit assessment does not support the use of Xolair in patients 6-<12 years of age.

[2]Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.

[3]In all three of the studies, a reduction of asthma exacerbations was not observed in the Xolair-treated patients who had FEV1 > 80% at the time of randomization.

[4]NHLBI Asthma Guidelines 2007.

Omalizumab

The Expert Panel recommends that omalizumab may be considered as adjunctive therapy in step 5 or 6 care for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and LABA (Evidence B).

(See Evidence Table 13, Immunomodulators: Anti-IgE.)

Omalizumab, a recombinant DNA-derived humanized monoclonal antibody to the Fc portion of the IgE antibody, binds to that portion preventing the binding of IgE to its high-affinity receptor (FcεRI) on mast cells and basophils. The decreased binding of IgE on the surface of mast cells leads to a decrease in the release of mediators in response to allergen exposure. Omalizumab also decreases FcεRI expression on basophils and airway submucosal cells (Djukanovic et al. 2004; Lin et al. 2004). That study also showed significant decreases in sputum and bronchial eosinophils as well as in CD3+, CD4+, and CD8+ T cells in bronchial biopsy (Djukanovic et al. 2004). The vast majority of patients in clinical trials of omalizumab had moderate or severe persistent asthma incompletely controlled with ICS (Walker et al. 2004); all had atopy and IgE ≥30 IU/mL. Adding omalizumab to ICS therapy generally produced a significant reduction in asthma exacerbations (Busse et al. 2001a; Soler et al. 2001; Vignola et al. 2004) but not always (Holgate et al. 2004; Milgrom et al. 2001). (See Evidence Table 13, Immunomodulators: Anti-IgE.) Omalizumab, added to ICS, was associated with a small but significant improvement in

lung function (Busse et al. 2001a; Soler et al. 2001). In two trials, one open-label, in patients who had severe persistent asthma inadequately controlled on ICS plus LABAs, omalizumab reduced asthma exacerbations and ED visits (Ayres et al. 2004; Humbert et al. 2005). Omalizumab appears to have a modest steroid-sparing effect, allowing a median reduction of 25 percent over that of placebo in the trials (Busse et al. 2001a; Holgate et al. 2004; Milgrom et al. 2001; Soler et al. 2001). Omalizumab has not been compared in clinical trials to the other adjunctive therapies for moderate persistent asthma (LABAs, leukotriene modifiers, and theophylline), all of which improve outcomes and allow reduction of ICS dose. Omalizumab is the only adjunctive therapy, however, to demonstrate added efficacy to high-dose ICS plus LABA in patients who have severe persistent allergic asthma (Humbert et al. 2005). In studies Section 3, Component 4: Medications 226 August 28, 2007 of patients who have severe persistent asthma, omalizumab resulted in clinically relevant improvements in quality-of-life scores in significantly more patients (approximately 60 percent) than did placebo (approximately 43 percent) (Holgate et al. 2004; Humbert et al. 2005). Omalizumab is approved for patients 12 years and older who have proven sensitivity to aeroallergens: studies have been done in patients who have sensitivity to dust mite, cockroach, cat, or dog. One study of omalizumab in children 6–12 years of age demonstrated nonsignificant reductions in exacerbations and no improvement in lung function but did show small but significant reduction in ICS dose compared to placebo (Milgrom et al. 2001). Urticaria and anaphylactic reactions have been reported in 0.1 percent of cases (Berger et al. 2003; FDA 2003; Holgate et al. 2004; Lanier et al. 2003). Postmarketing surveys have identified anaphylaxis in an estimated 0.2 percent of treated patients, which resulted in an FDA alert (FDA 2007). Most of these reactions occurred within 2 hours of the omalizumab injection, and after the first, second, or third injections. However, reactions have occurred after many injections and after many hours. Therefore, clinicians who administer omalizumab are advised to be prepared and equipped for the identification and treatment of anaphylaxis that may occur, to observe patients for an appropriate period of time following each injection (the optimal length of

the observation is not established), and to educate patients about the risks of anaphylaxis and how to recognize and treat it if it occurs (e.g., using prescription auto injectors for emergency

self-treatment, and seeking immediate medical care) (FDA 2007). Adverse effects reported from omalizumab in the trials have also included injection-site pain and

bruising in up to 20 percent of patients (Holgate et al. 2004). In the trials reported to the FDA, twice as many patients receiving omalizumab had malignancies (20 of 48,127, or 0.5 percent) as did those receiving placebo (5 of 2,236, or 0.2 percent), but there were no trends for a specific tumor type.

Date	What Changed?	Pharmacist's initials
?	Criteria written	JJ
10/3/11	Added information/references included.	JJ
6/2/15	I included the diagnosis of chronic idiopathic pruritis and specified what the patient must have in order to gain access.	JJ
12/8/2020	I reviewed the criteria. I lowered the age to 6y per FDA approval.	JJ

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Long-acting Opiates or short-acting opiates of users of 60/90 past days

EBRx PA Criteria

Criteria for new users with cancer, palliative care, or hospice
1. Dx of cancer, palliative care, or hospice
If any of the above conditions are fulfilled, the PA will be approved for 1 year. Any amount, and any product or combination of opiate product may be approved.

LONG-ACTING OPIATE: Criteria for new users WITHOUT cancer, palliative care, or hospice
If the following prior authorization is approved, the maximum amount of combined total opioid the plan will pay for is 50 morphine milligram equivalents (MMEs)/ day for new users of long acting opiates or for users of short acting opiates who exceed a day's supply limit of more than 90 days of short acting opiates within a rolling 180 days.
1. The prescriber must attest that he/she has a plan in the medical record to taper off the prescribed opiate.
2. The prescriber must attest to having prescribed other pain relief methods (physical therapy)
3. The prescriber must be attest to checking the AR Prescription Monitoring Program and provide the date of the most recent query:____/____/____
4. After checking the PMP, the prescriber must agree to being one of not more than 2 prescribers of LA opiates for the patient and have a written pain contract in the patient's medical record.
5. The prescriber must agree to order, complete, and document the results of the patient's urine drug screen annually.
If these criteria are fulfilled, the PA may be approved for 1 year. 30 days' supply, Allow up to 50 MME of combined total opioid.

SHORT-ACTING OPIATE USERS SEEKING MORE THAN A 7 DAYS SUPPLY: Criteria for new users WITHOUT cancer, palliative care, or hospice
If the following prior authorization is approved, the maximum amount of combined total opioid the plan will pay for is 50 morphine milligram equivalents (MMEs)/day for new users of long acting opiates or for users of short acting opiates who exceed a day's supply limit of more than 90 days of short acting opiates within a rolling 180 days.
1. The prescriber must share the plan to taper off the prescribed opiate.
2. The prescriber must attest to having prescribed other pain relief methods (physical therapy)
3. The prescriber must be attest to checking the AR Prescription Monitoring Program and provide the date of the most recent query:____/____/____
4. After checking the PMP, the prescriber must agree to being one of not more than 2

prescribers of opiates for the patient and have a written pain contract in the patient's medical record.
5. The prescriber must agree to order, complete, and document the results of the patient's urine drug screen annually.
If these criteria are fulfilled, the PA may be approved for 1 year. 30 days' supply, Allow up to 50 MME of combined total opioids.

Revision History:

Date	What changed	Pharmacist's initials
9/1/17	We wrote the criteria.	JJ/GB/JK
	Claim denials at the pharmacy counter: o **Fast acting**: These claims that hit either over the 7 day limit (8, 9, 10 days, etc) or over the QL/day will deny with a message back to the pharmacy that reads: "Plan limitations exceeded. Plan covers 50MED/Day for 7 days at a time. Call EBRx at 855-757-9526 with questions." o **Long acting:** These claims deny with the normal PA required denial. Calls will be directed to the PA pharmacy line. - PAs have been loaded on members who were identified as chronic opioid users. Anyone who used more than 60 days' worth of opioid in a 90 day time frame was granted a PA (and several others as well who weren't quite within that time frame). This was a manual process, so there will be people who were missed in the initial file load due to human (aka – me) error. Hopefully those are minimal. **If someone calls in stating they can't get the claim to pay and the member has been getting opioids, first check the following:** o Has the opioid changed? Opioid PAs are entered in at the HICL level (whereas most PAs are entered in at the GPID level.), so a member should be covered if the strength of the drug changes. (i.e. if Billy changes from hydrocodone-apap 5-325 to hydrocodone-apap 10-325, his PA will still work for that. However, if Billy switches from hydrocodone to oxycodone, the PA will not pick up.) For now, if this happens, please call or send a task to pharmacy services to confirm a PA update can be done. o No PA exists, but the pharmacy states the member is a chronic user and/or states that the member has an ongoing (not new) cancer diagnosis and they should not be subject to	

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	the limits: please gather as much info as you can from the pharmacy, and then call or send a task to pharmacy services so that someone can research the patient's history. o Has the patient filled another opioid in the last 7 days, thus explaining the denial? **Opioid claims will follow the same refill logic as other medications**. Meaning, a new claim will pay at 75% of the previous claim's day supply. A 7 day claim will allow for a refill at 5.5 days. - Pharmacists: an updated spreadsheet with QLs for the long acting opioids will be sent your way. When entering PAs on these members, please enter the PA at the GPID level. Also, please enter QL approved. The maximum for most people will be 50MED/day for 30 days on long acting. To do this, it will be the same as our normal QL PAs, but we'll want to make sure to enter in the max DS as well. Under overrides, you'll enter in your quantity under Max Qty Supply and 30 under the max day supply. - **Fast acting** opioids listed on the attached spreadsheet will have a set quantity limit per 7 DS depending on the drug. The qty allowed per 7 days is noted in column "L" - **Fast acting** opioids listed on the attached spreadsheet should not exceed more than a 90 day supply in a 6 month period cumulatively. - **Long acting** opioids listed on the attached spreadsheet should be coded as PA required. - A member should not be able to fill two opioids at the same time. Example: member is on their 3rd day of Tramadol and tries to fill an RX for Hydromorphone HCL. The claim for Hydromorphone should deny.	

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Osimertinib (Tagrisso®)

40 mg, 80 mg tablets

EBRx PA Criteria

FDA-approved for:

- Adjuvant treatment after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test
- metastatic non-small cell lung cancer (NSCLC) with EGFR T790M mutation which has progressed on or after EGFR tyrosine kinase inhibitor therapy
- first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations

Criteria for new users
1. Diagnosis of locally advanced or metastatic non-small cell lung cancer
2. Tumor is positive for EGFR mutation (exon 19 deletion or exon 21 L858R)
3. If patient was previously treated with afatinib, erlotinib, dacomitinib, or gefitinib, tumor is positive for T790M mutation
If all criteria are met, approve x 1 year

Notes:

Dose: 80 mg once daily

- Options for first-line treatment of EGFR-mutated advanced NSCLC include osimertinib OR an earlier generation EGFR inhibitor (dacomitinib, erlotinib, gefitinib, afatinib).
- After progression of disease on first-line therapy, patients treated initially with osimertinib must then be treated with chemotherapy. Patients who were first treated with an earlier generation EGFR inhibitor qualify for second-line osimertinib only if the T790M EGFR resistance mutation is present.
- Osimertinib improves overall survival and/or quality of life in these treatment settings and is associated with less toxicity.

References:

1. Soria JC et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Jan 11;378(2):113-125. PMID 29151359 NCT02296125

2. Ramalingam SS et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med. 2020 Jan 2;382(1):41-50. PMID 31751012 NCT02296125

3. Holleman MS et al. First-line tyrosine kinase inhibitors in EGFR mutation-positive non-small-cell lung cancer: a network meta-analysis. Onco Targets Ther. 2019 Feb 20;12:1413-1421. PMID 30863108

4. Mok TS et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017 Feb 16;376(7):629-640. PMID 27959700 NCT02151981

5. Lee CK et al. Patient-Reported Symptoms and Impact of Treatment With Osimertinib Versus Chemotherapy in Advanced Non-Small-Cell Lung Cancer: The AURA3 Trial. J Clin Oncol. 2018 Jun 20;36(18):1853-1860. PMID 29733770

Quantity Limits: 30 tablets/30 days

ADJUVANT (POSTOPERATIVE) TREATMENT OF EARLY STAGE NON-SMALL CELL LUNG CANCER (NSCLC)
1. Diagnosis of non-squamous (e.g. adenocarcinoma) non-small cell lung cancer
2. Patient has undergone complete resection of the tumor [e.g. no residual disease]
3. Postsurgical pathological stage is IB, II, or IIIA
4. Tumor is positive for EGFR mutation (exon 19 deletion or exon 21 L858R)
5. ECOG performance status is 0 or 1 (on a scale of 0 to 5, with higher numbers indicating greater disability)
If all criteria are met, approve x 1 year. PA may be renewed for up to 3 years MAXIMUM.
Dose: 80 mg once daily for 3 years total • Osimertinib was compared to placebo in this population. Prior adjuvant platinum-based chemotherapy was allowed but not mandatory. • Disease free survival (% of patients alive and disease free at 24 mo): 90% (osimertinib) vs 44% (placebo) HR 0.17; 99.06% CI, 0.11 to 0.26 • Percent of patients with distance/metastatic recurrence: 4% (osimertinib) vs 28% (placebo)

Revision History:

Date	What changed	Pharmacist's initials
6/17/19	Criteria written	SK
3/30/2020	Added study for updated OS data for first line use. No change to criteria	SK
1/28/2021	Add criteria for new indication (adjuvant treatment of EGFR mutated lung cancer)	SK

Oxycodone ER abuse deterrent (Xtampza® ER)

9, 13.5, 18, 27, 36mg ER capsules

EBRx PA Criteria

FDA-approved for: treatment of pain: It is an opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve XTAMPZA ER for use in patients for whom alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1) • XTAMPZA ER is not indicated as an as-needed (prn) analgesic.

Criteria
1. No overlapping days supply with another long acting opiate unless, by the discretion of the call pharmacist, they are in the process of switching from another long acting opiate to Xtampza ER.
2. Doses above 72mg per day may be allowed by the call pharmacist if the patient is opiate tolerant

Note: Quantity Limits: 2/1; max dose is 288mg per day

References:

1. Katz, Nathaniel, et al. "A phase 3, multicenter, randomized, double-blind, placebo-controlled, safety, tolerability, and efficacy study of Xtampza ER in patients with moderate-to-severe chronic low back pain." Pain 156.12 (2015): 2458-2467.

Revision History:

Date	What changed	Pharmacist's initials
7/1/16	I wrote the criteria.	JJ

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Palbociclib (Ibrance®)

75 mg, 100 mg, 125 mg capsules

EBRx PA Criteria

FDA Approved Indications:

- Treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in the following settings:
  - With an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or men (NOT COVERED) [alternative for first-line use: ribociclib+fulvestrant]

    NOTE: As of 11/25/19 EBRx P&T Committee meeting: **NEW** requests for palbociclib as FIRST-LINE therapy will no longer be covered due to lack of overall survival benefit. This indication is based on progression free survival (PFS) benefit only without quality of life benefit. Patients with a previously approved PA will be grandfathered.

    The phase 2 PALOMA-1 trial did not demonstrate statistical improvement of OS with palbociclib/letrozole compared to letrozole alone.

    In the phase 3 PALOMA-2 trial: for first-line treatment of metastatic breast cancer, palbociclib was given in combination with letrozole 2.5mg daily and compared with placebo+letrozole. The palbociclib group was found to have significantly improved progression free survival (25 mo vs 15 mo). Overall survival data are not mature after 38 months of follow up. Crossover was not allowed in study, but 10% of placebo patients received a CDK inhibitor after the trial. There was also no demonstrated significant improvement in QOL.

    References:

    1. Finn RS et al. Overall survival results from the randomized phase 2 study of palbociclib in combination with letrozole versus letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (PALOMA-1, TRIO-18). Breast Cancer Res Treat. 2020 Sep;183(2):419-428. PMID: 32683565; PMCID: PMC7383036.
    2. Rugo HS et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. Breast Cancer Res Treat. 2019 Jan 10. PMID 30632023 NCT01740427
    3. Rugo HS et al. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial. Ann Oncol. 2018 Apr 1;29(4):888-894. PMID 29360932

  - With fulvestrant in patients with disease progression following endocrine therapy (COVERED FOR ENDOCRINE SENSITIVE DISEASE ONLY)

Patients who have received prior endocrine therapy

1. Diagnosis of hormone-receptor positive (aka HR+ or ER/PR+), HER2-negative (aka HER2/neu-negative), advanced/unresectable or metastatic breast cancer
2. Presence of endocrine-sensitive disease (see definition below)
3. EITHER disease progression on endocrine therapy given for advanced disease OR disease progression/recurrence within 12 months of completion of adjuvant endocrine therapy (tamoxifen or aromatase inhibitor; see example scenarios below)
4. If patient is pre- or perimenopausal, concurrent ovarian suppression/ablation will be employed.
5. No prior treatment with a CDK 4/6 inhibitor (abemaciclib, palbociclib, ribociclib)
6. Palbociclib with be given with fulvestrant

If the above criteria are met, approve for 6 months.

QL: #21/28d

Not covered: HER2+ or HR/ER/PR negative disease; palbociclib monotherapy

Endocrine-sensitive disease

Defined as one of the following (may verify through pharmacy records):

1. At least one previous endocrine-based therapy (e.g. tamoxifen or aromatase inhibitor) was given for metastatic disease for a duration of at least 24 weeks without disease progression.
2. At least 24 months of adjuvant/postoperative endocrine therapy was given before recurrence of disease

Example scenarios that are covered:

1. Patient presented with metastatic disease, was treated initially with an aromatase inhibitor for 24 weeks, and now has progression of disease
2. Patient underwent surgery with a plan to continue adjuvant endocrine therapy (tamoxifen or aromatase inhibitor) for 5 years. Pt developed recurrent disease 2 years after starting endocrine therapy

Dosing:

125mg once daily for 21 days, followed by a 7-day rest period to complete a 28-day treatment cycle. Palbociclib is given in combination with fulvestrant (given IM) in this setting.

Evidence:

In patients with advanced/metastatic breast cancer who progressed on prior endocrine therapy, palbociclib+fulvestrant improved overall survival in a subgroup of patients with endocrine-sensitive disease as defined above.

PFS, months (ET + CDKi	OS	QOL

versus ET +)		
9.5 vs 4.6[3] [HR 0.42; 95% CI, 0.32 to 0.56]	45 mo f/u: ▪ All pt: 35 vs 28 mo (HR 0.81; 95% CI, 0.64 to 1.03; p=0.09) [Not significant] ▪ In prespecified subgroup sensitive to endocrine therapy: 39.7 mo vs 29.7 mo (HR 0.72, 95% CI 0.55-0.94) -Endocrine sensitive definition: documented clinical benefit (response or stable disease ≥24 weeks) from a prior endocrine therapy regimen given for metastatic disease OR receipt of ≥24 months of adjuvant endocrine therapy before recurrence.	EORTC QLQ-C30 (MCID 10):[4] ▪ Global QOL score: statistically more worsening in control group but did not meet MCID ▪ Time to deterioration (global QOL): prolonged in palbociclib group; medians not reached (HR 0.641; 95% CI: 0.451-0.910) ▪ Time to deterioration (pain): median 8 mo vs 2.8 mo (HR 0.642, 95% CI 0.487-0.846)

References:

1. Rugo HS et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. Breast Cancer Res Treat. 2019 Jan 10. PMID 30632023 NCT01740427

2. Rugo HS et al. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial. Ann Oncol. 2018 Apr 1;29(4):888-894. PMID 29360932

3. Turner NC et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2018 Nov 15;379(20):1926-1936. PMID 30345905 NCT01942135

4. Harbeck N et al. Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial. Ann Oncol. 2016 Jun;27(6):1047-54. PMID 27029704

Grade	**ECOG Performance Status**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

5	Dead.

Date	What changed	PharmD Initials
12/11/2015	PA criteria written	GBB
7/14/16	I removed the criteria that would deny the patient access if they had brain mets. Although these pts were excluded from the key trials, having brain mets is not a contraindication.	JJ
10/18/16	I added anastrozole as an acceptable endocrine therapy to have received as endocrine therapy. Should be in postmenopausal women.	JJ
1/15/19	Added "**[Note: HER2 is often referred to as HER2/neu]**" to first criteria. HER2 is often referred to as HER2/neu in path reports and chart notes and they represent the same thing.	SK
5/20/19	Revised criteria for first line use and added criteria for subsequent lines of therapy as above.	SK
11/25/19	Criteria reviewed. Remove first-line indication from criteria due to PFS benefit only.	SK
7/7/2020	Minor wording change	SK
8/3/2020	Typo correction in evidence discussion	SK
8/21/2020	Criteria reviewed. No change	SK
9/28/2021	Criteria reviewed. No change. Added new reference for first-line indication.	SK
10/21/2021	Added "not" to the following statement: The phase 2 PALOMA-1 trial did not demonstrate statistical improvement of OS with palbociclib/letrozole compared to letrozole alone.	SK

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Paliperidone (Invega© ER oral)

1.5mg, 3mg, 6mg, 9mg tablets Extended Release ORAL tablets

EBRx PA Criteria

Initial Access
1. Requires the patient to have a diagnosis of schizophrenia or schizoaffective disorder.
2. Must have a history intolerable extrapyramidal symptoms not responsive to benztropine, trihexyphenidyl, or propranolol in the medical records; look back 5 years or as long as our profile's history and as long a history available in the medical records.
3. Must have taken risperidone in the past 90 days and developed EPS.
If all of these criteria are fulfilled, approve for 12 months.

- No concurrent days supply of therapeutic duplication with other forms of paliperidone, risperidone, olanzapine, quetiapine, ziprasidone, chlorpromazine, haloperidol, trifluoperazine, prochlorperazine, thioridazine, thiothixene, aripiprazole, or brexpiprazole.
- Deny if the patient is taking concurrent risperidone.

Revision History

Date	What was changed?	Pharmacist's initials
10/30/15	I wrote the criteria.	JJ

References

1. PI, Invega. Accessed 10/29/15.

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Palivizumab (Synagis®)

EBRx PA Criteria

Synagis® (palivizumab) is a humanized monoclonal antibody produced by recombinant DNA technology that is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV).

PRESCRIBER

The typical RSV season runs from November 1 to March 31. A maximum of five (5) doses will be covered per recipient. The last dose must be administered to the patient before March 31.

The Synagis® Prior Authorization (PA) Form is expected to be completed by the prescriber or their assigned staff personnel, and signed by the prescriber. Signature of a pre-completed form received by an outside party will not be accepted. Additional information may be requested, such as a discharge summary.

The recommended Synagis® dose is based on weight at 15mg/kg. Prescribe minimum units necessary for the dosage.

PHARMACY

Dispensing Guide:

Weight	Dosage	Dispense Units
Up to 3.3 kg	up to 49.5 mg	1 x 50 mg vial
3.4 kg to 6.6 kg	51 mg to 99 mg	1 x 100 mg vial
6.7 kg to 10 kg	100.5 mg to 150 mg	1 x 100 mg vial + 1 x 50 mg vial
10.1 kg to 13.3 kg	151.5 mg to 199.5 mg	2 x 100 mg vials
13.4 kg to 16.6 kg	201 mg to 249.5 mg	2 x 100 mg vials + 1 x 50 mg vial
16.7 kg to 20 kg	250.5 mg to 300 mg	3 x 100 mg vials

Note: Synagis® is to be given every 28-30 days during RSV Season. The RSV season is November through March.

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American Academy of Pediatrics (AAP) Committee on Infectious Diseases, "Modified Recommendations for the Use of Palivizumab for the Prevention of Respiratory Syncytial Virus Infections," *Pediatrics*, 2009, 124:1-8.

American Academy of Pediatrics (AAP) Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134:e620-e638. (Technical Report)

American Academy of Pediatrics (AAP) Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134:415-420. (Policy Statement)

Date	What changed?	Pharmacist's initials
5/15/12	Revision History added	JJ
1/29/13	Updated dates to reflect 2012-2013 season and added reference	DD
7/30/14	Updated to include the 2014 RSV recommendations from AAP. Pediatrics. 2014;134:415-20.	JJ
9/29/16	Updated to match the AAP recommendations from 2014. *Removed* *Chronic lung disease of prematurity (CLD)* ***AND*** *≤12 months of age at the start of RSV season (November 1)*, redefined the requirement for CLD including coverage in the second year of life, updated the requirements for hemodynamically significant cyanotic congenital heart disease (CHD) or hemodynamically significant acyanotic CHD.	CP
10/28/2020	I searched for new recs. The CDC website and PubMed sent me to the same article. The 2014 guidelines are still the latest. https://pediatrics.aappublications.org/content/134/2/415.full	JJ
08/24/2021	Due to unusual summer spike in infections, EBRx P&T Committee voted to suspend the requirement for the month to be Nov-March. As of August 19th 2021 the requirement is suspended until September 30th, 2021. All other criteria remain intact. The criteria suspension will be revisited in September 2021 Pharmacy and Therapeutics Committee meeting.	OD
10/21/2021	The seasonal criteria suspension carries until March 2022.	OD

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Evidence-Based Prescription Drug Program
Synagis® Prior Authorization (PA) Request Form

Prescription Drug PA Call Center

FAX - ATTN: EBRx
FAX (501) 526-4189

The form on this page is to be **COMPLETED** by and **RECEIVED** from the **prescribing provider**. The form **will not** be accepted from the providing pharmacy. Please fax this completed form to the PA Call Center for evaluation and processing.

☑ PLEASE COMPLETE ALL SECTIONS

Prescriber Information	Recipient/Patient Information
NPI Number:	ID Number:
Name:	Name:
Phone: ( )	Date of Birth: / /
Fax: ( )	Address:
Address:	
City: State: ZIP:	City: State: ZIP:

☑ **Birth Weight: _____ kg,** ☑ **Current Weight*: _____ kg,** ☑ **Date Measured: ____/____/____**
*Current weight will need to be measured within the past 30 days

☑ **Estimated Gestational Age at Birth: _____**

☑ Select **ONE**** of the following criteria the patient currently meets to be considered for RSV prophylaxis:

☐ 1. Chronic lung disease of prematurity (CLD) AND < 12 months of age at ***start*** of RSV season. CLD of prematurity is defined as gestational age <32 weeks, 0 days and a requirement for >21% oxygen for at least the first 28 days after birth. Palivizumab prophylaxis is recommended in the second year of life only for infants with CLD of prematurity as defined above and who continue to require supplemental oxygen, chronic systemic corticosteroid therapy or diuretic therapy during the 6 month period before the start of the second RSV season.

☐ 2. Former premature (≤ 28 weeks, 6 days estimated gestational age (EGA)) **AND** < 12 months of age at the ***start*** of RSV season. For infants born during RSV season, fewer than 5 monthly doses will be needed.

☐ 3. Infants ≤ 12 months of age at start of RSV season with hemodynamically significant congenital heart disease (CHD). Children that meet this criteria will be: **a)** infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures and **b)** infants with moderate to severe pulmonary hypertension. Infants with cyanotic heart defects in the first year of life will be reviewed on a case by case basis.

☐ 4. Infants <12 months of age at the start of RSV season with neuromuscular disease or congenital anomaly that impairs the ability to clear secretions from the upper airway because of ineffective cough.

☐ 5. Severe immunocompromised AND patient is < 2 years of age.

☑ **Signature of person completing form: _____ Date: _____**

☑ **Prescriber Signature: _____ Date: _____**
(By signature, the prescriber confirms the criteria information above is accurate and verifiable in patient records)

****Note:** If none of the above criteria are met, an exception request may be submitted in the form of a letter by the prescriber, identifying the patient and documenting the conditions for which the exception is being requested. These letters may be faxed to EBRx at **501-526-4189.**

Panitumumab (Vectibix®)

100 mg/5 ml and 400 mg/20 ml vials

EBRx PA Criteria

FDA approved for:

- Vectibix is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC) either:
  - In combination with FOLFOX for first-line treatment.
  - As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.

  Limitation of Use: Vectibix is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.

Criteria for patients with NO PRIOR THERAPY for advanced colorectal cancer
1. The patient must have a diagnosis of advanced/metastatic colorectal cancer
2. The patient has received no prior therapy for advanced/metastatic colorectal cancer.
3. Primary tumor is left sided (e.g. from the splenic flexure to the rectum).
4. The tumor is documented to be wild type (e.g. no mutation) in KRAS, NRAS, and BRAF genes.
5. Panitumumab will be used in combination with fluorouracil-based chemotherapy
If the above criteria are met, approve for 1 year.
Notes: Panitumumab+FOLFOX was compared to FOLFOX alone in a patient population regardless of location of tumor. The panitumumab arm had improved overall survival compared to FOLFOX alone (median 23.8 mo vs 19.4 mo, HR 0.83 95% CI 0.70-0.98). Recent data show that left-sided tumors (splenix flexure to rectum) derive significantly more benefit from EGFR inhibitors compared to left-sided tumors. Right-sided tumors may even have worse outcomes if treated with EGFR inhibitors. Data is strongest for the first-line setting. NCCN guidelines support this. Colorectal tumors with KRAS, NRAS, and/or BRAF mutations do not derive benefit from

EGFR inhibitors and may even have worse outcomes if treated with EGFR inhibitors.

Panitumumab has not been shown to improve or be detrimental to quality of life.

References:

1. Douillard JY et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol. 2014 Jul;25(7):1346-55. PMID 24718886

2. Venook AP et al. Impact of primary (1º) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol 34, 2016 (suppl; abstr 3504).

3. Lee MS et al. Association of primary (1°) site and molecular features with progression-free survival (PFS) and overall survival (OS) of metastatic colorectal cancer (mCRC) after anti-epidermal growth factor receptor (αEGFR) therapy. J Clin Oncol 34, 2016 (suppl; abstr 3506).

4. NCCN Colon Cancer Guidelines (version 2.2019). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

5. Koukakis R et al. Skin toxicity and quality of life during treatment with panitumumab for RAS wild-type metastatic colorectal carcinoma: results from three randomised clinical trials. Qual Life Res. 2016 Oct;25(10):2645-2656. PMID 27083443

Criteria for advanced colorectal cancer which has been PREVIOUSLY TREATED
1. The patient must have a diagnosis of metastatic colorectal cancer
2. The tumor is documented to be wild type (e.g. no mutation) in KRAS, NRAS, and BRAF genes.
3. The patient had disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens
4. Panitumumab will be used as single agent
If the above criteria are met, approve for 1 year.
Notes: Panitumumab monotherapy was compared with best supportive care in this patient population and was found to improve overall survival in tumors with wild type RAS and wild type BRAF (median 10 mo vs 6.9 mo).

Colorectal tumors with KRAS, NRAS, and/or BRAF mutations do not derive benefit from EGFR inhibitors and may even have worse outcomes if treated with EGFR inhibitor monotherapy.

Panitumumab has not been shown to improve or be detrimental to quality of life.

Reference:

Kim TW et al. Final Analysis of Outcomes and RAS/BRAF Status in a Randomized Phase 3 Study of Panitumumab and Best Supportive Care in Chemorefractory Wild Type KRAS Metastatic Colorectal Cancer. Clin Colorectal Cancer. 2018 Sep;17(3):206-214. PMID 29703606

Koukakis R et al. Skin toxicity and quality of life during treatment with panitumumab for RAS wild-type metastatic colorectal carcinoma: results from three randomised clinical trials. Qual Life Res. 2016 Oct;25(10):2645-2656. PMID 27083443

Revision History:

Date	Notes	Pharmacist's initials
2/6/07	Criteria were written	JJ
5/16/12	Revision hx table added	JJ
11/8/17	PA criteria updated w/ first line and monotherapy revision; first line use is not covered because reference #3 showed a nonsignificant improvement in OS vs FOLFOX4 CTX.	JK
7/18/19	Criteria reviewed. Added first line indication due to OS benefit that was demonstrated in a follow up analysis. Revised refractory criteria to include BRAF mutation status	Sk
7/7/2020	Criteria reviewed. No change.	SK

Pasireotide (Signifor®)

[Signifor: 0.3mg/mL (1mL), 0.6mg/mL (1mL), 0.9mg/mL (1mL)]

[Signifor **LAR** 10, 20, 30, 40, 60mg]

EBRx PA Criteria

is FDA-approved for:

- (Signifor LAR) Treatment of acromegaly in patients with an inadequate response to surgery and/or for whom surgery is not an option.
- (Signifor or Signifor LAR) Cushing disease in patients for whom pituitary surgery is not an option or has not been curative.

Acromegaly (Signifor LAR—administered IM)
1. The patient must have the diagnosis of acromegaly with an inadequate response to surgery or else not be a candidate for surgery.
2. The patient must be either non-diabetic, or have HbA1c <8%.
Dosing: IM 40mg q28d; if GH and/or IGF-1 not normalized in 3m, may increase to 60mg q28d. If AE occur or IGF-1 level decreases to less than lower limit of normal, decrease dose by 20mg decrements. If miss a dose, it may be given up to but no later than 14 days prior to the next dose.

OR

Cushing Disease **(either Signifor –administered SC or Signifor LAR—administered IM)**
1. The patient must have the diagnosis of Cushing disease and is not a candidate for surgery or for whom surgery was not curative.
2. The patient's HbA1C must be less than 8% before pasireotide injection.
3. The patient must have tried and failed to normalize serum cortisol levels with adequately dosed cabergoline.
Dosing: Signifor subQ: 0.6 or 0.9mg BID. SigniforLAR (IM) initial 10mg q28d; may increase after 4m if 24h urinary free cortisol level is not normalized. Max 40mg q28d. If miss a dose, it may be given up to but no later than 14 days prior to the next dose.

Quantity Limits: 4 weeks' supply

Ref 2 stated the 2nd generation somatostatin analog, pasireotide, improved mean growth hormone concentration to <2.5ug/L and normalized IGF-1 concentration better than the 1st gen, octreotide; 31.3% vs 19.2%; OR 1.94, 95%CI 1.19-3.17, p=0.007, respectively.

However, the pasireotide group experienced more hyperglycemia, DM, and diarrhea; most were mild-moderate in severity. SAEs 10% in pasireotide 40mg, 3% in pasireotide 60mg group, and 5% in octreotide.

Specifically, hyperglycemia-related AEs: 67% pasireotide 40mg group, 61% pasireotide 60mg group, 30% octreotide group.

References:

1. Lexicomp. Signifor. Accessed 11/5/2020.

2. Gadelha, Mônica R., et al. "Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial." *The lancet Diabetes & endocrinology* 2.11 (2014): 875-884.

3. Colao A, Petersenn S, Newell-Price J, et al. A 12 month phase 3 study of pasireotide in Cushing's Disease. N Engl J Med. 2012;366:914-24.

4. Broersen, Leonie HA, et al. "Effectiveness of medical treatment for Cushing's syndrome: a systematic review and meta-analysis." *Pituitary* 21.6 (2018): 631-641.

Revision History:

Date	What changed	Pharmacist's initials
5/24/13	JJ wrote the PA.	JJ
12/8/2020	JJ reviewed the criteria. Added acromegaly indication. Required cabergoline use in Cushings before access to Signifor. Added references 1 and 4.	JJ

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Pazopanib (Votrient®)

200 mg tablets

EBRx PA Criteria

FDA-approved for:

- Advanced renal cell carcinoma
- Advanced soft tissue sarcoma previously treated with chemotherapy NOT COVERED
  - **Although there was a PFS advantage with pazopanib versus placebo, it translated to no improvement in OS. Grade 3 fatigue was worse with pazopanib 13% vs 5% with placebo.**
  - RCT, phase 3, N=372. Pts w/ angiogenesis inhibitor-naïve, metastatic STS, progressing despite previous standard CTX, randomized to pazopanib 800mg QD or placebo, with NO SUBSEQUENT CROSSOVER. 1` endpoint PFS, ITT. Median follow-up was 14.5 m. Median PFS was 4.6m for P vs 1.6m for placebo (HR 0.31, 95%CI 0.24-0.40, p<0.0001). OS was 12.5m (10.6-14.8) with P vs 10.7m (8.7-12.8) with placebo (HR 0.86, 0.67-1.11, p=0.25)

    References:

    - van der Graaf, Winette TA, et al. "Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial." *The Lancet* 379.9829 (2012): 1879-1886.
    - Cesne AL et al. Safety and efficacy of Pazopanib in advanced soft tissue sarcoma: PALETTE (EORTC 62072) subgroup analyses. BMC Cancer. 2019 Aug 13;19(1):794. doi: 10.1186/s12885-019-5988-3.

Renal Cell Carcinoma
1. Patient must have a diagnosis of advanced renal cell carcinoma.
"Yes" to allow PA to be approved for 1y. QL is 30 days supply.
Note: Pazopanib has been shown to improve overall survival in patients with metastatic renal cell carcinoma. It has also been shown to be non-inferior and better tolerated than sunitinib in the first line setting. See specifics of non-inferiority trial below. RCT, N=1110, phase 3. Pazopanib 800mg daily or sunitinib 50mg daily X4w, then 2 w w/o treatment. 1` outcome was PFS, 2` outcomes were OS, safety, and QOL. P was non-inferior to sunitinib for PFS (HR 1.05; 95%CI, 0.90 to 1.22), NI margin was upper bound of 95%CI, <1.25). OS was similar (HR for death with P, 0.91; 95%CI, 0.76 to 1.08). Sunitinib had higher fatigue (63% vs 55%), higher hand-foot syndrome (50% vs 29%), higher thrombocytopenia (78% vs 41%); Pazopanib had higher ALT (60% vs 43%). The mean change from baseline in 11 of 14 HRQoL domains during the first 6m favored P (p<0.05 for all 11 comparisons).[1]

Pazopanib may also be cost effective compared with sunitinib in the first-line setting.[2]

REFERENCES

1. Motzer RJ et al. Pazopanib versus sunitinib in metastatic RCC. N Engl J Med 2013;369:722-31. (COMPARZ) NCT00720941
2. Delea TE et al. Cost-effectiveness of pazopanib versus sunitinib for renal cancer in the United States. Journal of managed care & specialty pharmacy 21.1 (2015):46-54.

Revision History:

Date	Notes	Pharmacist's initials
1/11/10	DUEC voted to approve T2PA with 2 w supply allowed per fill.	JJ
1/19/10	IB voted for T3PA with 2 w supply allowed per fill	JJ
5/15/12	Revision Hx table added	JJ
10/1/12	CP said the PBM has already programmed a 2 w supply limit for pazopanib.	JJ
7/5/17	JB informed me the PBM (MI) did not hardwire the 2w supply once they took over from Optum. He said the drug is NOT limited distribution but that regular pharmacies (Walmart) will not break a bottle and will only supply 30ds.	JJ
7/28/17	I reviewed the data for soft tissue sarcoma. There was no OS improvement for angiogenesis inhibitor-naïve, metastatic STS patients who progressed despite previous standard CTX. Although pazopanib is FDA approved for tx of advanced STS in pts who have received prior CTX, we do not recommend coverage of pazopanib for this purpose until evidence supports a benefit.	JJ
4/18/19	Criteria reviewed. Formatting updated. No significant changes	SK
1/29/2020	Criteria reviewed, no changes. Added reference for subgroup analysis of sarcoma trial. I could not locate any studies showing an overall survival benefit of pazopanib over another therapy or placebo.	SK
11/19/2020	Criteria reviewed. No changes.	SK

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Peginterferon beta 1a (Plegridy®)

EBRx PA Criteria

is FDA-approved for: treatment of patients with relapsing forms of multiple sclerosis

Criteria for new users
1. The patient must have a diagnosis of a **relapsing form** of multiple sclerosis.
2. The patient must be receiving no other interferons, or MS disease-modifying drugs (no data).

Note: The dosing is SC. Initial 63mcg on day 1, 94mcg on day 15. Then maintenance dosing is 125mcg every 14 days beginning on day 29.
The maximum dose is 125mcg every 14 days. This is also the quantity limit.

Reference:

Tolley K, Hutchinson M, You X, Wang P, et al. A network meta analysis of efficacy and evaluation of safety of subcutaneous pegylated interferon beta-1a versus other injectable therapies for the treatment of RRMS. PLoS ONE 10(6):e0127960.doi:10.1371/journal.pone.0127960. Published June 3, 2015.

Revision History:

Date	What changed	Pharmacist's initials
3/8/17	I wrote the criteria. **In 11/2014, the committee voted to exclude Plegridy due to lack of comparative evidence. A newer network meta-analysis provides this evidence and shows that in RRMS patients, the product peginterferon beta 1A (Plegridy) provides similar efficacy for annualized relapse rate, 3- and 6-month confirmed disability progression when compared indirectly to Avonex 30ugQW, Betaseron 250ug QOD, Rebif 44ug TIW, and Copaxone 20mg QD. The injecting fatigue is less than the others while the injection site reactions are more frequent with Plegridy. The limitations regarding this paper are that it was authored by Plegridy makers, it is an indirect comparison that included RCTs with different durations, and inherent differences between trials and populations exist.**	JJ
8/12/2020	I added the no concurrent MS disease-modifying drugs due to no data on combination therapy.	JJ

Pegvisomant (Somavert®)

10mg, 15mg, 20mg injection , powder for reconstitution

EBRx PA Criteria

FDA use: treatment of acromegaly in patients who have had an inadequate response to surgery or radiation therapy, or for whom these therapies are not appropriate.

Criteria for new users
1. The patient must have the diagnosis of acromegaly and either an inadequate response to surgery or radiation OR is not a candidate for surgery or radiation.
2. The patient did not respond adequately to somatostatin analog therapy (octreotide, lanreotide, pasireotide).
3. The patient did not respond adequately to cabergoline.

Note: Pegvisomant may be given together with a somatostatin analog (octreotide or lanreotide or pasireotide) in patients with an inadequate response to somatostatin analog monotherapy.

The Acromegaly Consensus Group suggests use of pegvisomant as second-line therapy in acromegaly patients with persistent, significant disease despite surgical resection and minimal/no response to 1st line therapy, either as monotherapy (in patients without concern for tumor growth) or in combo with a somatostatin analog (in patients with concern for tumor growth). Pegvisomant may be a preferred option in patients with comorbid diabetes mellitus due to favorable glycemic effects. (ACG [Melmed 2018]).

Quantity Limits: Maximum dose is 30mg/day.

References:

1. LexiComp. Pegvisomant. Accessed 11/5/2020.

2. Ma, Lingyun, et al. "Combined therapy of somatostatin analogues with pegvisomant for the treatment of acromegaly: a meta-analysis of prospective studies." (2020) BMCC Endocrine Disorders; 20:126.

Revision History:

Date	What changed	Pharmacist's initials
2011	Someone wrote the criteria (JJ did not write the original criteria.)	JJ
11/5/2020	I updated the criteria. Not much changed. I added the references.	JJ

Pembrolizumab (Keytruda®)

100 mg vials

EBRx PA Criteria

FDA-approved for:

- **Melanoma**
  - Unresectable or metastatic melanoma [jump to criteria]
  - Adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection [jump to criteria]
- **Non-Small Cell Lung Cancer (NSCLC)** [jump to criteria]
  - In combination with pemetrexed and platinum chemotherapy as first line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
  - In combination with carboplatin and either paclitaxel or nab-paclitaxel, as first-line treatment of patients with metastatic squamous NSCLC. Covered with conventional paclitaxel only
  - As a single agent for the first-line treatment of patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 [tumor proportion score (TPS) ≥1%] with no EGFR or ALK genomic tumor aberrations
  - As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.
- **Small Cell Lung Cancer (SCLC)**
  - Metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy[a] NOT COVERED: data is limited to single arm, non-comparative trials reporting response rates only. EBRx does not cover a comparable drug in the same class for this treatment setting
- **Head and Neck Squamous Cell Carcinoma (HNSCC)**
  - In combination with platinum and fluorouracil for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC [jump to criteria]
  - As a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test [jump to criteria]
  - As a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum containing chemotherapy. [jump to criteria]
- **Classical Hodgkin lymphoma (CHL)** NOT COVERED (see nivolumab)
  - Treatment of adult patients with relapsed or refractory cHL.
    - Pembrolizumab was compared to brentuximab. Pembrolizumab was associated with an improvement in progression free survival only.
  - For the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.
  - References:

    -Chen R et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: Two-year follow-up of KEYNOTE-087. Blood. 2019 Aug 13. [Epub ahead of print] PMID 31409671;

    -Chen R et al. Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. J Clin Oncol. 2017 Jul 1;35(19):2125-2132. Epub 2017 Apr 25 .PMID 28441111

-Pembrolizumab Package Insert

- **Primary Mediastinal Large B-Cell Lymphoma (PMBCL)**
  - Treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy[a] NOT COVERED: lack of comparative data; EBRx does not cover any immunotherapy for PMBCL
- **Urothelial carcinoma**
  - Locally advanced or metastatic disease and not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] OR not eligible for any platinum-containing chemotherapy regardless of PD-L1 status[a] NOT COVERED: lack of comparative data
  - Locally advanced or metastatic disease with progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy [jump to criteria]
  - Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. NOT COVERED: data is limited to single arm non-comparative trial showing response rates only
    - Reference: Balar AV et al. Keynote 057: Phase II trial of Pembrolizumab (pembro) for patients (pts) with high-risk (HR) nonmuscle invasive bladder cancer (NMIBC) unresponsive to bacillus calmette-guérin (BCG). DOI: 10.1200/JCO.2019.37.7_suppl.350 Journal of Clinical Oncology 37, no. 7_suppl (March 01, 2019) 350-350. https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.7_suppl.350. Accessed 6/16/2020.
- **Microsatellite Instability-High Cancer** (regardless of tumor type)
  - Adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors that meet one of the following two criteria:
    - Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options[a] OR
    - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan[a]

    *Limitations of use: The safety and effectiveness of pembrolizumab in pediatric patients with MSI-H central nervous system cancers have not been established.

    *NOT COVERED: lack of comparative data; EBRx does not cover any immunotherapy for MSI-H/dMMR tumors
- **Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer** [jump to criteria]
  - *First-line* treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer
- **Gastric Cancer**
  - Recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors epress PD-L1 (CPS ≥1) with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/new-targeted therapy[a] NOT COVERED: initial registration trial was single arm data (NCT02335411; keynote 059). A subsequent RCT (NCT02370498; keynote 061) in previously treated PD-L1 positive patients randomized to pembrolizumab vs paclitaxel showed no improvement in PFS or OS. Reference: Shitara K et al. Lancet. 2018;392(10142):123-133. PMID 29880231

- **Esophageal Cancer** [jump to criteria]

  - Treatment of patients with recurrent locally advanced or metastatic **squamous cell carcinoma** of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.
- **Cervical Cancer**
  - Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS≥1)[a] NOT COVERED: lack of comparative data; EBRx does not cover any immunotherapy for cervical cancer
- **Hepatocellular Carcinoma (HCC)**
  - HCC previously treated with sorafenib[a] NOT COVERED: Head-to-head study of Pembrolizumab versus placebo in patients previously treated with or did not tolerate sorafenib did not find statistically significant difference for co-primary endpoints of overall survival or progression free survival; EBRx does not cover any immunotherapy for HCC

    References:
    - Press release: https://investors.merck.com/news/press-release-details/2019/Merck-Provides-Update-on-KEYNOTE-240-a-Phase-3-Study-of-KEYTRUDA-pembrolizumab-in-Previously-Treated-Patients-with-Advanced-Hepatocellular-Carcinoma/default.aspx
    - Clinical trials.gov: https://clinicaltrials.gov/ct2/show/NCT02702401?term=NCT02702401&rank=1
- **Merkel Cell Carcinoma (MCC)** [jump to criteria]
  - Adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma[a]
- **Renal Cell Carcinoma (RCC)** [jump to criteria]
  - In combination with axitinib, for the first-line treatment of patients with advanced RCC
- **Endometrial Carcinoma** NOT COVERED
  - In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation[a]
  - Data for this indication is limited to a single arm, non-comparing trial. Therefore, EBRx will not cover at this time.
- **Tumor Mutational Burden-High (TMB-H) Cancer**[a]
  - Treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options: Limitations of use: the safety and effectiveness of pembrolizumab in pediatric patients with TMB-H central nervous system cancer have not been established. NOT COVERED Data for this indication is limited to a single arm, non-comparing trial. Therefore, EBRx will not cover at this time.
- **Cutaneous Squamous Cell Carcinoma (cSCC)**
  - Treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation. NOT COVERED Data for this indication is limited to a single arm, non-comparing trial. Therefore, EBRx will not cover at this time.
- **Triple-Negative Breast Cancer (TNBC)** NOT COVERED
  - in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test[b]
    - Pembrolizumab + chemotherapy was compared to chemotherapy alone. In patients with CPS ≥10, pembrolizumab + chemotherapy improved progression

free survival. Improvement in overall survival or quality of life have not been demonstrated to date.

- Reference: Pembrolizumab PI

a=This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

b= This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials

Melanoma, metastatic
7. Diagnosis of unresectable or metastatic melanoma
8. The patient must be ECOG performance status 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity) at initiation
9. Patient does NOT have diagnosis of ocular/uveal melanoma.
10. Patient has NOT received prior PD-1 or PD-L1 inhibitor (e.g. nivolumab, pembrolizumab, atezolizumab, durvalumab)
If both criteria fulfilled, approve for 12 months
Criteria for continuation
3. No disease progression
4. No unacceptable toxicity
If both of the continuation criteria are fulfilled, approve for 12 months.
Notes: -Phase 3 KEYNOTE 006 (NCT01866319): in first or second line treatment setting (previous checkpoint inhibitor not allowed; previous BRAF targeted tx allowed), demonstrated improved overall survival vs ipilimumab (median OS not reached in pembro arm vs 16 mo in ipi arm (HR 0.68, 95% CI 0.53-0.86)[a] -Phase 2 KEYNOTE 002 (NCT01704287): in patients previously treated with ipilimumab, demonstrated improved progression free survival compared with chemo but no improvement in overall survival. Lack of improvement in OS may have been confounded by post-study immunotherapy use (25-35% of patients received post-study immunotherapy).[b] -Uveal/ocular melanoma behaves differently from cutaneous melanoma. Uveal/ocular melanomas were excluded from above trials. Data are emerging for use of immunotherapy in ocular melanoma, however, use should be limited to clinical trial at this time. - Pembrolizumab is continued until disease progression or unacceptable toxicity REFERENCES: a. Schachter J et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017 Oct 21;390(10105):1853-1862. NCT01866319

Melanoma, adjuvant
1. Diagnosis of stage III melanoma that has been completely resected
2. The patient must be ECOG performance status 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity) at initiation
3. Patient does not have diagnosis of ocular/uveal melanoma.
If all criteria fulfilled, approve for 12 months. NOTE: for adjuvant indication, maximum treatment duration is 1 year. Do not approve more than 1 year TOTAL.
Notes: -Pembrolizumab improved recurrence free survival (RFS) compared with placebo in this patient population. At a median f/u of 15 months, the RFS was 75% for pembrolizumab and 61% for placebo (HR 0.57, 95% CI 0.43-0.74). These numbers are similar to nivolumab data even though study included patients with less advanced disease (included stage IIIA and no stage IV). -Pembrolizumab is continued until disease progression or unacceptable toxicity REFERENCE:

Non-Small Cell Lung Cancer (NSCLC)
1. Presence of advanced or metastatic disease 2. ECOG performance status 0-2 3. No EGFR or ALK genomic tumor aberrations ***All of the above (1-3) must be met PLUS one of the following*** 1. PD-L1 TPS ≥1% and no prior systemic therapy 2. PD-L1 TPS ≥1% and disease progression on or after platinum-based chemotherapy and no prior immunotherapy for advanced disease (e.g. nivolumab, atezolizumab) 3. PD-L1 TPS <1%, no prior systemic therapy, and pembrolizumab will be used in combination with platinum-based chemotherapy
If criteria fulfilled, approve for 12 months Note: For squamous NSCLC, EBRx covers pembrolizumab in combination with conventional paclitaxel and carboplatin and NOT in combination with Abraxane and carboplatin. [See Abraxane criteria].
Criteria for continuation
No disease progression
No unacceptable toxicity
If both continuation criteria are fulfilled, approve for 12 months.
Notes: 1. General principles: Pembrolizumab monotherapy may be considered in the first or second line setting (after chemotherapy) as long as PD-L1 is ≥1%. Pembrolizumab plus chemotherapy is appropriate for any level of PD-L1. 2. FIRST LINE SETTING: a. PD-L1 >50%, any histology: pembrolizumab monotherapy was superior to standard chemotherapy. Median OS was 30 mo (pembro) vs 14 mo (chemo) (HR 0.63; 95% CI, 0.47 to 0.86). Fewer severe adverse events with pembrolizumab (31% vs 53%)[1] b. PD-L1 any level, non-squamous histology: pembrolizumab+pemetrexed+carboplatin improved OS vs pemetrexed+carboplatin. Median OS: 22 mo in pembrolizumab/chemo group and 10.7 mo in chemo group (HR 0.56; 95% CI, 0.45 to 0.70). One-year OS was 70% (pembro/chemo) vs 48% (chemo). Incidence of severe toxicities was similar between groups.[2,3] c. PD-L1 any level, squamous histology: pembrolizumab+carboplatin+paclitaxel/nab-paclitaxel improved OS vs carboplatin+paclitaxel/nab-paclitaxel. Median OS 15.9 mo (pembro/chemo) vs 11.3 mo (chemo) with HR 0.64 95% CI 0.49-

0.85). Incidence of severe toxicities was similar between groups.[4]

d. PD-L1 >1%, any histology: Pembrolizumab monotherapy improved OS vs chemotherapy for all levels of PD-L1 with fewer adverse effects. Difference in OS likely driven by subgroup with PD-L1 >50%. OS survival was similar between groups if PD-L1 was 1-49%.[5]

2. NON-FIRST LINE SETTING:

a. PD-L1 ≥1%: Pembrolizumab improved overall survival vs docetaxel with median OS of 10.4 mo (pembro) vs 8.5 mo (chemo) with HR 0.71, 95% CI 0.58-0.88). Incidence of severe toxicities was lower with pembrolizumab (13% vs 35%).[6]

REFERENCES:

1. Reck M et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol. 2019 Jan 8:JCO1800149. [KEYNOTE 024; NCT02142738]
2. Gandhi L et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018 May 31;378(22):2078-2092. [KEYNOTE 189; NCT02578680]
3. Gadgeel S et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2020;38(14):1505- 1517. [PMID 32150489; KEYNOTE 189; NCT02578680]
4. Paz-Ares L et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Nov 22;379(21):2040-2051. [KEYNOTE 407; NCT02775435]
5. Mok TSK et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019 May 4;393(10183):1819-1830. NCT02220894 PMID 30955977
6. Herbst RS et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016 Apr 9;387(10027):1540-50. [KEYNOTE 010; NCT01905657]

Head and Neck Squamous Cell Carcinoma (PREVIOUSLY UNTREATED)
4. Diagnosis of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) that is not amenable to local therapies. [not adenocarcinoma]
5. No prior therapy for advanced/recurrent disease AND, if applicable, it has been at least 6 months since completion of curative-intent systemic therapy for locoregionally advanced HNSCC* *if it has been <6 months since curative-intent systemic therapy, see "previously-treated" criteria
6. Patient does NOT have nasopharyngeal cancer
7. The patient must be ECOG performance status 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity).
8. If PD-L1 Combined Positive Score (CPS) <1, pembrolizumab will be used in combination with platinum and fluorouracil. If PD-L1 CPS is ≥1, pembrolizumab may be used as monotherapy.
If all criteria fulfilled, approve for 12 months
Criteria for continuation
No disease progression
No unacceptable toxicity
If both of the continuation criteria are fulfilled, approve for 12 months.

Note:

-KEYNOTE-048 (N=822) included patients with advanced/metastatic disease, any PD-L1 level, no prior therapy. Patients were randomized to three treatment groups (see below). Chemo was given x 6 cycles and the monoclonal antibodies were given until progression of disease.

- Among all patients, pembrolizumab/chemo has similar rates of severe toxicity as cetuximab/chemo, and pembro/chemo is associated with modest 2.3 mo benefit in OS. Monthly cost of maintenance pembrolizumab is

similar to cetuximab, so EBRx will cover.

- Due to less toxicity and modest improvement in OS, EBRx will cover pembrolizumab monotherapy **if** PD-L1 ≥1.

Overall survival

	Overall survival (median, months)			Difference (mo)	HR, 95% CI
	Pembro	Pembro/chemo	Cetuximab/chemo		
All patients	--	13	10.7	2.3	0.77, 0.63-0.93
PD-L1 ≥1	12.3	--	10.3	2	0.78, 0.64-0.96
PD-L1 ≥20	14.9	--	10.7	4.2	0.61, 0.45-0.83
PD-L1 1-19*	10.8	--	10.1	0.7	0.90, 0.68-1.18
Toxicity					
Grade 3-5 AEs incidence	54.7%	85.1%	83.3%		
Grade 3-5 AEs with ≥5% incidence^	None	Fatigue, mucosal inflammation, nausea, pneumonia, stomatitis	Fatigue, mucosal inflammation, nausea, pneumonia, rash		
Cost (as of 9/10/19)					
AWP/28 days	$15,328	$15,328+chemo	400 mg: $12,240 500 mg: $15,300 600 mg: $18,360		
ASP/28 days	$12,474	$12,474+chemo	400 mg: $9,375 500 mg: $11,719 600 mg: $14,063		

*exploratory endpoint

^not including lab abnormalities; most AEs listed occurred in <10% of patients

-Pembrolizumab is continued until disease progression or unacceptable toxicity

-Pembrolizumab has not been well studied for treatment of nasopharyngeal tumors. These tumors behave differently from other head and neck cancers and were excluded from referenced trial.

REFERENCES:

1. https://clinicaltrials.gov/ct2/show/NCT02358031. Accessed 9/10/19.
2. Keytruda Package Insert. https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed 9/10/19.
3. 2019 ASCO: Final Analysis of KEYNOTE-048: First-Line Pembrolizumab for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma https://www.ascopost.com/News/60093

Head and Neck Squamous Cell Carcinoma (PREVIOUSLY TREATED)
1. Diagnosis of recurrent or metastatic squamous cell carcinoma of the head and neck (not adenocarcinoma)
2. History of disease progression during or after platinum-containing treatment for recurrent/metastatic disease **OR** history of recurrence or progression within 3-6 months of previous multimodal therapy containing platinum for locally advanced disease
3. Patient does NOT have nasopharyngeal cancer
4. The patient must be ECOG performance status 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity).
5. Patient has not been treated with prior PD-1 or PD-L1 inhibitor (e.g. nivolumab, pembrolizumab, atezolizumab, durvalumab)
If all criteria fulfilled, approve for 12 months
Criteria for continuation
No disease progression
No unacceptable toxicity
If both of the continuation criteria are fulfilled, approve for 12 months.
Note: -OS benefit of pembrolizumab vs single agent systemic therapy (methotrexate, docetaxel, cetuximab) was 8.4mo vs 6.9 mo (HR 0.8, 0.65-0.98). Fewer severe adverse effects with pembrolizumab (13% vs. 36%). - Pembrolizumab is continued until disease progression or unacceptable toxicity -Pembrolizumab has not been well studied for treatment of nasopharyngeal tumors. These tumors behave differently from other head and neck cancers and were excluded from referenced trial. REFERENCE: Cohen EEW et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet. 2019 Jan 12;393(10167):156-167. [keynote 040; NCT02252042]

Urothelial Cancer (aka bladder aka transitional cell carcinoma)
1. Urothelial carcinoma with advanced/metastatic disease with progression of disease after platinum-based chemotherapy **OR** recurrence within 12 months of platinum-based adjuvant or neoadjuvant therapy.
2. Patient has not been treated with prior PD-1 or PD-L1 inhibitor (e.g. nivolumab, pembrolizumab, atezolizumab, durvalumab)
3. The patient must be ECOG performance status 0, 1, or 2 at initiation.
If all criteria fulfilled, approve for 12 months
Criteria for continuation
No disease progression
No unacceptable toxicity
If both of the continuation criteria are fulfilled, approve for 12 months.
Note: -OS was improved with pembrolizumab versus chemotherapy in this population (median OS 10.3 mo vs 7.4 mo; HR 0.73; 95% CI 0.59-0.91). Fewer severe adverse events in pembrolizumab arm (15% vs

49%).

-First line therapy for cisplatin or chemo-ineligible patients is not covered. Data is limited to single arm trials at this time. No other immunotherapy is covered by EBRx for first-line treatment of urothelial cancer and chemotherapy should be used.

- Pembrolizumab is continued until disease progression or unacceptable toxicity.

REFERENCE:

Bellmunt J et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017 Mar 16;376(11):1015-1026. [keynote 045; NCT02256436]

Renal Cell Carcinoma
7. Advanced or metastatic clear cell renal cell carcinoma
8. No prior therapy for advanced disease
9. Pembrolizumab must be given in combination with axitinib
10. Patient must have Karnofsky performance status of ≥70% (see below)
11. Intermediate or poor risk disease as measured by IMDC criteria (see below)
If all criteria fulfilled, approve for 12 months
Criteria for continuation
No disease progression
No unacceptable toxicity
If both of the continuation criteria are fulfilled, approve for 12 months.

Note:

In the first line setting, pembrolizumab + axitinib improved overall survival regardless of IMDC risk (12-month OS: 89.9% vs 78.3%). No difference was found in subgroup with favorable risk per IMDC criteria below. The lack of benefit seen in the favorable risk subgroup is consistent with the ipilimumab/nivolumab data.

IMDC risk:

Favorable risk: no risk factors

Intermediate risk: 1-2 risk factors

Poor risk: 3 or more risk factors

Risk factors:

- Less than 1 year from time of diagnosis to systemic therapy
- Performance status <80% (Karnofsky—see guide below)
- Hemoglobin < lower limit of normal (LLN)
- calcium > upper limit of normal (ULN)
- Neutrophil > ULN
- Platelets > ULN

Karnofsky Score (KS)	Definition
`100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease

80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

REFERENCE

Rini et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019 Mar 21;380(12):1116-1127. NCT02853331 PMID 30779529

Microsatellite Instability High/deficient mismatch repair COLORECTAL CANCER
1. Diagnosis of unresectable or metastatic colorectal cancer
2. Tumor is documented to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
3. The patient has not received prior treatment for unresectable/metastatic disease.
4. Pembrolizumab will be used as single agent
If all criteria fulfilled, approve for 12 months
Criteria for continuation
No disease progression
No unacceptable toxicity
If both of the continuation criteria are fulfilled, approve for 12 months.

Note:

Pembrolizumab was compared to standard chemotherapy in the above population. Progression free survival was improved in the pembrolizumab group (median 16.5 mo vs 8.2 mo). Overall survival results have not been reported.[1] Grade 3-5 adverse events were significantly decreased in the pembrolizumab group (22% vs 66%). Due to the reduction in adverse events, EBRx will cover this indication.[2]

REFERENCE

1. Keytruda PI. https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed 7/7/2020.

2. Andre T et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer:

The phase 3 KEYNOTE-177 Study. DOI: 10.1200/JCO.2020.38.18_suppl.LBA4 Journal of Clinical Oncology 38, no. 18_suppl. https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.18_suppl.LBA4. Accessed 7/7/2020.

Esophageal Squamous Cell Carcinoma
5. Diagnosis of either recurrent or metastatic esophageal squamous cell carcinoma [not adenocarcinoma]
6. Tumor expresses PD-L1 with a combined positive score (CPS) ≥10
7. Disease has progressed after at least one prior line of therapy given for advanced/recurrent disease
8. No prior treatment with a PD-1 or PD-L1 inhibitor
9. Pembrolizumab will be used as single agent
If all criteria fulfilled, approve for 12 months
Criteria for continuation
No disease progression
No unacceptable toxicity
If both of the continuation criteria are fulfilled, approve for 12 months.

Note:

Pembrolizumab is continued until disease progression or unacceptable toxicity

Evidence:

The KEYNOTE-181 study enrolled patients with advanced/metastatic regardless of histology (adenocarcinoma vs. squamous cell carcinoma) or PD-L1 expression. Pembrolizumab monotherapy was compared to investigator's choice of chemotherapy. In the PD-L1 CPS ≥10 squamous cell carcinoma subgroup (n=122), median overall survival was longer in the pembrolizumab arm (10.3 vs 6.7 mo). Among all patients, incidence of adverse events was lower in the pembrolizumab group (all grade: 64% vs 86%; grade 3-5: 18% vs 41%).

Note in the subgroup with adenocarcinoma and CPS ≥10, the median overall survival for pembrolizumab was similar to chemo (6.3 vs 6.9). FDA approval was granted for squamous cell carcinoma only.

REFERENCE

1. Shah et al. Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase 3 KEYNOTE-181 study. Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 4010-4010. https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.4010

2. Keytruda Package Insert. https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed 9/10/19.

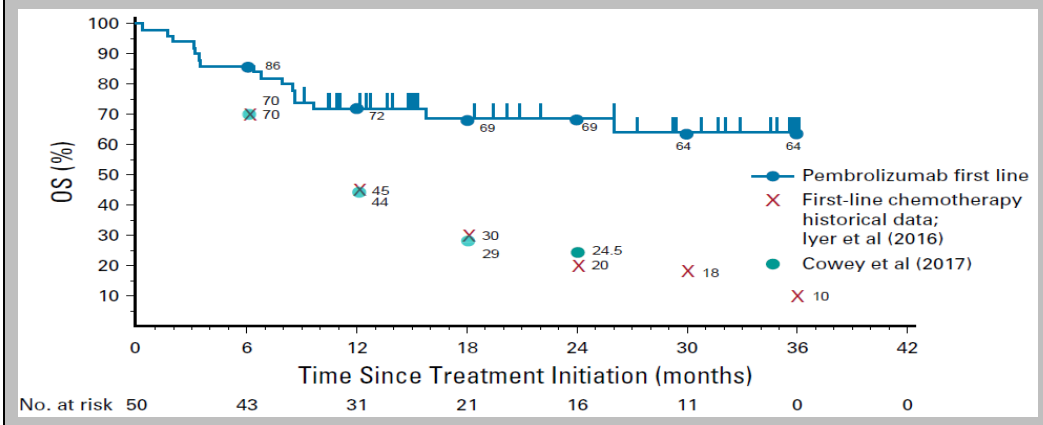
Merkel Cell Carcinoma
1. Diagnosis of either recurrent OR metastatic Merkel cell carcinoma
2. Disease is not amenable to definitive surgery or radiation therapy
3. No prior therapy for advanced/recurrent disease
4. Pembrolizumab will be used as single agent
If all criteria fulfilled, approve for 12 months
Criteria for continuation
No disease progression
No unacceptable toxicity
If both of the continuation criteria are fulfilled, approve for 12 months.

Note:

Pembrolizumab is continued until disease progression or unacceptable toxicity

Evidence:

Pembrolizumab was studied in a Phase II single arm trial (n=50) in patients with either distant metastatic disease or recurrent locoregional disease not amenable to definitive surgery or radiation therapy. No prior systemic treatment for unresectable/advanced disease was allowed. The overall response rate was 56% with a 24% complete response rate. Due to rarity of disease, an analysis was done to compare the phase II data with historical controls, which found an improved overall survival with pembrolizumab compared with chemotherapy.



REFERENCE

Nghiem P et al. Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy. J Clin Oncol. 2019 Mar 20;37(9):693-702. PMID 30726175

Revision History:

Date	What changed?	Pharmacist's initials
1/27/2016	I wrote the criteria with AM's help.	JJ, AM
6/10/2016	Keynote-010 subgroup results confirm that pembro 2mg/kg dose in NSCLC (Non squamous (adenocarcinoma)) patients with 1-49% PD-L1 expression has not shown statistically significant OS benefit vs docetaxel. 10mg/kg did show an OS benefit of 2.2m but is not the marketed dose. (per ASCO 2016 Annual Meeting Abstract 9024; http://abstracts.asco.org/176/AbstView_176_170351.html)	JJ
2/15/17	Determined Keytruda is not covered by the plans for head and neck cancer	JJ
7/12/17	DCWG reviewed. We collectively determined that Hodgkins, microsatellite instablility-high cancer would not be covered due to lack of clinical outcome data. Urothelial cancer would not be covered because the OS benefit was 2.8-2.9 months with pembrolizumab vs CTX (docetaxel or paclitaxel q3w)	JJ
1/9/18	I added gastric cancer to list of non-covered cancer due to it being FDA approved only on tumor response and durability of response. There are no OS or QOL data to date.	JJ
2/26/19	1. Made general updates to formatting and references 2. Melanoma: expanded coverage to first line and adjuvant setting; added ocular/uveal melanoma exclusion, no previous PD-1 or PD-L1 inhibitor allowed. 3. Head and neck cancer: added criteria (improved overall survival vs chemo) 4. Urothelial cancer: added criteria for non-first line use (improved overall survival vs chemo) 5. NSCLC: added coverage of new indications for first line monotherapy and combination therapy (improved OS vs standard therapy).	Sk
5/20/19	Focused review: renal cell carcinoma added as new covered indication, NSCLC criteria edited and simplified given recent expansion of FDA approval (monotherapy now approved for first line use if PDL1 $\geq$1%), added Merkel Cell carcinoma as a covered indication due to new data.	Sk
9/23/2019	All criteria reviewed. -changed approval period to 12 months for all indications. -modified criteria for previously treated head and neck to further specify what prior therapy is allowed -added references for classical hodgkins -added criteria for first line treatment of head and neck squamous cell carcinoma	SK

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	-added criteria for esophageal squamous cell carcinoma -reviewed new indication for endometrial carcinoma (not covered)	
12/5/19	Corrected minor typo	Sk
12/16/19	Criteria updated to reflect that for squamous NSCLC, EBRx covers pembrolizumab in combination with conventional paclitaxel and carboplatin and NOT in combination with Abraxane and carboplatin. [See Abraxane criteria].	Sk
6/9/2020	Added new reference with updated trial results for KEYNOTE-189 (nonsquamous, any PD-L1, pembro+chemo). No change to criteria.	SK
6/24/2020	All criteria and indications reviewed. Added new indications (small cell lung cancer, BCG refractory bladder cancer, TMB high tumors, cutaneous squamous cell carcinoma—none covered).	SK
11/19/20	• No changes to criteria • Added new triple negative breast cancer indication to criteria document. Pembrolizumab+chemo was compared to chemo alone. Only benefit demonstrated to date is progression free survival (do not cover). • Reviewed new data for hodgkins lymphoma indications. No change. Watch for full publication of QOL data (pembro vs brentuximab NCT02684292)	SK

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Penicillamine (Depen Titratabs®)

250mg tablets

EBRx PA Criteria

FDA-approved for: Wilson's disease, cystinuria, or as adjunctive treatment of severe, active rheumatoid arthritis.

Must have one of the diagnoses:
1. Wilson's Disease or cystinuria. If so, proceed to the relevant box below to see if the criteria are COMPLETELY fulfilled:

Wilson's Disease Criteria:
1. Must have the diagnosis of Wilson's Disease.
2. Must be symptomatic with either clinical hepatic symptoms or neurologic symptoms; If not symptomatic, profile must include zinc 150mg/day administered in 2-3 divided doses.
3. Must ingest a low copper diet (AVOID: lamb; pork; pheasant quail; duck; goose; squid; salmon; organ meats including liver, heart, kidney, brain; shellfish including oysters, scallops, shrimp, lobster, clams, and crab; meat gelatin; soy protein meat substitutes; tofu; nuts and seeds, vegetable juice cocktail, mushrooms, nectarine, commercially dried fruits including raisins, dates, prunes; avocado, dried beans including soy beans, lima beans, baked beans, garbanzo beans, pinto beans; dried peas; lentils; millet; barley; wheat germ; bran breads and cereals; cereals with >0.2 mg of copper per serving (check label); soy flour; soy grits; fresh sweet potatoes, chocolate milk, soy milk, cocoa, desserts that contain high amounts of ingredients rich in copper; candy with nuts, chocolate, or cocoa, instant breakfast beverages, mineral water, soy-based beverages, copper-fortified formulas, brewer's yeast, multiple vitamins with copper or minerals)

Quantity Limit: 8 tabs/day (2g max/day)

Notes:

1. Trientine is sometimes used initially, especially in those presenting with neurologic symptoms since there is less commonly a flare of neurologic symptoms with the initiation of the drug as compared to penicillamine. Trientine is FDA-approved for Wilson's who are intolerant of penicillamine.

Cystinuria Criteria:
1. Must have the diagnosis of cystinura.
2. The patient's profile must show they have used 3-4meq/kg per day of potassium citrate or potassium bicarbonate in 3-4 divided doses/day or else have a contraindication to it. Potassium citrate and K bicarbonate are used to alkalinize the urine and solubilize the cystine stones.

(Sodium citrate and sodium bicarbonate should be AVOIDED.)
3. Must ingest a low copper diet (AVOID: lamb; pork; pheasant quail; duck; goose; squid; salmon; organ meats including liver, heart, kidney, brain; shellfish including oysters, scallops, shrimp, lobster, clams, and crab; meat gelatin; soy protein meat substitutes; tofu; nuts and seeds, vegetable juice cocktail, mushrooms, nectarine, commercially dried fruits including raisins, dates, prunes; avocado, dried beans including soy beans, lima beans, baked beans, garbanzo beans, pinto beans; dried peas; lentils; millet; barley; wheat germ; bran breads and cereals; cereals with >0.2 mg of copper per serving (check label); soy flour; soy grits; fresh sweet potatoes, chocolate milk, soy milk, cocoa, desserts that contain high amounts of ingredients rich in copper; candy with nuts, chocolate, or cocoa, instant breakfast beverages, mineral water, soy-based beverages, copper-fortified formulas, brewer's yeast, multiple vitamins with copper or minerals)

Quantity Limit: of 8tab/day (2g max/day)

Revision History:

Date	What changed	Pharmacist's initials
10/2/15	I wrote the criteria. I did not include RA as a covered use since the RA guidelines state this is more toxic and there are more effective alternatives.	JJ

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References:

1. Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: An update. Hepatology. 2008;47(6): 2089-2111.

2. Dietary Special Considerations. http://gicare.com/diets/copper-restriction/

(accessed 10/2/15).

3. Cystinuria treatment. www.uptodate.com (Accessed 10/2/15).

4. Weiss KH, Stremmel W. Clinical considerations for an effective medical therapy in Wilson's disease. Annals of the New York Academy of Sciences. 2014;1315:81-85. (Review Article)

5. Brewer GJ, Askari F, et al. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. Arch Neurol. 2006. 63(4):521-7.

6. Penicillamine for Wilson's disease. Coch Sys Rev protocol only. No results. 2012.

7. Suarez-Almazor ME, Belseck E, Spooner C. Penicillamine for treating rheumatoid arthritis (RA). Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD001460. DOI: 10.1002/14651858.CD001460.

8. Qureshi MJ, Kumar M. D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Cochrane

9. Klingenberg SL, ChenW. D-penicillamine for primary sclerosing cholangitis (PSC). Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004182. DOI: 10.1002/14651858. CD004182.pub3.

10. Gong Y, Klingenberg SL, Gluud C. D-penicillamine for primary biliary cirrhosis (PBC). Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD004789. DOI: 10.1002/14651858. CD004789.pub2.

11. Thornton J, Rangaraj S. Disease modifying anti-rheumatic drugs in people with cystic fibrosis(CF)-related arthritis. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD007336. DOI: 10.1002/14651858.CD007336.pub3.

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Pertuzumab (Perjeta®)

420 mg/14 ml vial

EBRx PA Criteria

FDA-approvals:

- Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
- Use in combination with trastuzumab and chemotherapy as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.
- Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence Covered for node-positive disease only

Metastatic Breast Cancer
1. Diagnosis of unresectable or metastatic breast cancer
2. Breast cancer is HER2 positive
3. No prior chemotherapy or anti-HER2 therapy for unresectable or metastatic breast cancer
4. Pertuzumab will be used in combination with trastuzumab and docetaxel
If above criteria are fulfilled, approve x 1 year [therapy continues until disease progression or unacceptable toxicity]
Notes: Pertuzumab should not be given to patients whose tumors have previously progressed on pertuzumab. For metastatic breast cancer, pertuzumab is ALWAYS given in combination with trastuzumab and docetaxel. In the Cleopatra study, the population described in the above criteria was given pertuzumab, trastuzumab, and docetaxel OR placebo, trastuzumab, and docetaxel. The pertuzumab group had improved median overall survival (56.5 mo vs 40.8 mo, HR 0.68, 95% CI 0.56-0.84). Dose: 840 mg IV x 1 followed 3 weeks later by 420 mg IV every 3 weeks. Therapy continues until disease progression or unacceptable toxicity REFERENCES: 1. Swain SM et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind,

placebo-controlled, phase 3 study. Lancet Oncol. 2013 May;14(6):461-71. PMID 23602601 NCT00567190
2. Swain SM et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015 Feb 19;372(8):724-34. PMID 25693012 NCT00567190

Neoadjuvant Treatment of Breast Cancer (therapy begins BEFORE
1. Diagnosis of breast cancer
2. Breast cancer is HER2 positive
3. Breast cancer falls into one of the following categories: a. Inflammatory breast cancer b. Primary tumor is >2 cm in diameter c. Lymph node involvement is present
4. Pertuzumab will be used in combination with trastuzumab and taxane-based chemotherapy
If above criteria are fulfilled, approve x 12 months [maximum duration of therapy is 1 year or 18 doses of pertuzumab]
Notes: Total duration of perioperative pertuzumab therapy is 1 year. Pertuzumab/trastuzumab+chemo is given x 3-6 cycles before surgery. After surgery, pertuzumab and trastuzumab are resumed to complete one year of therapy. In studies, the population described in the above criteria was given pertuzumab, trastuzumab, and mostly taxane-based chemotherapy. Compared to conventional rates of pathological complete response (pCR) of ~40%[1], the pCR rates with these pertuzumab-containing regimens were ~60%[2,3,4]. Attainment of pCR has been strongly associated with overall survival in multiple analyses.[1,5,6] Dose: 840 mg IV x 1 followed 3 weeks later by 420 mg IV every 3 weeks x 3-6 cycles, then proceed to surgery. After surgery, resume pertuzumab with trastuzumab to complete one year of therapy. REFERENCES: 1. Gianni L et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Jan;13(1):25-32. NCT00545688 PMID 22153890 2. Schneeweiss A et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in

patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013 Sep;24(9):2278-84. PMID 23704196

3. Swain SM et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol. 2018 Mar 1;29(3):646-653. PMID 29253081 NCT02132949
4. Cortazar P et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Jul 12;384(9938):164-72. PMID 24529560
5. Mieog JS, van der Hage JA, van de Velde CJ. Preoperative chemotherapy for women with operable breast cancer. Cochrane Database Syst Rev 2007;2:CD005002-CD005002. PMID 17443564
6. Kong X et al. Meta-analysis confirms achieving pathological complete response after neoadjuvant chemotherapy predicts favourable prognosis for breast cancer patients. Eur J Cancer. 2011 Sep;47(14):2084-90. PMID 21737257

Adjuvant Treatment of Breast Cancer (therapy begins AFTER surgery)
1. Diagnosis of breast cancer
2. Breast cancer is HER2 positive
3. Lymph node involvement is present
4. Pertuzumab will be used in combination with trastuzumab and chemotherapy
If above criteria are fulfilled, approve x 1 year [maximum duration of therapy is 1 year or 18 doses]

Notes:

Total duration of pertuzumab therapy is 1 year. Pertuzumab/trastuzumab+chemo is given x 4-6 cycles, then pertuzumab and trastuzumab are continued to complete one year of therapy.

In the APHNITY study[1] (n=4804), the population described in the above criteria was given pertuzumab, trastuzumab, and chemotherapy OR placebo, trastuzumab, and chemotherapy. The primary endpoint was invasive disease free survival (IDFS). At 3 years, the rates of IDFS were as follows:

-all patients (pertuzumab group vs placebo group): 94.1% vs 93.2% (HR 0.81, 95% CI 0.66-1.00; p=0.045)

-node-positive subgroup (pertuzumab group vs placebo group): 92% vs. 90.2% (HR 0.77, 95% CI 0.62-0.96; p=0.02)

-node-negative subgroup (pertuzumab group vs placebo group): rates not given (HR 0.1.13, 95% CI 0.68-1.86; p=0.64)

The study concluded that there was “no treatment effect” in the node-negative subgroup. NCCN

also recommends pertuzumab for node-positive disease only in this treatment setting. Additionally, a cost-effective analysis found the pertuzumab may be cost effective in node-positive disease (ICER $87,929/QALY gained).[2]

Dose:

840 mg IV x 1 followed 3 weeks later by 420 mg IV every 3 weeks x 1 year.

REFERENCES:

1. von Minckwitz G et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017 Jul 13;377(2):122-131. PMID 28581356 NCT01358877

2. Garrison LP Jr et al. Cost-Effectiveness Analysis of Pertuzumab With Trastuzumab and Chemotherapy Compared to Trastuzumab and Chemotherapy in the Adjuvant Treatment of HER2-Positive Breast Cancer in the United States. Value Health. 2019 Apr;22(4):408-415. PMID 30975391

Revision History:

Date	Notes	Pharmacist's initials
12/4/19	Drug reviewed at DCWG. Criteria written.	sk

CONFIDEN

Pimavanserin (Nuplazid®)

17mg tablets

EBRx PA Criteria

FDA-approved for: Treatment of hallucinations and delusions associated with Parkinson disease psychosis

Criteria for new users
1. Diagnosis of Parkinson's Disease
2. Psychotic symptoms must be present that developed after the diagnosis of Parkinson's Disease, and which have lasted at least 1 month and occurred at least weekly during this time.
3. Age 40 or older
4. Must have a mini-mental status exam score of ≥21 and with NO delirium.
5. No concurrent anti-dopaminergic drugs on the profile

Note: Quantity Limits: 2 tablets/day; 60 tablets in 30 days

References:

1. Cummings, Jeffrey, et al. "Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo-controlled phase 3 trial." *The Lancet* 383.9916 (2014): 533-540.

2. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM492452.pdf

Notes:

Revision History:

Date	What changed	Pharmacist's initials
9/6/16	I wrote the criteria. ((NOTE: EBRx voted to cover it because although a 3pt difference does not meet the MCID according to the FDA document, when you use a loftier response of 7pts, the difference between groups is still a 20% absolute difference.)) By comparison with other antipsychotics, pimavanserin's treatment effects were not associated with exacerbation of motor disability, sedation, or other safety challenges.	JJ

CONFIDENTIAL

	Pimavanserin (ACADIA Pharmaceuticals, San Diego, CA, USA) is a selective serotonin 5-HT2A inverse agonist without dopaminergic, adrenergic, histaminergic, or muscarinic affinity, and is in development as a treatment for Parkinson's disease psychosis.12 In Parkinson's disease, the binding of 5-HT2A receptors is increased in the neocortex, and visual hallucinations are associated with increased numbers of 5-HT2A receptors in visual processing areas.13 Post-mortem and genetic studies also suggest that in Parkinson's disease dementia, dementia with Lewy bodies, and Alzheimer's disease, delusions and hallucinations are linked to alterations in the 5-HT system.14,15 Polymorphisms of 5-HT2A, 5-HT2C, and the 5-HT transporter are linked to psychosis, and possibly with treatment response to atypical antipsychotics in Alzheimer's disease.16–18 Atypical antipsychotics target the 5-HT2A pathway but at varying levels and also affect other receptor families. With its receptor selectivity, pimavanserin has been developed to provide antipsychotic benefit without the adverse effects of current antipsychotics.	

CONFIDENTIAL

Pirfenidone (Esbriet®)

267mg oral capsules

EBRx PA Criteria

Pirfenidone (Esbriet) is FDA-approved for: the treatment of idiopathic pulmonary fibrosis.

Criteria for STARTING therapy
1. The patient must have the diagnosis of idiopathic pulmonary fibrosis by high resolution CT (or lung biopsy indicating interstitial pneumonia)
2. The patient must have a predicted forced vital capacity (FVC) of 50-90%.
3. The patient must have a predicted carbon monoxide diffusing capacity (DLCO) of 30-90%
4. The patient must have a ratio of the forced expiratory volume in 1 second (FEV1) to the FVC of 0.80 or more
5. The patient must have a 6-minute walk distance of 150m (492 feet) or more at baseline.
If all 5 of the above criteria are met, access may be given not to exceed the QL. The PA is valid for 1 year.

Criteria for CONTINUING therapy—this should be assessed after each 12 months of taking the drug
1. The patient must have pulmonary function tests repeated. If the FVC decreased by ≥10%, this likely represents progressive disease and the drug should be stopped.
If the above criterium is met, access may be given not to exceed the QL. The PA is valid for 1 year.

Max dose is 2403 mg daily (3 capsules TID).
[1]The minimal clinically important difference for the 6MWT is 24-45 meters in IPF.
[2]Pooled analysis of CAPACITY and ASCEND showed death from any cause was 3.5% vs 6.7% in the pirfenidone vs placebo, respectively. Pooled analysis also showed death due to IPF was 1.1% vs 3.5%, respectively, over 1 year. The difference in 6MWT at 52 weeks was 26.7m, achieving (barely) the MCID between pirfenidone and placebo. (Ref is supplemental materials @NEJM.)

Quantity Limits: 270 capsules/30 days.

References:

1. Roland M. du Bois1, Derek Weycker2, Carlo Albera3, Williamson Z. Bradford4, et al. Six-Minute-Walk Test in Idiopathic Pulmonary Fibrosis Test Validation and Minimal Clinically Important Difference. Am J Respir Crit Care Med Vol 183. pp 1231–1237, 2011.

2. King T, Bradford W, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. The New England Journal of Medicine, May 2014; 270: 2083-92.

3. Noble, P Albera, C. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomized trials. Lancet 2011; 377: 1760-69.

4. Jiang C, Huang H, Liu J, Wang Y, Lu Z, et al. (2012) Adverse Events of Pirfenidone for the Treatment of Pulmonary Fibrosis: A Meta-Analysis of Randomized Controlled Trials. PLoS ONE 7(10): e47024. doi:10.1371/journal.pone.0047024

5. NICE guidance for pirfenidone in idiopathic pulmonary fibrosis. https://www.nice.org.uk/guidance/ta282/chapter/4-consideration-of-the-evidence. (Note: this guidance was issued prior to the latest phase 3 trial (reference #2 above-ASCEND) which when pooled data with reference 3 above (CAPACITY) showed a modest improvement in death from any cause from 6.7%plac vs 3.5% with pirfenidone.)

6. Fleetwood, Kelly, et al. "Systematic review and network meta-analysis of idiopathic pulmonary fibrosis treatments." *Journal of Managed Care & Specialty Pharmacy* 23.3-b Suppl (2017): S5-S16.

7. Rochwerg, Bram, et al. "Treatment of idiopathic pulmonary fibrosis: a network meta-analysis." BMC medicine 14.1(2016): 18.

8. Skandamis, A., Kani, C., Markantonis, S. L., & Souliotis, K. (2019). Systematic review and network meta-analysis of approved medicines for the treatment of idiopathic pulmonary fibrosis. *Journal of Drug Assessment*, (just-accepted), 1-1.

9. Canestaro, W. J., Forrester, S. H., Raghu, G., Ho, L., & Devine, B. E. (2016). Drug treatment of idiopathic pulmonary fibrosis: systematic review and network meta-analysis. *Chest*, *149*(3), 756-766.

Revision History:

Date	What changed	Pharmacist's initials
2/6/15	I wrote the criteria.	JJ
2/26/15	I added info regarding the 6MWT and MCID. From supplementary materials, ref 2, NEJM website. I also added the NICE website, ref #5, and the continuation criteria.	JJ
4/22/19	I added references 6 and beyond.	JJ
4/1/2021	Criteria reviewed. No change	JJ

CONFIDENTIAL

Pitolisant (Wakix®)

4.45 and 17.8mg tablets

EBRx PA Criteria

FDA-approved for: treatment of excess daytime sleepiness or cataplexy in adult patients with narcolepsy

Narcolepsy w/ Cataplexy
1. The patient must have the diagnosis of narcolepsy with cataplexy.
2. The patient must have at least 3 cataplexy episodes per week, prior to appropriate treatment and as documented in the medical record.
If all of the above criteria are met, approve for 1 year
Dose: 8.9 po QD initially, titrate up to 17.8 mg QD after one week (max dose: 35.6 mg po QD)

References:

1. Carter, Lawrence P et al. “A randomized, double-blind, placebo-controlled, crossover study to evaluate the human abuse liability of solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor.” Journal of psychopharmacology (Oxford, England) vol. 32,12 (2018): 1351-1361. doi:10.1177/0269881118796814
2. Dauvilliers, Y., Bassetti, C., Lammers, G. J., Arnulf, I., Mayer, G., Rodenbeck, A., ... & HARMONY I study group. (2013). Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. The Lancet Neurology, 12(11), 1068-1075.
3. Highlighting of Prescribing Information (2019). *FDA*.https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211150s000lbl.pdf
4. LexiComp: sumatriptan. Accessed 10/18/19.
5. Scammell T., Benca R., Eichler A.. Treatment of narcolepsy in adults (Sept 2019). UptoDate. Web. https://www.uptodate.com/contents/treatment-of-narcolepsy-in-adults?search=narcolepsy%20treatment&source=search_result&selectedTitle=1~125&usage_type=default&display_rank=1
6. Setnik, Beatrice, et al. "Evaluation of the abuse potential of pitolisant, a selective H3-receptor antagonist/inverse agonist, for the treatment of adult patients with narcolepsy with or without cataplexy." Sleep (2019).
7. Wakix (pitolisant) (2019). *CenterWatch*.https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100415/-wakix-pitolisant.
8. Szakacs, Zoltan, et al. "Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial." *The Lancet Neurology* 16.3 (2017): 200-207.

Revision History:

Date	What changed	Pharmacist's initials
3/2020	JJ wrote the PA criteria	JJ
3/18/20	I added the threshold of minimum number of cataplexy episodes the patient must have experienced prior to effective cataplexy therapy, as per the clinical trial (ref 8).	JJ
3/8/2021	I corrected the indication to include cataplexy.	JJ

CONFIDENTIAL

Plecanatide (Trulance®)

3mg tablets

EBRx PA Criteria

FDA-approved for: chronic idiopathic constipation in adults

Criteria for new users
1. The patient must fulfill the Rome III functional criteria for constipation below: Diagnostic criteria* 1. Must include two or more of the following: a. Straining during at least 25% of defecations b. Lumpy or hard stools in at least 25% of defecations c. Sensation of incomplete evacuation for at least 25% of defecations d. Sensation of anorectal obstruction/blockage for at least 25% of defecations e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor) f. Fewer than three defecations per week 2. Loose stools are rarely present without the use of laxatives 3. Insufficient criteria for irritable bowel syndrome * Criteria fulfilled for the last □ months with symptom onset at least 6 months prior to diagnosis
2. The patient must be 18 or older.
3. Per the prescriber, the patient must currently be receiving fiber laxatives.
4. The prescriber of plecanatide must state they have queried the AR PMP to assess the patient's current opioid use.[to ascertain the constipation actually is idiopathic]
5. There must be no overlapping days supply of plecanatide with any of the following: lubiprostone, linaclotide, naloxegol, or methylnaltrexone.
If yes to all of the above, the PA may be approved for 1 year. QL is 1/1 for a 30 days supply.
NOTE: The dose is 3mg once daily.

Quantity Limits: 1/1

CONFIDENTIAL

Revision History:

Date	What changed	Pharmacist's initials
5/23/17	I wrote the criteria.	JJ

References:

1. Miner Jr, Philip B., et al. "A randomized phase III clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation." *The American Journal of Gastroenterology* (2017).

CONFIDENTIAL

Plerixafor (Mozobil®)

24 mg/1.2 ml vial

EBRx PA Criteria

FDA-approved for:

- In combination with filgrastim, mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma or multiple myeloma.

Criteria	
1. Diagnosis of non-Hodgkin's lymphoma, Hodgkin's lymphoma, or multiple myeloma	☐Yes ☐No
2. Must have received or be planning to receive at least 4 consecutive days of filgrastim leading up to plerixafor and without delay between filgrastim and plerixafor days	☐Yes ☐No
3. Hematopoietic stem cell transplantation is planned.	☐Yes ☐No

If criteria are met, approve for 4 days.

Quantity Limits: One course of plerixafor is comprised of up to 4 daily doses of plerixafor.

Revision History:

Date	What changed	Pharmacist's initials
5/12/15	I wrote the criteria after the DCWG meeting 5/12/15.	JJ
8/18/15	IB approved.	JJ
8/26/19	Criteria reviewed. Added duration of approval to 4 days.	SK
2/10/2020	Criteria reviewed. No change.	SK

CONFIDENTIAL

Polatuzumab vedotin-piiq (Polivy®)

140 mg vial

EBRx PA Criteria (Medical)

FDA-approved for:

- In combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies.

Criteria for new users
1. Diagnosis of diffuse large B-cell lymphoma (DLBCL) that is progressing
2. Previously treated with at least two prior regimens
3. Patient is not eligible for stem cell transplant
4. Polatuzumab will be used in combination with bendamustine and rituximab
If all of the above criteria are met, approve for 5 months. -The maximum duration of therapy is 6 doses. -If renewal of PA is requested, approve ONLY if 6 doses have not been completed. -Reapproval time frame should be determined according to how many doses remain.

Note:

-Efficacy and safety of polatuzumab have not been established in patients who are eligible for stem cell transplant. Stem cell transplant would still be preferred at this time.

-Survival benefit seen regardless of cell of origin and double expressor status.

Polatuzumab/bendamustine/rituximab was compared to bendamustine/rituximab in the above patient population (n=80). Overall survival was improved in the polatuzumab group (median 11.8 mo vs 4.7 mo). The rate of 1-year overall survival was 48% vs 24%. The FDA only gave accelerated approval based on improved response rates (45% vs 18%) since the population was small.

Dose:

1.8 mg/kg IV over 30-90 minutes every 3 weeks x 6 doses (in combination with bendamustine/rituximab).

References:

1. San Miguel JF et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. Haematologica. 2015 Oct;100(10):1334-9. PMID 26160879 NCT01311687
2. Miguel JS et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1055-1066. PMID 24007748 NCT01311687

Quantity Limits: n/a

Revision History:

Date	What changed	Pharmacist's initials
8/26/19	Criteria written.	SK
10/13/2020	Criteria reviewed. No changes	SK

CONFIDENTIAL

Pomalidomide (Pomalyst®)

1, 2, 3, 4 mg capsules

EBRx PA Criteria

FDA-approved for:

- Treatment of adults in combination with dexamethasone, after at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy SEE CRITERIA
- Treatment of adults with AIDS-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART) or in patients with KS who are HIV negative. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
    - NOT COVERED data limited to single arm trial with response rate data only (alternative: Doxil)

The following indications are not included in the pomalidomide package insert but are FDA approved per the elotuzumab (Empliciti), daratumumab (Darzalex), and isatuximab (Sarclisa) package inserts:

- Pomalidomide with dexamethasone and EITHER elotuzumab OR daratumumab OR isatuximab after at least 2 prior therapies, including lenalidomide and a proteasome inhibitor
    - NOT COVERED Elotuzumab/Pomalidomide/Dexamethasone was compared to pomalidomide/dexamethasone. The triplet therapy improved progression free survival (median 10.3 mo vs 4.7 mo), but an overall survival benefit has not been demonstrated at this time. This regimen also did not result in improved QOL.
        - Dimopoulos MA et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. N Engl J Med. 2018 Nov 8;379(19):1811-1822. PMID 30403938 NCT02654132
        - Weisel K et al. Impact of Elotuzumab Plus Pomalidomide and Dexamethasone on Health-Related Quality of Life in Patients with Relapsed/Refractory Multiple Myeloma Enrolled in the ELOQUENT-3 Study. Blood (2019) 134 (Supplement_1): 3480. https://ashpublications.org/blood/article/134/Supplement_1/3480/428330/Impact-of-Elotuzumab-Plus-Pomalidomide-and?searchresult=1
    - NOT COVERED Daratumumab/Pomalidomide/Dexamethasone: data is limited to a single arm trial.
        - Reference: Chari A et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood. 2017 Aug 24;130(8):974-981. PMID 28637662 NCT01998971 (EQUULEUS; MMY1001)
    - SEE CRITERIA Isatuximab/Pomalidomide/Dexamethasone

CONFIDENTIAL

Criteria for new users
1. Diagnosis of multiple myeloma
2. Patient has been treated with at least two prior therapies, which included lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, ixazomib).
3 Patient has not experienced disease progression on pomalidomide.
4. Pomalidomide will be used in combination with dexamethasone with or without isatuximab (Sarclisa) [See isatuximab criteria]
If all of the above criteria are met, approve for 12 months

Note:

Pomalidomide + dexamethasone

Pomalidomide+low dose dexamethasone (40 mg weekly) was compared to high-dose dexamethasone (40 mg daily, 4 days on, 4 days off) in patients with relapsed/refractory multiple myeloma. Most patients had received at least 3 prior lines of therapy. Pom/dex improved overall survival compared to dex alone (median 13.1 mo vs 8.1 mo). [1,2]

Isatuximab + pomalidomide + dexamethasone

This combination was compared to pomalidomide/dexamethasone in patients who were previously treated with at least two prior therapies including lenalidomide and a proteasome inhibitor. The triplet therapy improved progression free survival (median 11.53 mo vs 6.47 mo). In the overall population, a statistically significant overall survival benefit has not been demonstrated at this time. However, in the subset of patients who were age ≥75 y, a statistically significant improvement in overall survival was demonstrated (median not reached in triplet group versus 10.25 mo in the control group (HR 0.404 95% CI 0.171- 0.956).[3,4]

Dose:

4 mg PO daily x 21 days, then take 7 days off. Treatment is continued until progression of disease or unacceptable toxicity.

References:

3. San Miguel JF et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. Haematologica. 2015 Oct;100(10):1334-9. PMID 26160879 NCT01311687

4. Miguel JS et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1055-1066. PMID 24007748 NCT01311687

5. Attal M et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019 Dec 7;394(10214):2096-2107. doi: 10.1016/S0140-6736(19)32556-5. Epub 2019 Nov 14. PMID 31735560 NCT02990338

6. Schjesvold FH et al. Efficacy of Isatuximab with Pomalidomide and Dexamethasone in Elderly Patients with Relapsed/Refractory Multiple Myeloma: Icaria-MM Subgroup Analysis. Blood (2019) 134 (Supplement_1): 1893. https://ashpublications.org/blood/article/134/Supplement_1/1893/427649/Efficacy-of-Isatuximab-with-Pomalidomide-and

Quantity Limit: 21/28

Revision History:

Date	What changed	Pharmacist's initials
8/26/19	Criteria written.	SK
4/27/2020	Updated approved indications to include the isatuximab/pom/dex indication (not covered)—see above for rationale.	SK
6/5/2020	Added new FDA indication (Kaposi's sarcoma). Not covered.	SK
10/8/2020	Added new QOL reference for elotuzmab/pom/dex indication (no change in coverage).	SK
10/22/2020	Added coverage for pomalidomide in combination with dex/isatuximab	SK

CONFIDENTIAL

Pralatrexate (Folotyn®)

20mg/mL (1mL); 40mg/2mL (2mL), for IV push

EBRx PA Criteria—for Medical use only

FDA-approved for:

Relapsed or refractory peripheral T-cell lymphomas

Criteria for new users
1. The patient must be >18 years of age and be diagnosed with peripheral T-cell lymphoma that has progressed after at least 1 prior treatment.
2. The patient must be ECOG 0-2.
If above criteria are met, approve x 1 year

Notes:

The dose is 30mg/m^2/week for 6 weeks followed by 1 week of rest. Then the cycle is repeated until progressive disease or unacceptable toxicity. B_{12} 1mg IM injection every 8-10w + daily folic acid 1-1.25mg was also administered.

An indirect comparison of patients who received pralatrexate and historical controls who did not receive pralatrexate found an improvement in overall survival in the pralatrexate arm (15.2 mo vs 4.07 mo). Although this is not a randomized controlled trial, EBRx will cover pralatrexate based on this data.

Quantity limits: n/a (medically administered drug)

References:

1. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral t-cell lymphoma: results from the pivotal PROPEL study. J Clin Onc. 2011;29(9):1182-1189.

2. O'Connor OA et al. Strategy for Assessing New Drug Value in Orphan Diseases: An International Case Match Control Analysis of the PROPEL Study. JNCI Cancer Spectr. 2018 Dec 1;2(4):pky038. doi: 10.1093/jncics/pky038. eCollection 2018 Oct. PMID 31360868

Revision History:

Date	What changed	Pharmacist's initials
2/3/15	I wrote the criteria as was decided by DCWG. The drug was previously covered only on the medical side and without known PA criteria. It was decided EBRx would PA along the FDA-approved guidelines with parameters set also by the clinical trial that supported its use (PROPEL). The trial was single arm showing the median PFS was 3.5m and the OS was 14.5m. 43% of patients were censored for OS because they were still alive at the data cutoff date. For those patients, the OS was 18m. 23% withdrew from the trial due to AEs.	JJ
3/28/18	I wrote the PA criteria wrong—for cutaneous (off-label) instead of the FDA-approved (peripheral) T-cell lymphoma. Rachael is correcting it.	JJ
3/28/18	Unable to locate any pertinent data other than PROPEL, current dosing regimen and pre-medication recommendations are appropriate for the peripheral indication	RM
6/17/19	Criteria reviewed. No changes	SK
6/16/2020	Added reference for indirect comparison. Continue coverage per 6/2020 DCWG	SK

CONFIDENTIAL

Radium-223 Dichloride (Xofigo®)

1,000 kBq/mL (27 microcurie/mL); 6 mL vial

EBRx PA Criteria

FDA Approved for:

- Castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease

Criteria for new users
Diagnosis of castration-resistant prostate cancer
Presence of at least 2 bone metastases
The patient does NOT have visceral metastases (e.g. metastases to organs, such as lungs, liver, etc)
Presence of symptomatic bone disease, defined as either regular use of analgesic medication OR history of treatment with radiation therapy for bone pain
ECOG (Eastern Cooperative Oncology Group) performance status of is 2 or less
If all criteria are met, approve for 6 months (maximum treatment duration is a TOTAL of 6 doses).
Notes: Radium-223 was compared to placebo in patients with castration-resistant prostate cancer with at least 2 metastases to the bone and no visceral metastases. Overall survival was improved from 11.2 mo to 14 mo and more patients in the radium-223 group had a clinically meaningful increase in the FACT-P quality of life score (25% vs 16%, p=0.02). Time to first symptomatic skeletal event was also prolonged (15.6 mo vs 9.8 mo). Dose: 50 kBq/kg (1.35 microcurie/kg) q 4 weeks for 6 doses REFERENCE: Sartor O, Coleman R, Nilsson S, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomized trial. Lancet Oncol 2014; 15:738-46. PMID: 24836273.

ECOG Performance Status
0 – Fully active, able to carry on all pre-disease performance without restriction
1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (light house work, office work)
2 – Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than about 50% of waking hours
3 – Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4 – Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5 - Dead

Revision History

Date	What changed	PharmD Initials
12.30.14	PA criteria written	GBB
4/18/19	Criteria review. Formatting updated but no other change made.	Sk
3/27/2020	Criteria reviewed. No change.	SK

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Regorafenib (Stivaraga®)

40 mg tablets

EBRx PA Criteria

FDA-approved for:

- Metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an antiVEGF therapy, and, if RAS wild-type, an anti-EGFR therapy. NOT COVERED
  - Regorafenib statistically improved overall survival compared to placebo (6.4 mo vs 5 mo; HR 0.77 (95% CI 0.64-0.94). This different is not felt to be clinically significant and, therefore, CRC will not be a covered indication for regorafenib.
    Reference: Grothey A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan 26;381(9863):303-12. PMID 23177514 NCT01103323
- Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate. SEE CRITERIA
  - Regorafenib improved progression free survival compared to placebo (4.8 mo vs 0.9 mo). Overall survival was not different between groups. 85% of patients who received placebo crossed over to regorafenib. Per 10/29/19 P&T discussion, this will not be a covered indication for regorafenib.
    Reference: Demetri GD et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan 26;381(9863):295-302. NCT01271712 PMID 23177515
- Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib SEE CRITERIA

Gastrointestinal Stromal Tumor (GIST) Criteria for new users
1. Diagnosis of advanced/unresectable/metastatic GIST
2. Disease has progressed on sunitinib and imatinib
If all criteria met, approve x 1 year
Note: Dose is 160 mg daily x 21 days then take 7 days off. In this patient population, progression free survival was improved in the regorafenib group compared with placebo (median 4.8 mo vs 0.9 mo). Overall survival (OS) in the intention to treat population was not different between groups. However, OS is likely confounded by a high rate

of crossover from placebo to regorafenib (85%).[1] Two analyses conducted to adjust for crossover effect. Each analysis found an improvement in overall survival (median 17.4 mo vs ~11 mo).[2]

References:

1. Demetri GD et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan 26;381(9863):295-302. NCT01271712 PMID 23177515
2. Demetri GD et la. Final overall survival (OS) analysis with modeling of crossover impact in the phase III GRID trial of regorafenib vs placebo in advanced gastrointestinal stromal tumors (GIST). J Clin Oncol 34, 2016 (suppl 4S; abstr 156) https://meetinglibrary.asco.org/record/120256/abstract

Hepatocellular Carcinoma Criteria for new users
1. Diagnosis of advanced/unresectable/metastatic hepatocellular carcinoma
2. Child-Pugh A liver function
3. Previous disease progression of disease on sorafenib
If all criteria met, approve x 1 year
Note: Dose is 160 mg daily x 21 days then take 7 days off. In this patient population, regorafenib improved overall survival compared to placebo (10.6 mo vs 7.8 mo; HR 0.63 [95% CI 0.5-0.79]). References: Bruix J et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan 7;389(10064):56-66. PMID 27932229 NCT01774344

Quantity Limits: #84 tablets/28 days

Revision History:

Date	What changed	Pharmacist's initials
10/28/19	Criteria written	SK
6/24/2020	Criteria reviewed. Added criteria for GIST	SK
9/28/2021	Criteria reviewed. No change.	SK

Ribociclib (Kisqali®)

200 mg tablets

EBRx PA Criteria

FDA-approved for:

- in combination with an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy
- in combination with fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.

Ribociclib + aromatase inhibitor: first line, any menopausal status
1. The patient is female
2. Diagnosis of advanced or metastatic breast cancer
3. No prior therapy for advanced/metastatic disease
4. Tumor is hormone receptor positive (e.g. HR+, ER+ and/or PR+)
5. Tumor is HER2 negative
6. Ribociclib will be used in combination with an **aromatase inhibitor**.
If all criteria met, approve x 1 year

Ribociclib + fulvestrant: first line or subsequent therapy, postmenopausal only:
1. The patient is female
2. No prior treatment with fulvestrant or a CDK 4/6 inhibitor (abemaciclib, ribociclib, palbociclib)
3. Diagnosis of advanced or metastatic breast cancer
4. Tumor is hormone receptor positive (e.g. HR+, ER+ and/or PR+)
5. Tumor is HER2 negative
6. Patient is postmenopausal
7. Ribociclib will be used in combination with **fulvestrant**
If all criteria met, approve x 1 year

Quantity Limits: #63 tablets/30 days

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Note:

Dose is 600 mg daily x 21 days then take 7 days off.

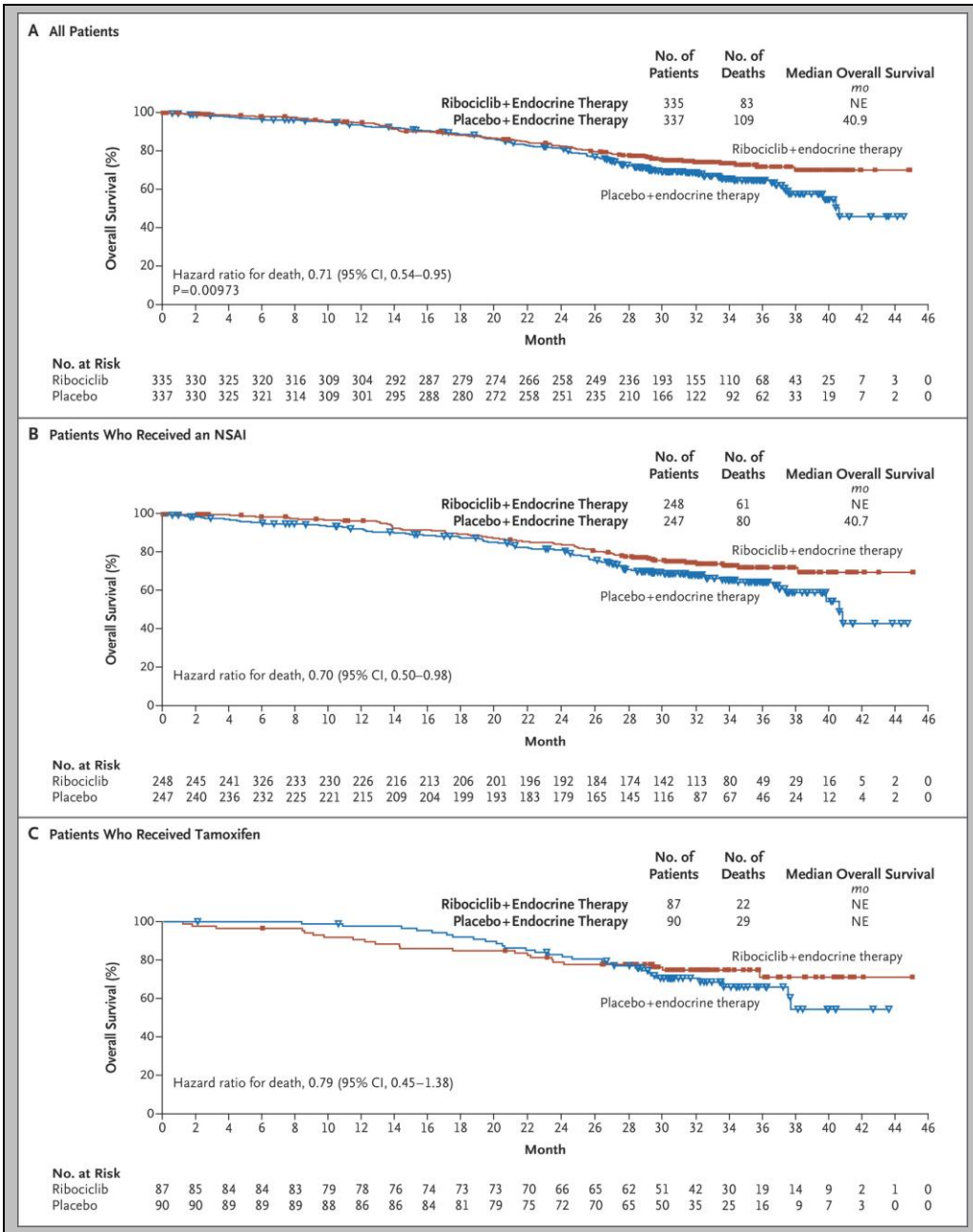
POSTMENOPAUSAL PATIENTS, FIRST LINE (ribociclib + aromatase inhibitor):

An overall survival benefit was reported with ribociclib+aromatase inhibitor compared to an aromatase inhibitor alone in the MONALEESA-2 trial (NCT01958021) (median, 63.9 vs 51.4 mo; HR, 0.76; 95% CI, 0.63-0.93; P=.004).

Reference: Hortobagyi GN et al. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741. https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/overall-survival-os-results-from-the-phase-iii-monaleesa-2-ml-2-trial-of-postmenopausal-patients-pts-with-hormone-receptor-positive-human-epi . Accessed 9/27/2021

PRE/PERIMENOPAUSAL PATIENTS, FIRST LINE (ribociclib + aromatase inhibitor):

EBRx covers for this patient population described in criteria due to overall survival benefit demonstrated in the MONALEESA-7 trial. This trial enrolled pre- and perimenopausal women with advanced/metastatic HR+ and HER2- breast cancer. Patient were given either ribociclib+tamoxifen, ribociclib+aromatase inhibitor, placebo+tamoxifen, or placebo+aromatase inhibitor. The overall survival benefit of ribociclib was demonstrated in the overall population (median OS not reached in ribociclib group; 42-month rate of OS: 70% vs 46%). However, the benefit was driven by the aromatase inhibitor subgroup.



NSAI: nonsteroidal aromatase inhibitor (e.g. anastrozole, letrozole)

References:

1. Tripathy D et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018 Jul;19(7):904-915. PMID 29804902 NCT02278120

2. Seock-Ah I et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. NEJM 2019; published online June 4 DOI: 10.1056/NEJMoa1903765. 31166679 NCT02278120

POSTMENOPAUSAL PATIENTS, FIRST OR SECOND LINE (ribociclib+fulvestrant):

EBRx covers for this patient population described in criteria due to overall survival benefit demonstrated in the MONALEESA-3 trial. This trial enrolled postmenopausal women with advanced/metastatic HR+ and HER2- breast cancer. Patient were given either ribociclib+fulvestrant or placebo+fulvestrant. The overall survival benefit of ribociclib was demonstrated in the overall population (median OS not reached in ribociclib group vs 40 mo in placebo group.

References:

1. Slamon DJ et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018 Aug 20;36(24):2465-2472. PMID 29860922 NCT02422615

2. Slamon DJ et al. Overall survival (OS) results of the Phase III MONALEESA-3 trial of postmenopausal patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2−) advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB). https://oncologypro.esmo.org/Meeting-Resources/ESMO-2019-Congress/Overall-survival-OS-results-of-the-Phase-III-MONALEESA-3-trial-of-postmenopausal-patients-pts-with-hormone-receptor-positive-HR-human-epidermal-growth-factor-2-negative-HER2-advanced-breast-cancer-ABC-treated-with-fulvestrant-FUL-ribocicl. Accessed 11/12/19.

3. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2020;382(6):514- 524. doi:10.1056/NEJMoa1911149 [PMID 31826360, NCT02422615]

Revision History:

Date	What changed	Pharmacist's initials
6/17/19	Criteria written	SK
11/25/19	Added criteria for first or second line use with fulvestrant in postmenopausal, HER2 neg, HR pos patients.	SK
6/12/2020	Added reference for postmenopausal indication	SK
8/21/2020	Criteria reviewed. No change.	SK
10/8/2020	Added that the patient should be female per FDA approval	SK
9/28/2021	Added criteria for first line ribociclib+AI due to new data showing OS improvement.	SK

Rifaximin (Xifaxan®)

EBRx PA Criteria

FDA Approved Indications:

1. Traveler's diarrhea in people ≥12y old.
2. Hepatic encephalopathy in adults
3. Irritable Bowel Syndrome-Diarrhea in adults-NOT A COVERED USE
4. Cdif (off-label; but supported in 2018 Cdif guidelines for second or subsequent recurrence)

Traveler's Diarrhea[1,2]
1. Must have diagnosis of traveler's diarrhea caused by noninvasive strains of *E.coli*
2. Is the patient at least 12 years of age?
3. Must NOT have diarrhea complicated by fever or blood in the stool
QL is 200mg #9.
Dosing: 200mg TID for 3 days. **Please note that only the 200mg tablets are indicated for Traveler's Diarrhea.**

Hepatic encephalopathy[1]
1. Must have the diagnosis of overt hepatic encephalopathy recurrence in adults
If yes, approve coverage for 1 year. QL is 550mg #60/30
Dosing: 550mg BID daily, **Please note that the 550mg tablets are indicated for Hepatic Encephalopathy.**

Cdif toxin + Diarrhea[5]. (off label use but supported by the IDSA CDif guidelines 2018)
1. May be used for treatment of second or subsequent C dif infection with Cdif toxin + diarrhea.
2. The patient must have been taking vancomycin 125mg QID by mouth for the previous 10 days.
QL of #120 of the 200mg dosage form with a days supply of 20.
Dosing: 400mg TID for 20 days.

References:

1. Xifaxan Package Insert. https://www.xifaxan.com/

2. Conner BA. Traveler's Diarrhea. http://wwwnc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/travelers-diarrhea

3. Pimentel M, Lembo A, Chey WD, et al. Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation. N Engl J Med 2011;364:22-32.

4. Wald A, et al. Treatment of Irritable Bowel Syndrome in adults. Up to Date. Jan 28, 2016.

5. McDonald, L. Clifford, et al. "Clinical practice guidelines for Clostridium difficile Infection in Adults and Children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)." *Clinical Infectious Diseases* 66.7 (2018): e1-e48.

6. Rivkin, Anastasia, and Sergey Rybalov. "Update on the management of diarrhea-predominant irritable bowel syndrome: focus on rifaximin and eluxadoline." *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 36.3 (2016): 300-316.

Date	What changed	PharmD Initials
4.26.2016	PA criteria written	GBB
4/25/18	I added Cdif to the criteria as well as reference 5.	JTJ
6/7/19	I edited the criteria to no longer cover IBS-D per the EBRx P&T meeting on 5/20/2019. For IBS-D, UpToDate says, "Although rifaximin is FDA-approved for IBS-D, relapse is usual and this may indicate the microbiome is not altered. TCAs were shown effective vs placebo in a meta-analysis of 11 RCTs and may have to do with their anticholinergic properties and slow intestinal transit. Authors recommend starting with dietary modifications, instituting a low-FODMAP diet, increasing exercise and stress reduction (since the pathophys is related to the Brain-Gut pathway, adding a probiotic and/or an antispasmodic agent or a TCA. A 1-month trial of therapy is reasonable before it is stopped. Then alosetron, eluxadoline, or rifaximin may help those with IBS-D. Cure of refractory IBS is generally not possible; avoid opiates." I also added reference 6.	JJ

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Rimegepant (Nurtec® ODT)

EBRx PA Criteria

FDA-approved for: Acute treatment of migraine with or without aura in adults.

Criteria for new users
1. The patient must have the diagnosis of acute migraine before the age of 50y, and have the diagnosis for at least 1 year.
2. The patient's history must have migraines that lasted between 4 and 72 hours and separated by at least 48 hours of freedom from headache pain.
3. The patient must have a history of 2-8 migraines per month in each of the 3 previous months.
4. The patient must NOT have a history of chronic migraine (≥15 migraine headache days per month).
5. The patient must NOT be taking erenumab, fremanezumab, or galcanezumab or have overlapping days supply with ubrogepant. (Patients taking injectable monoclonal antibodies to CGPR receptors were not studied; excluded from trials)
6. The patient must have failed 2 triptans including sumatriptan and eletriptan OR have contraindications to triptans (must provide medical chart). Failure is defined as sumatriptan 100mg for at least a month (with corresponding quantity limit) AND a different month with eletriptan. [Eletriptan was chosen because it is the most efficacious triptan, per the ICER review 2020.]
IF approved, the PA is good for 6 months.

Criteria for continuation
1. The patient's profile should be reviewed and there should be no triptans on the profile in the previous 6 months. This would indicate they are able to tolerate triptans.
If approved, the PA is good for 12 months.

Note: Dosing is up to 100mg once, then another dose 2 hours later if needed (max dose in a 24 h period is 200mg). Safety has not been established for treating more than 8 headaches in a 30d period.

Ubrelvy 50mg is supplied in packets. A packet contains 1 tablet. Box of 6 packets, Box of 8, box of 10, box of 12, box of 30.

Ubrelvy 100mg is supplied as a box of 6, 8, 10, 12, or 30 packets.

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Quantity Limits: 16 tablets per 30 days (so 1 headache can be treated with the second dose). Giving 2 of the 50's to make a 100mg dose should be avoided. Instead, the dose should be increased to the larger strength.

References:

1. **Lexicomp. Ubrogepant. Accessed 2/27/2020.**
2. **Ubrelvy.com. PI. Accessed 2/27/2020.**
3. **Dodick, David W., et al. "Ubrogepant for the Treatment of Migraine." *New England Journal of Medicine* 381.23 (2019): 2230-2241.**
4. **Lipton, Richard B., et al. "Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: the ACHIEVE II randomized clinical trial." *Jama* 322.19 (2019): 1887-1898.**
5. **ICER. Acute Treatments for Migraine. https://icer-review.org/wp-content/uploads/2019/06/ICER_Acute-Migraine_Final-Evidence-Report_022520.pdf**

Revision History:

Date	What changed	Pharmacist's initials
2/27/2020	I wrote the criteria.	JJ
3/4/2020	I removed the word "NOT" from criteria 6.	JJ
6/30/20	Changed medication name on form to rimegepant because it is the preferred med under the plan.	CP

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Riociguat (Adempas©)

Oral tablets 0.5mg, 1mg, 1.5mg, 2mg, 2.5mg

EBRx PA Criteria

Ventavis is FDA-approved for: chronic thromboembolic pulmonary hypertension (WHO group 4) in adults after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class, AND

Adults with pulmonary artery hypertension (PAH) (WHO group 1) to improve exercise capacity, to improve WHO functional class and to delay clinical worsening.

Criteria for PAH (Group 1)	
1. The patient must have the diagnosis of PAH (Group 1), have tried CCB or is currently taking/cannot tolerate CCB/ or have a negative vasoreactivity test	☐Yes ☐No
2. The patient must NOT be taking a PDE5 inh. (sildenafil or other)	☐Yes ☐No
3. The patient must have a pulmonary vascular resistance greater than 300 dyn sec/cm, and a mean pulmonary artery pressure of at least 25mmHg.	☐Yes ☐No
4. The patient must have a documented baseline 6MWT of 150-450 meters at baseline.	☐Yes ☐No
If all 4 of the criteria listed above are “yes”, allow access for 1 year.	
Dosing is 1mg TID initially. Max dose is 2.5mg TID.	

OR

Criteria for CTEPH (Group 4)	
1. The patient must have the diagnosis of CTEPH (Group 4) documented by either a ventilation-perfusion scan, pulmonary angiography, spiral CT, or MR angiography	☐Yes ☐No
2. The patient must have undergone pulmonary endarterectomy or be inoperable	☐Yes ☐No
3. The patient must have a pulmonary vascular resistance greater than 300 dyn sec/cm, and a mean pulmonary artery pressure of at least 25mmHg.	☐Yes ☐No
4. The patient must have a documented baseline 6MWT of 150-450 meters at	☐Yes

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baseline.	☐No
If all 4 of the criteria listed above are "yes", allow access for 1 year.	
Dosing is 1mg TID initially. Max dose is 2.5mg TID.	

1. Shah SJ. Pulmonary Hypertension. JAMA. 2012;308(13):1366-1374.

2. Hopkins W, Rubin LJ. Treatment of pulmonary hypertension in adults. UpToDate. http://www.uptodate.com/contents/treatment-of-pulmonary-hypertension-in-adults?source=search_result&search=pulmonary++hypertension&selectedTitle=2~150. Accessed 2/11/14.

3. Liu C, Chen J, Gao Y, Deng B, Liu K. Endothelin receptor antagonists for pulmonary arterial hypertension. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD004434. DOI: 10.1002/14651858.CD004434.pub5.

4. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369:809-18.

5. Ghofrani H, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med. 2013;369:319-29.

6. Ghofrani H, Galie N, Grimminger F, Grunig E, et al. Riociguat for the treatment of pulmonary arterial hypertension. (PATENT-1). N Engl J Med. 2013;369:330-40.

7. Archer SL. Riociguat for pulmonary hypertension—a glass half full. N Engl J Med. 2013;369(4):386-88.

Revision History:

Date	What changed	Pharmacist's initials
2/6/15	I wrote the criteria.	JJ

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Addendum:

Diagnostic Criteria and WHO categorization of PH						
	All Groups	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 5**

Description	**Elevated PAP**	**Pulmonary arterial hypertension**	**Pulmonary venous hypertension**	**PH due to hypoxemia**	**Chronic thromboembolic PH**	**Miscellaneous or multifactorial PH**
Estimated prevalence	**Up to 10-20% of the general population**	**15 cases/1,000,000 overall; 6 cases per 1mil for idiopathic PAH**	**>3-4 mil in US**	**20% in COPD pts w/ a prior hospitalization for COPD**	**0.5-2% (up to 3.8%) in survivors of acute PE**	**Unclear**
Diagnostic criteria						
Mean PA pressure, mmHg	**≥25**	**≥25**	**≥25**	**≥25**	**≥25**	**≥25**
PCWP or LVEDP, mmHg		**≤15**	**>15**	**≤15**	**≤15**	**≤15**
PVR, dynes/s/cm		>240		>240	>240	>240

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Ripretinib (Qinlock©)

50 mg tablets

EBRx PA Criteria

FDA-approved for:

Treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who received prior treatment with 3 or more kinase inhibitors, including imatinib.

Criteria for new users
1. Diagnosis of advanced gastrointestinal stromal tumor (GIST)
2. Disease progression on or intolerance of imatinib (Gleevec), sunitinib (Sutent), AND regorafenib (Stivarga).
If all criteria met, approve x 6 months. Ripretinib continues until disease progression or intolerance.

Note:

Ripretinib was compared to placebo in the above patient population. Despite ~65% of placebo patients crossing over to active drug, an improvement in overall survival was shown for the group originally assigned to ripretinib (median 15.1 mo vs 6.6 mo; HR 0.36). Progression free survival was also improved in the ripretinib group (6.3 mo vs 1 mo).

Quantity Limits: #90/30 days

References:

Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial [published correction appears in Lancet Oncol. 2020 Jul;21(7):e341]. *Lancet Oncol*. 2020;21(7):923-934. doi:10.1016/S1470-2045(20)30168-6. PMID 32511981 NCT03353753

NCCN Guidelines for Soft Tissue Sarcoma. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf.

Qinlock PI. https://www.qinlockhcp.com/content/files/qinlock-prescribing-information.pdf.

Revision History:

Date	What changed	Pharmacist's initials
6/24/2020	Criteria Written	SK/EF

Risperidone ER injection (Risperdal® Consta)

12.5mg, 25mg, 37.5mg, 50mg vials

EBRx PA Criteria

Initial Access
1. Requires the patient to have a diagnosis of schizophrenia or bipolar disorder.
2. Must have a history intolerable extrapyramidal symptoms from taking haloperidol decanoate or fluphenazine decanoate long-acting injections not responsive to benztropine, trihexyphenidyl, or propranolol in the medical records; look back 5 years or as long as our profile's history and as long a history available in the medical records.
If all of these criteria are fulfilled, approve for 12 months.

- Concurrent use of other forms of olanzapine, quetiapine, ziprasidone, chlorpromazine, haloperidol, trifluoperazine, prochlorperazine, thioridazine, thiothixene, aripiprazole, or risperidone should be given concurrently for **ONLY the first 3 weeks**.
- Max dose is 50mg injected q2w.

Continuation Criteria
1. Requires the patient to have a diagnosis of schizophrenia or bipolar disorder.
2. Requires the patient have no overlapping days supply of any other antipsychotic drug beyond the first 3 weeks of taking Risperdal Consta.

Ref:

1. PI Risperdal Consta. Accessed 10/30/15.

Date	What was changed?	Pharmacist's initials
10/30/15	I wrote the criteria.	JJ

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Rotigotine (Neupro©)

EBRx PA Criteria

FDA-approved for:

- the treatment of Parkinson disease.
- The treatment of moderate to severe primary restless legs syndrome

Criteria for new users
1. The patient must have the diagnosis of Parkinson disease.
2. The patient must have be unable to take pramipexole or have failed to get desired effect.
3. The patient must be taking or be unable to take oral levodopa.

QL: 1 patch per day; 30/30

References:

1. Kim, Jong-Min, et al. "Rotigotine transdermal system as add-on to oral dopamine agonist in advanced Parkinson's disease: an open-label study." *BMC neurology* 15.1 (2015): 17.

2. Poewe, Werner H., et al. "Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial." *The Lancet Neurology* 6.6 (2007): 513-520.

Revision History:

Date	What changed	Pharmacist's initials
4/25/19	I wrote the criteria.	JJ

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Rufinamide (Banzel®)

EBRx PA Criteria

FDA-approved for: Lennox-Gastaut syndrome: adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in adults and children 1y and older.

Criteria for new users
1. The patient must have a diagnosis of Lennox-Gastaut syndrome.
2. Rufinamide must be used as an add-on therapy to other anti-seizure drugs.

Note: The dose is 400-800mg daily in 2 equally divided doses; may increase to a max of 3200mg daily in 2 equally divided doses.

Quantity Limits:

Revision History:

Date	What changed	Pharmacist's initials
4/24/09	Insurance Board voted to accept DUEC rec to T3PA drug	JJ
5/16/12	Revision hx added	JJ
11/5/2020	I added the criteria that rufinamide must be used as add-on therapy.	JJ

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Ruxolitinib (Jakafi®)

Tablet 5, 10, 15, 20, 25mg

EBRx PA Criteria

FDA approved for:

- Intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults
- Polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea.
- Steroid-refractory acute graft-versus-host disease in adult and pediatric patients 12 years and older

CRITERIA FOR MYELOFIBROSIS AND POLYCYTHEMIA VERA
1. For myelofibrosis indication, the patient must meet all of the following criteria: • SYMPTOMATIC intermediate-2 or high-risk myelofibrosis (including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis), [See risk calculation tool below] • Platelet count >50,000 cells/mm^3 • Previous treatment with hydroxyurea or contraindication to hydroxyurea 2. For polycythemia vera indication, the patient must meet the following criterion: • refractory to or intolerant of hydroxyurea therapy.
If criteria for either indication are met, approve for 6 months
Continuation criteria
For myelofibrosis: Patient has reduction in spleen size or symptom improvement and no unacceptable toxicity
For polycythemia vera: Improvement in hemoglobin control or symptoms and no unacceptable toxicity
QL: all strengths: 60 units/30 days
Notes: 4. Myelofibrosis: -Main benefit in myelofibrosis is reduction of spleen size and symptoms. Symptoms of myelofibrosis include fatigue, bone pain, fever, pruritus, symptomatic splenomegaly (early satiety, pain), hepatomegaly.[1] -COMFORT trials showed possible improvement in overall survival versus best available treatment which could have included systemic medication, observation, or placebo. The majority of patients received prior hydroxyurea.[1] -Ruxolitinib may cause thrombocytopenia. Baseline platelets count should be at least

>50,000 cells/mm3

-In a sponsor-independent analysis from Mayo Clinic, there was a 92% discontinuation rate primarily for loss of treatment benefit after 9.2 months, but also because of drug AEs[2]. The "ruxolitinib withdrawal syndrome" is manifested by acute relapse of disease symptoms, accelerated splenomegaly, worsening of cytopenias, and occasional hemodynamic decompensation including septic shock-like syndrome. Reduce dose by ~5 mg bid per week.

-Side effects such as thrombocytopenia, worsening anemia, and the withdrawal syndrome should be communicated with the patients before beginning therapy.

-The package insert directs the physician to discontinue after 6 months if no spleen reduction or symptom improvement.[3]

2. Polycythemia vera (PV)

-Main benefit for PV is hemoglobin control and reduction in spleen volume compared with other therapies[4]. No mortality data available.

IPSS RISK STRATIFICATION for primary myelofibrosis[1]

IPSS Risk Factors*
Age >65 years
White cell count >25 x 10^9/l
Hemoglobin <10 g/d
Peripheral blood blasts ≥1%
Constitutional symptoms

*The presence of each factor is assigned 1 point:

- Low risk: 0 points
- Intermediate-1 risk: 1 point
- Intermediate-2 risk: 2 points
- High risk: 3 or more points

References

1. Verstovsek S et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses. J Hematol Oncol. 2017 Sep 29;10(1):156.
2. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clin Proc. 2011;86(12):1188-1191.
3. Jakafi PI. http://www.incyte.com/products/uspi_jakafi.pdf Accessed 2/2/12. And 1/13/15.
4. Vannucchi, Alessandro M., et al. "Ruxolitinib versus standard therapy for the treatment of polycythemia vera." *New England Journal of Medicine* 372.5 (2015): 426-435.

CRITERIA FOR ACUTE GRAFT VERSUS HOST DISEASE (GVHD)
1. Age at least 12 years
2. Previous allogeneic stem-cell transplant
3. Grade II, III, or IV acute GVHD
4. Inadequate treatment response or intolerance to corticosteroid therapy
5. Absence of serious active infection
If all criteria met, approve for 6 months
QL: all strengths: 60 units/30 days
Notes: Ruxolitinib was compared to best available therapy (BAT). The ruxolitinib group showed a higher response rate than BAT (62% vs 39%). Response rate is based on improvement of any combination of symptoms caused by GVHD (rash, liver dysfunction, diarrhea, nausea/vomiting).

Revision History:

Date	Notes	Pharmacist's initials
4/2/12	Criteria written	JJ
4/9/12	DUEC voted T3PA	JJ
5/15/12	IB accepted DUEC's rec	JJ
5/16/12	Revision Hx table added	JJ
1/13/15	I added the indication of PV based on reference 5. I added reference 5.	JJ
2/29/2016	I changed to allow for diagnosis 1 OR 2.	JJ
5/7/2016	PA Length Consolidated and now good for 6 months	AM
2/4/19	Added that myelofibrosis pt need to be symptomatic since the main benefit of the drug was symptom improvement; added that risk level should be intermediate-2 instead of just intermediate; added note listing symptoms of MF. Added suggested tapering schedule. General update of formatting and notes/references. Added continuation criteria and MF risk calculator.	sk
6/26/19	J Barr asked me to review the PA criteria for GVHD (a new indication in 5/2019). I reviewed SKeisner's notes and agree that since there are several less toxic alternatives, only 1 single-arm trial assessing response rates, and no RCT, and UpToDate stating the risk is high for withdrawal syndrome upon discontinuation. UTD also notes that one of two patients who received a higher dose (10mg/d) of ruxolitinib died with recurrence of GVHD shortly	JJ

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	after discontinuation of the medication. There are limited data to guide the choice of therapy. I searched the FDA.gov website for data they based their approval on and was not able to locate it. EBRx considers this indication, GVHD, not covered. Will reconsider once comparative data in a GVHD population is available.	
8/7/19	Criteria reviewed. Added FDA approved indications to top of page and that GVHD is not covered as above.	SK
9/23/19	Criteria reviewed. For MF indication, require platelets to be at least 50k per PI and require prior use of hydroxyurea. In study, most patients had received prior hydroxyurea.	SK
5/27/20	Added criteria for steroid refractory acute GVHD per 5/27/2020 P&T meeting discussion	SK

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Sacubitril-Valsartan (Entresto®)

24/26mg, 49/51mg, 97/103mg

EBRx PA Criteria

FDA-approved:

- In adults to reduce the risk of CV death and hospitalization for heart failure in patients with chronic heart failure. Benefits are most clear in patients with reduced LVEF.
- In pediatric patients for treatment of symptomatic HF with systemic LV systolic dysfunction in pediatric patients ≥1y.

Criteria for new users
1. Must have the diagnosis of chronic heart failure, NYHA Class II-IV with a reduced ejection fraction of ≤40%
2. Must be age 18 or older
3. Must be currently on a stable dose of a HF-specific beta blocker or be unable to tolerate these (carvedilol, metoprolol succinate, bisoprolol) (GDMT=guideline-directed medical therapy per ACC)
4. Must NOT have any history of angioedema.
5. Must NOT be currently taking an ACE inhibitor OR plans to discontinue and begin Entresto 36 hours after discontinuation of ACE inhibitor. (GDMT)
6. Patients are **encouraged to be on spironolactone**. Please ask if patient is on spironolactone. Providers should **provide justification** for avoiding use of spironolactone as it is a **category 1, level of evidence A recommendation** for the following patients with **Heart Failure with reduced ejection fraction (LVEF ≤ 35%)**: • NYHA class II-IV with estimated CrCl > 30 mL/min and serum potassium < 5.0 mEq/L. • (Also GDMT)
Approval of Entresto is based on fulfilment of criteria 1 through 5. Category 6 is encouraged for patients who meet spironolactone utilization criteria, but not a requirement.

Quantity Limits: 2tabs/1day

Revision History:

Date	What changed	Pharmacist's initials
8/27/15	I wrote the criteria	JJ
10/14/15	I deleted a criterium "must NOT have symptomatic hypotension";	JJ

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	assume provider would not seek this drug if pt is symptomatically hypotensive.	
5/23/16	I added criterium 6 with the requirement of an aldosterone antagonist as the 2016 ACC/AHA/HFSA Focused Update on HF recommends.	JJ
12/19/17	Updated PA criteria to initiate Entresto upon discontinuation of ACE inhibitor 36 hours prior. Utilization of spironolactone is no longer a REQUIREMENT for Entresto approval. It is now a highly encouraged recommendation. Call center pharmacists, please ask providers if their patient is on spironolactone. If their patient is not on spironolactone, please make them justify why their patient with HFrEF (LVEF ≤ 35%) is not on spironolactone if they meet the criteria above.	JK
10/27/2020	I added the pediatric indication. I also reviewed the criteria. No changes.	JJ
3/9/2021	Reference 3 added.	JJ
10/8/21	I changed the EF requirement from <35% to <40% per the ACC 2021 guidelines.	JJ

References:

1. McMurray JJV, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014; 371(11): 993-1004.

2. ACC/AHA/HFSA Focused Update. http://www.acc.org/latest-in-cardiology/ten-points-to-remember/2016/05/18/16/26/2016-acc-aha-hfsa-focused-update-on-new-pharmacological-therapy-for-hf Accessed 5/23/16.

3. Maddox, Thomas M., et al. "2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee." *Journal of the American College of Cardiology* 77.6 (2021): 772-810.

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Sapropterin (Kuvan©)

100mg tablet & 100mg Powder Packet

(NOTE: 500mg powder packet is excluded from coverage)

EBRx PA Criteria

FDA-approved for: reduction of phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) secondary to BH4-responsive Phenylketonuria (PKU). Kuvan is used in conjunction with a Phe-restricted diet.

Criteria for new users
1. Patient must have the diagnosis of phenylketonuria.
2. Must have a blood phenylalanine level above 360 umol/L (6mg/dL), despite dietary protein/phenylalanine restriction
3. Must have failure of PKU dietary restriction (no protein intake)
4. Prescriber must report the phenylalanine level at the time of request (in mg/dL and in micromol/L). We need the baseline in order to establish whether or not the patient is a "responder" (30% reduction in phyenylalanine level) during evaluation for continuation (below).
The initial PA is good for 3 months.

Criteria for continuation
1. The phenylalanine concentration after at least 3 months of therapy should be <360umol/L (occurred by week 10 in one trial Trefz, Friedrich, et al.)
2. All of the above criteria for new users must still be true.
The subsequent PA is good until age 12 years and 364 days; or until the pregnancy is over in the case of pregnant females.

Note: The EBRx P&T Committee determined the ability to comply with a PKU-restricted diet, the mainstay of therapy, would be possible after age 12.

Quantity Limits: none

References:
1. Levy, H.L.; et al. “Efficacy Of Sapropterin Dihydrochloride (Tetrahydrobiopterin, 6R-BH4) For Reduction Of Phenylalanine Concentration In Patients With Phenylketonuria: A Phase III Randomized Placebo-Controlled Study.” Lancet 2007, 370(9586), 504-510.
2. Trefz, Friedrich K. et al. "Efficacy Of Sapropterin Dihydrochloride In Increasing Phenylalanine Tolerance In Children With Phenylketonuria: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study". The Journal of Pediatrics 154.5 (2009): 700-707.e1. Web. 25 July 2016.
3. González, María J., et al. "Neurological complications and behavioral problems in patients with PKU in a follow-up unit." Molecular genetics and metabolism 104 (2011): S73-S79.
4. AR Dept of Health. Newborn health screenings. http://www.healthy.arkansas.gov/programsServices/familyHealth/ChildAndAdolescentHealth/newBornScreening/HealthProfessionals/Documents/list_conditions_screened_arkansas.pdf
5. Bodamer OA. Overview of phyenylketonuria. UpToDate. Accessed 7/24/2020.
6. Vockley, Jerry, et al. "Phenylalanine hydroxylase deficiency: diagnosis and management guideline." *Genetics in Medicine* 16.2 (2014): 188.

UpToDate 7/24/2020:

- The NIH Consensus Development Conference on PKU recommended maintaining a blood concentration of:
  - 2-6mg/dL (120-360 umol/L) for affected children through 12 y of age;
  - 2-15 mg/dL (120-900 umol/L) after age 12.
  - No consensus exists in the US, to date.
- Data are limited, but higher blood phenylalanine conc. Appears to adversely affect brain function, even in adults.
  - Maintenance of lower levels (2-10mg/dL, 120-600 umol/L) is strongly encouraged during adolescence or even beyond.
- Long-term data on sapropterin therapy are limited.
- High phenylalanine levels are associated with low IQ (<85), regardless of whether IQ was measured during childhood or beyond.
- Longterm neurologic function in patients with PKU treated with sapropterin has not been assessed.
- [6]ACMG Practice Guidelines suggests the goal of maintaining blood phenylalanine in the range of 120-360 (2-6 mg/dL) umol/L.

Revision History:

Date	What changed	Pharmacist’s initials
2016	I wrote the criteria.	JJ
7/24/2020	[5,6]I reduced the phenylalanine level at which someone qualifies for treatment from 600 umol/L to 360umol/L per	JJ

	UpToDate (accessed 7/20/2020) that defines “mild hyperphenylalaninemia” as 360-600 umol/L. Call center pharmacists will need to record the initial phenylalanine level to be able to determine whether or not there was a 30% drop when they seek continuation of sapropterin. I also removed the upper age limit of 12y due to ongoing need for sapropterin after that age.	

Sargramostim (Leukine®)

250mcg powder for reconstitution,

500mcg/mL (1mL) solution for inj

IV or SC

EBRx PA Criteria

FDA-approved indications:

1. Autologous or allogeneic bone marrow transplant failure or engraftment delay (select link to see criteria)
    - For treatment of delayed neutrophil recovery or graft failure after autologous or allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older
2. Mobilization of Peripheral Blood Progenitor Cells (PBPC) for autologous transplantation
    - For the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation in adult patients
    - Not a covered use. Filgrastim is preferred by American Society of Blood and Marrow Transplantation guidelines and EBRx. Reference: Duong HK et al. Biol Blood Marrow Transplant. 2014 Sep;20(9):1262-73. PMID 24816581
3. Acute myeloid leukemia (AML)
    - To shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML).
    - Not a covered use . Filgrastim is preferred due to similar or lower cost and more convenient dosage forms.
4. Autologous bone marrow or peripheral blood progenitor cell (PBPC) Transplantation
    - For the acceleration of myeloid reconstitution following autologous bone marrow or peripheral blood progenitor cell transplantation in adult and pediatric patients 2 years of age and older

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- Not a covered use. Filgrastim is preferred due to similar or lower cost and more convenient dosage forms.

5. Allogeneic bone marrow transplantation
    - For the acceleration of myeloid reconstitution following allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older
    - Not a covered use. Filgrastim is preferred due to similar or lower cost and more convenient dosage forms.
6. Hematopoietic Syndrome of Acute Radiation Syndrome
    - To increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation
    - Not a covered use. Filgrastim is preferred due to similar or lower cost and more convenient dosage forms.

Off-label indications (none are covered uses):

1. Crohn's Disease
    - Cochrane analysis shows that sargramostim is no better than placebo for induction of remission
    - Sargramostim is not recommended by the American College of Gastroenterology guidelines
    - Per UpToDate: sargramostim is discussed in "***Investigational*** Therapies in the Medical Management of Crohn's Disease.
    - See critique of Korzenik NEJM study below (by JJ)
    - References:
        i. Korzenik, JR, et al. Sargramostim for Active Crohn's Disease. NEJM 2005;352(21):2193-2201
        ii. Roth L et al. Sargramostim (GM-CSF) for induction of remission in Crohn's disease: a cochrane inflammatory bowel disease and functional bowel disorders systematic review of randomized trials. Inflamm Bowel Dis. 2012 Jul;18(7):1333-9. PMID 22552871
        iii. Lichtenstein GR et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018 Apr;113(4):481-517. PMID 29610508

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iv. UpToDate "Investigational Therapies in the Medical Management of Crohn's Disease." https://www.uptodate.com/contents/investigational-therapies-in-the-medical-management-of-crohn-disease?search=crohns%20disease%20sargramostim&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed 7/30/19.

2. Non-chemotherapy drug-induced neutropenia
    - Filgrastim is preferred due to more and better data. It also has similar or lower cost and more convenient dosage forms
        i. Anderson, F, Konzen C, and Edeltraut, G. Systematic Review: Agranulocytosis Induced by Nonchemotherapy Drugs. *Annals of Internal Medicine*. 2007;146(9):657-666
        ii. Andrés, E and F Maloisel. Idiosyncratic drug-induced Agranulocytosis or acute neutropenia. *Current Opinion in Hematology.* 2008;15:15-21
        iii. Andrés, E; Maloisel, F; and Zimmer, J. The role of haematopoietic growth factors granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor in the management of drug-induced agranulocytosis. *British Journal of Haematology.* 2010;150:3-8
3. Oral mucositis—this is not a covered use
    - There are no hematopoietic agents covered by EBRx for this indication.
    - Data are conflicting for this indication. Most trials showed no benefit over placebo, and even those that demonstrated modest benefit were weak in quality. CSFs should not be used in this population, based on the best current evidence.
    - References:
        i. Sargramostim. Clin-*e*guide: Facts & Comparisons® eAnswers (Accessed 7/11/12)
        ii. Rubenstein EB, et al. Clinical Practice Guidelines for the Prevention and Treatment of Cancer Therapy-Induced Oral and Gastrointestinal Mucositis. CANCER supplement May 1, 2004;100(9):2026-2046. doi 10.1002/cncr.20163
        iii. Worthington HV, et al. Interventions for preventing oral mucositis for patients with cancer receiving treatment (review). *The Cochrane Library* 2011;4:1-275
4. Primary prophylaxis of neutropenia in patients receiving chemotherapy (outside transplant and AML)—not covered, prefer filgrastim due to similar or lower cost and more convenient dosage forms.
5. Neutropenia associated with myelodysplastic syndromes
    - Filgrastim is preferred due to similar or lower cost and more convenient dosage forms.

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Criteria for autologous or allogeneic BMT failure or engraftment Delay	
1. The patient meets one of the following conditions: ☐ It is at least day 28 post-transplantation AND The patient's ANC ≤100 cells/mm^3. ☐ It is at least day 21 post-transplantation AND The patient's ANC ≤100 cells/mm^3 AND The patient has evidence of an active infection. ☐ The patient lost his/her marrow graft after transient neutrophil recovery.[†]	□ Yes □ No
If the answer is NO, stop and deny coverage. **If the answer is YES, approve sargramostim (Leukine®) for coverage. The PA is good for 6 months.** **The PA is to allow access to sargramostim for the purpose of improving survival in the setting of delayed engraftment or graft failure.**	

[†]This was manifested in the trial by ANC > 500 cells/mm^3 for at least 1 week followed by loss of engraftment with ANC < 500 cells/mm^3 for at least 1 week beyond day 21 post-transplantation.

References:

1. Genzyme, Inc. (2009). Sargramostim (Leukine®). Cambridge, MA: Author. http://www.leukine.com/pi . Accessed 7/31/19.

Rationale for coverage:

The patients had to meet one of the criteria above to be considered eligible for the trial. It is unknown whether patients outside these criteria will derive benefit from sargramostim therapy following BMT failure.

Critique of Korzenik et al study regarding use of sargramostim for Crohn's Disease (written by JJ):

The results of the large, randomized, controlled trial by Korzenik et al. (Ref 2 above) is the basis of the PA criteria set forth here. The PA criteria (#1-#3 and #5-#8) reflect the inclusion/exclusion criteria of the trial. Criterion #4 results from a subgroup analysis that determined current users of tobacco will experience no significant benefit from sargramostim use when compared to placebo. Criterion #9 is an extrapolation from the ACG guidelines (Ref 4 above) in which sargramostim therapy is not mentioned anywhere. Thus, expert-recommended second-line therapy (i.e. anti-TNF agents) should be tried and failed before experimental therapy is appropriate.

The weaknesses of the trial by Korzenik, et al, are discussed below. First and foremost, patient baseline characteristics were not equivocal between treatment and control groups. Differences are as noted (C=control arm, T=treatment arm): 1. Sex (#males): C=51%, T=43%; 2. Median Age (yr): C=41.0, T=36.0; 3. Duration of disease (yr): C=9.9, T=7.7; 4. Tobacco use (any): C=67%, T=48%; 5. Tobacco use (current): C=33%, T=17%; 6. Prior medications (infliximab): C=60%, T=47%. Several of these differences (and in combination) may have skewed the results of the trial. The treatment arm effectively had younger patients, patients with shorter duration of disease, less tobacco use, and less treatment-resistant disease. Furthermore, after a subgroup analysis was performed, the authors state that "sargramostim-treated patients who had ongoing tobacco use… had response and remission rates that were similar to those of the overall group." The authors themselves therefore concede that current tobacco use negates use of sargramostim. Why, then, was there a discrepancy in <u>current</u> tobacco use of nearly two-fold between the control and treatment groups? It would also be beneficial to know whether smoking at any time in the past affects the efficacy of sargramostim, as there was a 19% difference in any prior tobacco use between arms.

That patients in the treatment arm were, on average, 5 years younger than those in the control arm, does not in and of itself necessarily cause skewed results. After all, it is not logical to assume that every patient in the control arm, for all 5 of those years, had CD. However, couple this discrepancy with the discrepancy in duration of disease between trial arms (2.2 years), and that argument suddenly becomes more robust. It causes one to question whether the patients in the treatment arm were in better health at baseline than those in the control arm. And it causes one to question the validity of the results.

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Fewer patients in the treatment arm had been tried on infliximab therapy (i.e. second-line therapy) than had the control arm. Again, here is a quote by the authors following yet another subgroup analysis: "…response and remission rates were higher among those who had not received prior second-line therapy than among those who had." In other words, patients who had been on infliximab previously did worse than those who were naïve to infliximab therapy. This begs the question: Why, then, was there a discrepancy in prior infliximab use of 13% between the control and treatment arms, favoring the treatment arm? If patients did worse if they had tried infliximab, doesn't it follow logically that less patients in the control arm would respond to sargramostim, since 60% of them had tried second-line therapy?

Finally, the authors confound trial with another observation: "The mean time to the loss of a clinical response [in the sargramostim group] was 9.7 weeks, and to the loss of remission 7.5 weeks." Time to loss of clinical response and remission was not an endpoint specified a priori *in the trial, but it is still a valid clinical endpoint (arguably more valid than improved CDAI scores). The error doesn't lie with the authors reporting this result; it lies with the fact that time to loss of clinical response and remission was not reported for patients in the placebo arm. Thus the true ability of sargramostim to bring about a meaningful clinical endpoint remains unascertained. True, the authors might not have been able to measure statistical difference, but to know if sargramostim therapy trended toward sustained clinical response would be helpful.*

Revision History:

Date	Changes	Pharmacist
7/19/12	Document created	JLB
7/31/12	Inserted the comments regarding evidence substantiating whether the use would be covered after committee discussion.	JJ
8/26/19	Reduced criteria to include only treatment of delayed engraftment/graft failure after transplant. For the rest of indications, either do not cover or prefer filgrastim as noted above.	SK
10/13/2020	Criteria review. No change.	SK

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Secukinumab (Cosentyx®)

EBRx PA Criteria

Secukinumab is FDA-approved for:

- moderate to severe chronic plaque psoriasis in adult patients
- adults with active psoriatic arthritis
- adults with active ankylosing spondylitis

Criteria for Plaque Psoriasis	
1. The patient must have tried and failed Humira and Enbrel.	
1. Is the patient 18 years of age or older?	☐Yes ☐No
2. Does the patient have a diagnosis of moderate to severe plaque psoriasis, defined as: • A score of 12 or higher on the psoriasis area-and-severity index (PASI) **AND** • A score of 3 or 4 on the modified investigator's global assessment **AND** • Involvement of 10% or more of the body-surface area	☐Yes ☐No
3. **Has the patient experienced failure to achieve all items in #2 above AFTER receiving broadband UV light therapy (must have received 25 treatments at a frequency of 5x/w) or narrow band UV light therapy (must have received at least 20 treatments at a frequency of 5x/w)?	☐Yes ☐No
4. Has the patient experienced failure to achieve all items in #2 above AFTER receiving 4 weeks of topical corticosteroid therapy?	☐Yes ☐No
5. Has the patient experienced failure to achieve all items in #2 above AFTER receiving 4 weeks of topical calcipotriene therapy (may be overlapped with topical corticosteroid)?	☐Yes ☐No
6. Has the patient experienced failure to achieve all items in #2 above AFTER receiving 8 weeks of topical tacrolimus 0.1% w/ pimecrolimus 1% therapy?	☐Yes ☐No
7. Has the patient experienced failure to achieve all items in #2 above AFTER	☐Yes ☐No

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receiving 16 weeks of high-dose methotrexate (0.5mg/kg/w)?	
8. Has the patient experienced failure to achieve all items in #2 above AFTER receiving 8 weeks of systemic cyclosporine (7.5mg/kg) therapy?	☐Yes ☐No

**If the patient has a concurrent diagnosis of lupus erythematosus or xeroderma pigmentosum, the requirement of UV light therapy is waived.

If the answer to questions 1-8 is **yes**, then approve for 3 months.

Continuation Criteria	
1. Has the patient achieved a 75% reduction in their psoriasis area-and-severity index (PASI) score since beginning secukinumab treatment?	☐Yes ☐No

If **yes**, approve for 12 months.

For Plaque Psoriasis, secukinumab is dosed 300mg subq once weekly at weeks 0, 1, 2, 3, and 4 followed by 300mg every 4 weeks. Some patients may only require 150mg/dose.

Initial approval: 7 doses/12 weeks

Continuation approval: 13 doses/52 weeks

Special dosing considerations: Some patients may only require 150mg/dose.

PASI	Psoriasis Area Severity Index. Used to express the severity of psoriasis based on a combination of erythema, induration, and desquamation over the percentage of affected body area. Scale ranges from 0 (no disease) to 72 (maximal disease).
Modified Investigator's Global Assessment	Scale of 0 to 4 with higher scores indicating more severe disease.

Criteria for Psoriatic Arthritis
1. The patient must have tried and failed Humira and Enbrel.
2. Patient must have active disease, defined as ≥3 tender joints AND ≥3 swollen joints, despite previous NSAIDs, DMARDs, or TNF inhibitors.
3. Patient must be age 18 or older.
If the above are true, PA may be approved for 4 months.
Dose for Psoriatic Arthritis is • With a loading dose, 150mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter. • Without a loading dose, 150mg q4w. • May increase to 300mg

Continuation Criteria
1. In the previous 4 months, the patient must have achieved at least a 20% improvement in the number of tender joints, in the number of swollen joints. If so, approve PA for 12 months.
2. After the first 12 month approval, the patient must maintain the improvement of 20% from baseline to keep access to recurring 12 month approvals.

Criteria for Ankylosing Spondylitis
1. The patient must have tried and failed Humira and Enbrel.
2. Patient must be age 18 or older.
3. Patient must have dx of ankylosing spondylitis fulfilling the modified New York criteria: **Table 2.** New York clinical criteria for ankylosing spondylitis (6) 1. Limitation of motion of the lumbar spine in all 3 planes (anterior flexion, lateral flexion, and extension). 2. A history of pain or the presence of pain at the dorsolumbar junction or in the lumbar spine. 3. Limitation of chest expansion to 1 inch (2.5 cm) or less, measured at the level of the fourth intercostal space. Definite ankylosing spondylitis if 1) grade 3–4 bilateral sacroiliitis associated with at least 1 clinical criterion; or 2) grade 3–4 unilateral or grade 2 bilateral sacroiliitis associated with clinical criterion 1 or with both clinical criteria 2 and 3. Probable ankylosing spondylitis if grade 3–4 bilateral sacroiliitis exists without any signs or symptoms satisfying the clinical criteria.
Continuation Criteria
1. In the previous 4 months, the patient must have achieved at least a 20% improvement in the Assessment of Spondyloarthritis International society 20(ASAS) response criteria [i.e. improvement of ≥20% and absolute improvement of >1 unit on a 10-unit scale in at least 3 of the 4 main ASA domains, without worsening by >20% in the remaining domain. If so, approve PA for 12 months.
2. After the first 12 month approval, the patient must maintain the improvement of 20% from baseline to keep access to recurring 12 month approvals.
Dose for Ankylosing Spondylitis is • With a loading dose, 150mg at weeks 0, 1, 2, 3, and 4 and q4w thereafter • Without a loading dose, 150mg q4w.

Revision History:

Date	What changed	Pharmacist's initials
5/7/15	Wrote the PA	GBB
5/29/15	I added specifically what therapies a patient must have received prior to gaining access to secukinumab. I also added references 2-5.	JJ
10/13/15	I corrected the mistake on what to do with items 4-8. All the answers must be "yes" to gain access to secukinumab. I did not change the continuation criteria.	JJ
2/22/17	I added to the PA two new indications and wrote the criteria including psoriatic arthritis and ankylosing spondylitis. Added references 6 & 7.	JJ

References:

1. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in Plaque Psoriasis – Results of Two Phase 3 Trials. N Engl J Med 2014;371:326-38.

2. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. J Am Acad Dermatol. 2010;62:114-35.

3. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 3. Guidelines w/ topical therapies. J Am Acad Dermatol. 2009;60:643-59.

4. Gelfand JM, Wan J, Duffin KC, et al. Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. Arch Dermatol. 2012;148(4)487-494.

5. UpToDate. http://www.uptodate.com/contents/treatment-of-psoriasis?source=machineLearning&search=plaque+psoriasis&selectedTitle=1~47&sectionRank=2&anchor=H30#H30. Accessed 5/29/15.

6. Mease, Philip J., et al. "Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis." *New England Journal of Medicine* 373.14 (2015): 1329-1339.

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7. Baeten, Dominique, et al. "Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis." *New England Journal of Medicine* 373.26 (2015): 2534-2548.

Selegiline transdermal (Emsam™)

EBRx PA Criteria

1. Is the patient ≥ 18 years old with major depressive disorder?	☐ Yes ☐ No
2.* Is the patient unable to take oral tablets?	☐ Yes ☐ No
3. Is the patient currently **NOT** taking any of the following: other medications to treat depression including but not limited to fluoxetine, paroxetine, Celexa®, Effexor®, Lexapro™, Paxil®, Zoloft®, duloxetine, amitriptyline, doxepin, nortriptyline, imipramine, Wellbutrin®, mirtazapine, buspirone, Eldepryl®, Marplan®, Nardil®, Parnate®, or St. John's wort?	☐ Yes ☐ No
4. Is the patient currently **NOT** taking any of the following pain medications including, meperidine, tramadol, methadone, or propoxyphene?	☐ Yes ☐ No
5. Is the patient currently **NOT** taking any of the following medication for seizures, such as carbamazepine or oxcarbazepine?	☐ Yes ☐ No
6. Is the patient currently **NOT** taking any of the following: cough medicines, such as dextromethorphan, medicine to treat muscle spasms, such as cyclobenzaprine, or cold medicines, such as pseudoephedrine, phenylephrine, phenylpropanolamine, or ephedrine?	☐ Yes ☐ No
7. Is the patient currently **NOT** taking any of the following: any herbal or dietary supplement that contains tyramine, or medications with amphetamine?	☐ Yes ☐ No

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ALL of the above questions must be answered "yes" to allow approval. **Authorization period is 1 year.**

Revision History:

Date	Notes	Pharmacist's initials
8/7/06	Criteria were written	JJ
10/17/06	IB voted to accept DUEC's rec to T3PA this drug	JJ
5/16/12	Revision history table added	JJ

Selegiline (Zelapar®)

EBRx PA Criteria

1. Is the patient able to swallow pills?	**□ Yes □ No**
If "no", approve for 1 year. If "yes", then deny coverage.	

Revision History:

Date	Notes	Pharmacist's initials
8/7/06	Criteria were written	JJ
10/17/06	IB voted to accept DUEC's rec to T3PA this drug	JJ
5/16/12	Revision history table added	JJ

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Selexipag (Uptravi©)

200, 400, 600, 800, 1000, 1200, 1400, 1600mcg tablets, Tablet Therapy Pack: 200mcg (140s) and 800 (60s); total 200/pack

EBRx PA Criteria

FDA-approved for: treatment of PAH (WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

Criteria for new users
1. Patients must have the diagnosis of World Health Organization (WHO) Group 1 pulmonary artery hypertension.
2. Chart notes must confirm the documentation of a right heart catheterization showing pulmonary vascular resistance of at least 5 Wood units or 400 dyn-sec-cm^{-5}.
3. Chart notes must confirm the patient has a 6 min walk distance of at least 50 meters in the past 12 months.

QL of 2 tablets per day.

This is a specialty medication so only a 30 days supply will be allowed per month.

Note: The dosing is 200mcg BID up to a max dose of 1600mcg BID.

It is imperative dose optimization occur since all strengths are priced the same per tablet.

NOTE TO CALL CENTER PHARMACISTS: Please make a note when the PA call comes in. The titration pack should be allowed only during the first 3 months of starting the drug and ideally be used only 1 month. Patients should be titrated by 12 weeks. After 3 months, NON-titration packs should be used with QL of 2/1 and appropriate days supply.

Please ensure the QL is also entered within the PA. Max daily dosage is 2 tablets. AWP Titration Packs 200 & 800 (#200)= $26,136 200mcg (#60) = $11208 400, 600, 800, 1000, 1200, 1400, 1600mcg (any #60) = $17424

References:

1. **Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med. 2015;373:2522-33. (GRIPHON)**

Revision History:

Date	What changed	Pharmacist's initials
4/5/16	I wrote the criteria. Awaiting the Insurance Board's approval before this is covered.	JJ
2/9/17	I wrote the note to call center pharmacists to get help in optimizing the use of the QL and minimize use of multiple titration paks.	JJ

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Selumetinib (Koselugo®)

10 mg, 25 mg capsules

EBRx PA Criteria

FDA-approved for:

Treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

Criteria for new users
1. Age is 2 years or older
2. Diagnosis of neurofibromatosis type 1 (NF1)
3. Presence of plexiform neurofibroma(s) (PN) that is/are unable to be resected.
4. Plexiform neurofibromas are symptomatic (e.g. cause pain, disfigurement, motor dysfunction, visual impairment, airway dysfunction, etc).
If all criteria met, approve for 1 year.

Note:

In a single arm, phase II trial (n=50), selumetinib induced tumor shrinkage in 70% of patients. Clinically meaningful improvements in pain, functional, and overall health-related quality of life were also reported.

Quantity Limits: 31 day supply

Revision History:

Date	What changed	Pharmacist's initials
5/27/2020	Reviewed at EBRx P&T. Criteria written	SK

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Semaglutide (Ozempic®)

EBRx PA Criteria

FDA-approved for:

- treatment of type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control in adults; and for risk reduction of major cardiovascular events in adults with T2DM and established CV disease (Ozempic only; not Rybelsus).
- Chronic weight management (Wegovy)—NOT A COVERED USE

Criteria for new users
1. The patient must have the diagnosis of T2DM.
2. The patient have a documented HbA1C in the previous 3 months of 7.0%-9.5%.
3. Patient must be receiving metformin at 1000mg twice daily for the past 4-5 months. Pharmacist should look back to be sure this occurred. OR The patient must have a contraindication to metformin that must be documented by the pharmacist.
4. No duplication of therapy with exenatide or other GLP-1 agonists (liraglutide, exenatide, albiglutide, dulaglutide) or concurrent SGLT2 inhibitor.

Criteria for continuation
1. The patient should have liraglutide on the profile as having filled for 10 of the 12 previous months.
2. The patient should have metformin on the profile as having filled for 10 of the 12 previous months.

Note:
a. Metformin must be titrated slowly upward. Metformin 500mg BID is the initial dose.

References:

1. Marso, Steven P., et al. "Semaglutide and cardiovascular outcomes in patients with type 2 diabetes." *New England Journal of Medicine* 375.19 (2016): 1834-1844.

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Revision History:

Date	What changed	Pharmacist's initials
10/28/19	I wrote the criteria. I put an upper limit on initial A1C because the drug does not reduce A1C by more than 1%.	JJ
4/28/21	I added no concurrent SGLT2 inhibitor therapy due to uncertainty of combination therapy. Also to be consistent with the contract, omitted secondary CV prevention requirement	JJ
3/28/22	I updated the FDA approval, noting weight-management in not a covered use. Also updating the CV risk reduction was shown only in patients with established CV disease.	JJ

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Semaglutide (Rybelsus®)

EBRx PA Criteria

is FDA-approved for:

- Treatment of T2DM as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

Criteria for new users
1. Patient must have the diagnosis of type 2 diabetes mellitus.
2. Patient must have a documented Hb A1C in the previous 3 months of >7.0%-9.5%.
3. Patient must be receiving metformin at 1000mg twice daily for the past 4 out of 5 months. Pharmacist should look back to be sure this occurred. OR The patient must have a contraindication to metformin that must be documented by the pharmacist.
4. No duplication of therapy with other GLP-1 agonists (dulaglutide, albiglutide, semaglutide, exenatide) or SGLT2 inhibitor therapy.

Criteria for continuation
1. The patient should have semaglutide on the profile as having filled for 10 of the 12 previous months.
2. The patient should have metformin on the profile as having filled for 10 of the 12 previous months.

Note: a. Metformin must be titrated slowly upward. Metformin 500mg BID is the initial dose.

References:

1. Lexicomp. Semaglutide. Accessed 1/6/22.

2. Husain, Mansoor, et al. "Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes." *New England Journal of Medicine* 381.9 (2019): 841-851.

Revision History:

Date	What changed	Pharmacist's initials
1/6/22	I wrote the criteria.	JJ
1/20/22	I put an upper limit on initial A1C because the drug does not reduce A1C by more than 1%.	JJ

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3/28/22	I updated the FDA-approval, noting Rybelsus (oral semaglutide) does not have the approval for CV risk reduction.	JJ

Sildenafil (Revatio©)

20mg tablets, 10mg/mL suspension reconstituted

EBRx PA Criteria

FDA-approved for: Treatment of pulmonary arterial hypertenstion (PAH) (WHO Group 1) in adults to improve exercise ability and delay clinical worsening.

Criteria	
1. The patient must have the diagnosis of pulmonary arterial hypertension, WHO Group 1	☐Yes ☐No

Dosing is 5-20mg 3 times daily taken 4-6h apart. Max dose is 20mg TID.

Revision History:

Date	What changed	Pharmacist's initials
2/6/2015	I wrote the criteria.	JJ
3/30/2021	ED drugs are no longer covered by the Plan; the forms used for PAH are covered.	JJ
8/25/2021	Corrected typos/ misdates. No content change	OD

CONFIDENTIAL

Sipuleucel T (Provenge®)

EBRx PA Criteria

FDA-approved for: treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer

Criteria for new users
1. Diagnosis of metastatic prostate adenocarcinoma (not small cell or neuroendocrine prostate cancer).
2. Patient does not have visceral metastasis (e.g. metastasis to sites other than bone, lymph nodes, or other soft tissue. Visceral metastases include, but are not limited to, metastases to organs such as lung, brain, liver, adrenal, or peritoneum).
3. Prostate cancer is castration resistant (disease has progressed while serum testosterone level is <50 ng/dl)
4. Patient exhibits no symptoms or has minimal symptoms due to prostate cancer defined as follows: -No requirement for treatment of cancer-related pain with opioids -Average weekly pain score of 4 or more on a scale of 10
5. Patient has a life expectancy of at least 6 months
6. Current serum testosterone level is less than 50 ng/dl
7. ECOG performance status is 0 or 1 (see table below)
8. Sipuleucel T will not be used in combination with other prostate cancer therapy (exception: androgen deprivation such as goserelin or leuprolide should continue)
9. Patient has been treated with 0 or 1 prior therapies in the castration-resistant metastatic setting.
If all criteria are met, approve for 3 months only. Renewals not allowed, as treatment course is limited to 3 doses only.

Note:

Sipuleucel T was compared to placebo in patients with metastatic castration resistant prostate cancer (mCRPC) who were asymptomatic or minimally symptomatic. Overall survival was longer

in the sipuleucel T group compared to placebo (25.8 mo vs 21.7 mo). Placebo patients were allowed to receive a sipuleucel T-like product after progression, so the overall survival in the placebo group may be overestimated. Placebo patients who did not receive the sipuleucel T-like product after progression of disease had a median overall survival of 12 months.[1]

When patients were broken into groups by PSA level, the effect on overall survival was only significant and even larger in patients with lower PSA levels (see chart below).[2] This indicates that therapy may be more effective when used in earlier lines of therapy when disease burden is lower. NCCN recommends sipuleucel T only in patients with mCRPC in the first or second line setting. EBRx criteria mirror this recommendation.[3]

Baseline PSA (ng/ml)	Median OS (sipuleucel T vs placebo; months)	HR (95% CI)
≤22.1	**41 vs. 28**	**0.51 (0.31-0.85)**
>22.1 – 50.1	27 vs 20	0.74 (0.47-1.17)
>50.1-134.1	20 vs 15	0.81 (0.52-1.24)
>134	18 vs 16	0.84 (0.55-1.29)

Dosing:

Sipuleucel T is administered as 3 IV infusions, given 2 weeks apart. The sipuleucel T product is manufacturered by taking a sample of the patient's antigen presenting cells (via apheresis) and sensitizing them to prostatic acid phosphatase (PAP), which is expressed on prostate tumors. The cells are reinfused into the patient, and they elicit a T cell response against cells expressing PAP. The most common side effects are fever, fatigue, and headache.

References:

1. Kantoff PW et al. Sipuleucel T Immunotherapy for castration-resistant prostate cancer. NEJM 2010; 363:411-422. PMID 20818862

2. Schellhammer PF et al. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the immunotherapy for prostate adenocarcinoma treatment (IMPACT) trial. Urology 2013 Jun;81(6):1297-302. PMID 23582482

3. NCCN Prostate Cancer Guidelines. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 3/17/2020.

ECOG Performance Status

0 – Fully active, able to carry on all pre-disease performance without restriction

1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (light house work, office work)

2 – Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than about 50% of waking hours

3 – Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 – Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

5 - Dead

Quantity Limits: n/a

Revision History:

Date	What changed	Pharmacist's initials
3/17/2020	Discussed at P&T and will cover with medical PA. Criteria written.	SK

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Somatropin (Zorbtive®)

EBRx PA Criteria

is FDA-approved for: Treatment of short-bowel syndrome in patients receiving specialized nutritional support

Criteria for new users
1. The patient must have a diagnosis of short bowel syndrome.
2. The patient must be receiving specialized nutritional support.
If the above criteria are satisfied, the PA is good for 12 months.

Note: **Zorbtive is dosed at 0.1mg/kg up to a max of 8mg daily. Administration beyond 4 weeks of therapy has not been adequately studied and is not recommended.

Revision History:

Date	What changed	Pharmacist's initials
4/22/21	I simplified the criteria; no effective changes.	JJ

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Sorafenib (Nexavar©)

200 mg tablets

EBRx PA Criteria

Is FDA approved for:

- Unresectable hepatocellular carcinoma
- Advanced renal cell carcinoma
- Locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment NOT COVERED Benefit compared with placebo is limited to progression free survival (PFS) only, and the incremental improvement was small at 3 months (median 10.8 mo vs 5.8 mo).
    - Reference: Brose MS et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014 Jul 26;384(9940):319-28. PMID 24768112 NCT00984282

Advanced renal cell carcinoma OR hepatocellular carcinoma
1. Diagnosis of advanced/metastatic clear cell renal cell carcinoma AND previous treatment with at least one prior therapy
2. Diagnosis of advanced, unresectable hepatocellular carcinoma AND Child Pugh Class A (see guide below)
If one of the above criteria is met, approve x 1 year

Notes:

Dose: 400 mg twice daily

Renal Cell Carcinoma:

Sorafenib was compared to placebo in previously-treated patients with advanced renal cell carcinoma. Progression free survival was improved with sorafenib (median 5.5 mo vs 2.8 mo). Crossover from placebo was allowed which may have confounded the overall survival (OS) analysis. A censored overall

survival analysis found an improvement in OS however (median 17.8 mo vs 14.3 mo).[1]

Hepatocellular Carcinoma:

Sorafenib was compared to placebo in patients with advanced HCC, child pugh class A liver function not eligible for surgical or locoregional therapies. Sorafenib improved OS compared with placebo (median 10.7 mo vs 7.9 mo).[2] There is also evidence that sorafenib has QOL benefits.[3]

Reference:

1. Escudier B et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol. 2009 Jul 10;27(20):3312-8. doi: 10.1200/JCO.2008.19.5511. Epub 2009 May 18.
2. Llovet JM et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008 Jul 24;359(4):378-90. PMID 18650514 NCT00105443
3. Bukowski R, Cella D, Gondek K, Escudier B. Effects of sorafenib on symptoms and QOL: Results from a large randomized placebo-controlled study in renal cancer. Am J Clin Oncol. 2007;30:220-227. PMID 17551296

Guidelines:

1. NCCN guidelines for kidney cancer. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf
2. NCCN guidelines for hepatobiliary cancers. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

Quantity Limits: 120 tablets/30 days

Revision History

Date	Notes	Pharmacist's initials
2/22/07	PA criteria were written	JJ
3/11/13	Added HCC as an indication; added references 2-5.	JJ
3/4/14	I reviewed the trial with sorafenib in metastatic thyroid carcinoma (since it received FDA approval).	JJ
12/1/16	I searched for new overall survival data for differentiated thyroid cancer and found no new data, only reference 5 which evaluated	JJ

	overall survival but was confounded by placebo patients switching over to active sorafenib at progression. The mean PFS was 10.8m with sorafenib and 5.8m with placebo (HR 0.59, 95%CI 0.45-0.76;p<0.0001. There was no ASCO Framework on thyroid cancer that I could find. I scored this article using the ESMO Magnitude of Clinical Benefit scale from the Annals of Oncology and it reached a 3 (4 &5 are considered to represent a high level of proven clinical benefit	
6/17/19	Criteria reviewed. Added that patients should have prior therapy before accessing sorafenib for renal cell carcinoma. Added that HCC indication requires that Child Pugh Class be A as done in the study	SK
6/16/2020	Criteria reviewed, no changes	SK

Table A2. Child–Pugh Classification.[16,17] Copyright 1973, copyright British Journal of Surgery Society Ltd. Reproduced with permission. Permission is granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.

	Score*		
Measure	**1 point**	**2 points**	**3 points**
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time, sec (seconds prolonged)	<4	4–6	>6
Encephalopathy grade†	None	1–2	3–4

* Child–Pugh A: 5 or 6 points; Child–Pugh B: 7–9 points; Child–Pugh C: >9 points

† Encephalopathy grades were defined as follows; grade 0: normal consciousness, personality, neurological examination, electroencephalogram; grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps (cycles per second) waves; grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves; grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves; grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2–3 cps (cycles per second) delta activity

Above Child Pugh scoring scheme taken from Supplementary Appendix of Llovet JM et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008 Jul 24;359(4):378-90. PMID 18650514 NCT00105443

Spinosad (Natroba©)

EBRx PA Criteria

FDA-approved for: treatment of Pediculosis capitis (head lice) infestation in adults and children >6 months old.

Criteria for new users
1. The patient must have a diagnosis of head lice infestation.
2. The patient must have had a course of treatment with permethrins in the past 30 days or have resistance to permethrins (confirmed locally).

In clinical studies Natroba Topical Suspension has been shown to be effective in eliminating head lice infestations in most patients with a single treatment. If live lice are seen one week (7 days) after the first application, Natroba Topical Suspension should be used again. A fine-tooth comb may be used to remove dead lice and nits from the hair and scalp, but combing is not required.

2015 AAP AAP Updates Treatments for Head Lice: “in areas where resistance to permethrin or pyrethrins has been demonstrated or for a patient with a documented infestation that has failed to respond to appropriately administered therapy with permethrin or pyrethrins. Spinosad and topical ivermectin are newer preparations that might prove helpful in difficult cases” (1)

Quantity Limits:
quantity limit of 2 fills per 3 months

AWP: March 2021: $2.45 per mL (120 mL, $294 for generic)

References

1. AAP. (2015). Head lice clinical report. Accessed 11/22/19 at https://pediatrics.aappublications.org/content/pediatrics/early/2015/04/21/peds.2015-0746.full.pdf
2. CDC. (2019). Lice treatment. Accessed 11/22/19 at https://www.cdc.gov/parasites/lice/head/treatment.html

3. FDA. (2011) Natroba topical solution. Accessed 11/22/19 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022408lbl.pdf
4. Lexicomp. Spinosad alpha/monograph. Accessed 11/22/19

Revision History:

Date	What changed?	Pharmacist's initials
4/4/11	IB accepted DUEC's rec to place at T2PA	Jj
4/4/11	PA criteria were written	JJ
5/17/12	Revision history added	JJ
11/22/19	Criteria for new user as first line option, AWP added	CS;JJ
8/31/2020	Criteria reviewed. No changes.	JJ
3/9/21	I updated the AWP cost; required the diagnosis of head lice infestation	JJ

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Sunitinib (Sutent®)

12.5, 25, 37.5, 50mg capsules

EBRx PA Criteria

FDA approved for:

- treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate.
- treatment of advanced renal cell carcinoma (RCC).
- adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy NOT COVERED
  - Notes: In patients with stage II-IV resectable renal cell carcinoma, sunitinib or placebo was given x 1 year after resection. Disease free survival was improved (6.8 versus 5.6 years) but overall survival was not improved. Sunitinib also was associated with significant toxicity. NCCN recommends this treatment as a category 3 recommendation. Pazopanib and sorafenib have also been studied in this setting and did not improve outcomes although study populations differed. Use of sunitinib in the adjuvant setting of RCC is not a widespread accepted treatment and is associated with significant toxicity and has not been shown to improve overall survival. Therefore, EBRx will not cover at this time.
  - REFERENCES
    -Ravaud et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. N Engl J Med. 2016;375(23):2246. PMID 27718781.
    -Motzer RJ et al. Adjuvant Sunitinib for High-risk Renal Cell Carcinoma After Nephrectomy: Subgroup Analyses and Updated Overall Survival Results. Eur Urol. 2018 Jan;73(1):62-68.)
- treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease.

GI Stromal Tumor (GIST):
1. The patient been diagnosed with gastrointestinal stromal tumor (GIST)
2. The patient has experienced disease progression on imatinib or is intolerant to imatinib (Gleevec)
If both criteria are met, approve x 1 year
Evidence: -In patients with GIST with disease progression on or intolerance to imatinib, OS was improved compared with placebo in first analysis[1] (medians not reached; HR 0.49, 95% CI 0.29-0.83). Per

study design, pt were allowed to cross over to active treatment after first analysis was complete. In follow-up analysis[2], OS was similar between groups likely due to crossover effect.

-Usual starting dose: 50 mg daily x 4 weeks, then take two weeks off. Alternative dosing: 37.5 mg daily (continuous).

REFERENCES:

1. Demetri GD et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006 Oct 14;368(9544):1329-38. [NCT00075218 PMID 17046465]

2. Demetri GD et al. Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res. 2012 Jun 1;18(11):3170-9. PMID 22661587

Metastatic Renal Cell Carcinoma (RCC)

1. The patient been diagnosed with advanced or metastatic renal cell carcinoma

If above criterion is met, approve x 1 year

Evidence:

-In patients with metastatic RCC, sunitinib improved progression free survival compared to interferon alfa (11 mo vs 5 mo; P<0.001). Overall survival trended toward significance compared to interferon (medians not reached; HR 0.65; 95% CI, 0.45 to 0.94; p=0.02→did not meet prespecified level of significance)[1]. An exploratory analysis that excluded interferon patients who crossed over to sunitinib after progression found a median OS of 26 mo (sunitinib) vs 20 mo (IFN) HR 0.808; 95% CI, 0.661 to 0.987)[2]. Quality of life scores were clinically and statistically better in sunitinib group[1].

REFERENCES:

Motzer RJ et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007 Jan 11;356(2):115-24. [NCT00083889, PMID 17215529

Motzer RJJ et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Clin Oncol. 2009 Aug 1;27(22):3584-90. PMID 19487381

Pancreatic Neuroendocrine Tumor of the Pancreas (PNET)
1. The patient has been diagnosed with unresectable or metastatic pancreatic neuroendocrine tumor
2. The patient has progression of disease
3. The patient does NOT have a poorly differentiated tumor
If above criteria met, approve x 1 year

Evidence:

Sunitinib was compared to placebo in patients with advanced/metastatic/unresectable well-differentiated pancreatic neuroendocrine tumors (PNETs) with progression of disease. Patients could have had prior therapy, but it was not required (observation is appropriate for some patients due to indolent nature of disease). PFS was statistically better with sunitinib vs placebo (11 mo vs 5 mo)[1]. OS trended toward significance but may have been confounded by crossover which was allowed (70% of placebo patients crossed over to sunitinib). An analysis that censored pt who crossed over found a statistically improved OS with sunitinib (median OS 38.6 mo vs 13 mo)[2]. Study was stopped early due to PFS difference and more "serious" adverse events occurring in the placebo group (data published in supplementary material[3]).

REFERENCES:

Raymond E et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011 Feb 10;364(6):501-13. NCT00428597, PMID 21306237

Faivre S et al. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. Ann Oncol. 2017 Feb 1;28(2):339-343. PMID 27836885

Faivre et al appendix/supplement: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1003825/suppl_file/nejmoa1003825_appendix.pdf Accessed 2/15/19

Revision History

Date	Notes	Pharmacist's initials
2/22/07	PA criteria were written	JJ
11/27/12	I removed the criteria that required a mRCC paitent to fail or be intolerant to prior cytokine therapy (interferon alpha, interleukin-2, or both used together), based on a trial that showed a net clinical benefit of sunitinib when compared with interferon. Although sunitinib toxicity days were longer than interferon, PFS was much longer with sunitinib. OS was longer but not stat significantly	JJ

	longer with sunitinib, however, many patients crossed over to sunitinib, most likely masking the margin of OS benefit with sunitinib. QOL was better for sunitinib.	
4/29/13	I rearranged the questions above and added the use of sunitinib in pancreatic neuroendocrine tumors in TKI-naïve patients without sympt brain mets who are ECOG 0-1 at first request.	JJ
7/28, 2014	Added 37.5mg tab to "covered" as a line extension.	JJ
3/18/19	General formatting updates; added references and rationale; added new indication for adjuvant RCC (not covered). PNET: modified criteria slightly: poorly differentiated tumors not covered; removed requirement for "no previous TKI"→no other TKIs are approved for PNET. Removed specification about brain mets.	Sk
9/23/19	All criteria reviewed. -for GIST, changed criteria to statements -change PNET approval period to 1 year for consistency -no change in criteria	SK
12/13/2020	All criteria reviewed. No changes	SK

CONFIDENTIAL

Tadalafil (Adcirca©)

20mg tablets

EBRx PA Criteria

FDA-approved for: the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA functional class II to III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

Criteria for new users (must have ALL the following)
1. Patient must have the diagnosis of Group 1 pulmonary artery hypertension*
2. Must be WHO functional class II or III
3. Patient must be on concurrent ambrisentan (otherwise use sildenafil).
§4. Must have in the medical record a past history of a right heart catheterization which showed all of the following: a. mPAP of ≥25 mmHg b. PVR ≥240 dyne-sec/cm^5 c. PCWP or LVEDP of ≤15 mmHg
§5. Must have in the medical record in the previous 24 weeks both results from pulmonary function tests: a. Total lung capacity (TLC) ≥60% of predicted normal, AND b. Forced expiratory volume in one second (FEV1) ≥55% of predicted normal.
6. Must have in the medical record a walk distance of between 125m and 500meters.

*Group 1 PAH=idiopathic, hereditary, or PAH associated with connective tissue disease, drugs or toxins, HIV, or repaired congenital heart defects.

§From the trial protocol's inclusion criteria which showed the benefit. (Galiè, Nazzareno, et al.)

Criteria for continuation
1. Must have satisfied the above 1-6 items previously.

Notes:

- Tadalafil must be given in combination with ambrisentan for PAH. (Otherwise use sildenafil.)
- Dose is 40mg QD. If taking ritonavir, the dose is 20mg QD.
- PA is good for 1 year.
- Quantity Limits: 2/1

CONFIDENTIAL

References:

1. Shah SJ. Pulmonary Hypertension. JAMA. 2012;308(13):1366-1374.

2. Hopkins W, Rubin LJ. Treatment of pulmonary hypertension in adults. UpToDate. http://www.uptodate.com/contents/treatment-of-pulmonary-hypertension-in-adults?source=search_result&search=pulmonary++hypertension&selectedTitle=2~150. Accessed 2/11/14.

3. Liu C, Chen J, Gao Y, Deng B, Liu K. Endothelin receptor antagonists for pulmonary arterial hypertension. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD004434. DOI: 10.1002/14651858.CD004434.pub5.

4. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369:809-18.

5. Ghofrani H, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med. 2013;369:319-29.

6. Ghofrani H, Galie N, Grimminger F, Grunig E, et al. Riociguat for the treatment of pulmonary arterial hypertension. (PATENT-1). N Engl J Med. 2013;369:330-40.

7. Archer SL. Riociguat for pulmonary hypertension—a glass half full. N Engl J Med. 2013;369(4):386-88.

8. Gabler NB, French B, Strom BL, et al. Validation of 6-minute walk distance as a surrogate end point in pulmonary arterial hypertension trials. Circulation.2012;126:349-356.

9. Savarese G, Paolillo S, et al. Do changes in 6MWD predict clinical events in patients with PAH? A meta-analysis of 22 randomized trials. J Am Coll Cardio. 2012;60(13):1192-1201.

10. ESC and ERS. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal. 2016;37:67-119.

11. Tadalafil. Lexicomp, accessed 4/5/16 for dosing and dosage forms.

12. Galiè, Nazzareno, et al. "Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension."*New England Journal of Medicine* 373.9 (2015): 834-844.

Revision History:

Date	What changed	Pharmacist's initials
4/5/16	I wrote the PA criteria and provided the references.	JJ

CONFIDENTIAL

Teriflunomide (Aubagio®)

14mg tablets (7mg is excluded)

EBRx PA Criteria

FDA-approved for: Treatment of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults.

Criteria for new users
1. The patient must have the diagnosis of a relapsing form of multiple sclerosis.
2. The patient must have experienced at least 2 clinical relapses in the previous 2 years or one relapse during the preceding 1 year.
3. There should be no overlapping days supply with other MS therapy including interferon, natalizumab, glatiramer, mitoxantrone, immunoglobulins, fingolimod, dimethyl fumarate, or diroximel fumarate.
If criteria are true, allow coverage for new users. If patient has teriflunomide approved for coverage in the past, continue access.

Quantity Limits: 31 days supply; 1/1.

References:

1. Zimmermann, Marita, et al. "Disease-modifying therapies for relapsing–remitting and primary progressive multiple sclerosis: a cost-utility analysis." CNS drugs 32.12 (2018): 1145-1157.

Revision History:

Date	Notes	Pharmacist's initials
2/27/13	JJ created the criteria.	JJ
5/5/14	I added the 1/1 QL and the statement about no overlapping days supply with other MS therapy.	JJ
5/20/14	I added the requirement for new users to have tried Rebif as the interferon prior to access to teriflunomide. Reference #4 added.	JJ
8/1/17	I removed the requirement to fail interferon first based on the ICER report that showed a similar point estimate for interferon and teriflunomide in reducing disability progression	JJ
8/31/2020	I updated the criteria. No effective changes.	JJ
8/25/2021	Removed empty note section. No effective changes.	OD

CONFIDENTIAL

Tetrabenazine (Xenazine©)

EBRx PA Criteria

FDA-approved for: **Chorea associated with Huntington disease**

Off-label:

- **Tardive dyskinesia; Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline. Specifically, based on American Academy of Neurology guidelines, tetrabenazine is possibly effective and may be considered in the treatment of patients with tardive dyskinesia. NOT A COVERED USE BECAUSE GINKGO BILOBA IS A LESS COSTLY, EFFECTIVE ALTERNATIVE.**

Criteria for new users
1. The patient must have the diagnosis of Huntington's Disease with choreaform movements.
2. If the dose requested is above 50mg daily, CYP2D6 genotyping must be completed and results provided to call center.
3. The patient must NOT have hepatic impairment. (USE IS CONTRAINDICATED.)
4. The patient must NOT have taken reserpine in the last 20 days or an MAOI in the last 14 days. (CONTRAINDICATED)
5. The patient must NOT co-administer with deutetrabenazine or valbenazine (CONTRAINDICATED)

For the treatment of chorea in HD:

"There is moderate evidence that the drug tetrabenazine (TBZ) can be helpful."(8)

Lack of efficacy in TD:

"4.1 TD symptoms 4.1.1 Not improved to a clinically important extent

We found no significant benefit of tetrabenazine over haloperidol for 'no clinically relevant improvement after 18 weeks' treatment' (1 trial, 13 people; RR 0.93, 95% CI 0.45 to 1.95; Analysis 4.1)"[7]

Quantity Limits: 30 days supply, max 100 mg daily dose, 3000 mg/month

AWP-November 2019: 12.5 mg/$ 15.70-78.81, 25 mg/$ 31.39-157.62

References:

1. Lexicomp. Tetrabenazine pricing and FDA approval. Accessed 11/23/19.

2. Soares-Weiser, Karla, et al. "Miscellaneous treatments for antipsychotic-induced tardive dyskinesia." *Cochrane Database of Systematic Reviews* 3 (2018).

3. Godwin-Austen, R. B., and T. Clark. "Persistent phenothiazine dyskinesia treated with tetrabenazine." *Br Med J* 4.5778 (1971): 25-26.

4. Leung, Jonathan G., and Ericka L. Breden. "Tetrabenazine for the treatment of tardive dyskinesia." *Annals of Pharmacotherapy* 45.4 (2011): 525-531.

5. ICER. Tardive Dyskinesia. 2017. https://icer-review.org/wp-content/uploads/2017/04/NECEPAC_TD_FINAL_REPORT_122217.pdf

6. Zhang WF, Tan YL, et al. Extract of ginkgo biloba treatment for tardive dyskinesia in schizophrenia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2011; 72(5):615-621.

7. El-Sayeh HG et al. (2018) Non-antipsychotic catecholaminergic drugs for antipsychotic-induced tardive dyskinesia. Cochrane Database of Systematic Reviews. Accessed 11/23/19 at https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000458.pub3/full?highlightAbstract=tetrabenazine%7Cwithdrawn%7Ctetrabenazin

8. AAN. (2012). Drug treatments for chorea in Huntington's disease. Accessed 11/23/19 at https://www.aan.com/Guidelines/home/GetGuidelineContent/560

Revision History:

Date	What changed	Pharmacist's initials
2011	I created criteria.	JJ
7/26/2019	I revised the criteria. I also found that Med Impact was not PAing this drug. When I ran a claim on MedAccess, the only rule was "QL of 30ds". I also found a Cochrane Systematic Review that says the ginkgo trial is awaiting confirmation from ongoing trials. Cochrane fell short of recommending tetrabenazine for TD.	JJ
11/23/2019	Additions: contraindication of co-administrations, dose maximums for CYP polymorphisms, AWP; Added supporting notes from chorea guidelines, review results for lack of efficacy in TD	CS/JJ

CONFIDENTIAL

Tezacaftor-ivacaftor (Symdeko©)

100mg TEZ/150mg IVA) tablets plus an additional IVA 150mg

EBRx PA Criteria

Initial approval criteria:
10. The patient must be age 6-12 years old.
11. The patient must have the diagnosis of cystic fibrosis and be homozygous for the F508del mutation or have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that has clinical evidence of benefit with Symdeko.
12. The patient must be currently demonstrating adherence with the evidence-based standard of care for inhaled therapies for cystic fibrosis.[1] (Or else the patient must have documented experience of intolerance to dornase alfa &/OR bronchospasm or irritability with inhaled hypertonic saline and therefore cannot use it.—This must be documented in the medical record and represented to the call pharmacists.)
13. The patient must be a nonsmoker.

*Quantity limit of 62/31 days; normal dose is 150 mg BID

Continuation criteria:
16. The patient must be currently demonstrating adherence with the evidence-based standard of care for inhaled therapies for cystic fibrosis.[1] (or the patient must have experienced intolerance to dornase alfa &/OR bronchospasm or irritability with inhaled hypertonic saline and therefore cannot use it).
17. The patient must have had transaminases (ALT and AST) drawn in the past 6 months and they were lower than 5 times the ULN
18. The patient must be a nonsmoker.
19. The patient must demonstrate a clinical benefit with tezacaftor-ivacaftor as shown by lung function (FEV1), weight gain, or reduction in CF exacerbations or CF hospitalizations.
20. The patient must be adherent (1 fill/1 month) with therapy as determined by refill history or reported by physician.

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References:

1. **Mogayzel PJ, Naureckas ET, Robinson KA, Mueller G, et al. cystic Fibrosis Pulmonary Guidelines: Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013;187(7):680-689.**
2. Ramsey, B et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation. N Engl J Med 2011; 365: 1663-72

Revision History

Date	Notes	Pharmacist
2/25/2019	I wrote the criteria.	JJ
12/16/19	I updated the format and limited Symdeko coverage to only ages 6-12y because Trikafta is recommended and superior in homozygotes older than 12.	JJ

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Tobramycin Inhaled (TOBI®)

EBRx PA Criteria

The patient must have a diagnosis of cystic fibrosis.
If the request is for diagnosis outside of cystic fibrosis, a manual review will be required. Physician should include literature to support use in diagnosis outside of CF.
NOTE: There is a QL of 28 days per 56 days consistent with the FDA indication of 28 days ON then 28 days OFF.

References:

1. Flume PA, et al. Cystic Fibrosis Pulmonary Guidelines Chronic Medications for Maintenance of Lung Health. *Am J Respir Crit Care Med*. 2007;176. pp 957–969.

2. Lexi-Comp, FDA-approved dosing. Accessed 11/16/17.

Revision history:

Date	Notes	Pharmacist's initials
5/16/12	I added references and revision history. DUEC has not ever addressed the topic since Jan 2004. The criteria are supported by the current (2007) CF guidelines.	JJ
11/16/17	I added a note for QL of 28 days ON, then 28 days OFF. GBB is communicating with MI to program the QL restriction.	JJ

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Trametinib (Mekinist®)

0.5mg, 2mg tablets

EBRx PA Criteria

FDA approved for the following:

As monotherapy:

- treatment of BRAF-inhibitor treatment-naïve patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. NOT COVERED
  - EBRx prefers combination therapy over monotherapy. Trametinib monotherapy did improve overall survival compared with chemotherapy. However, monotherapy with trametinib appears inferior to BRAF inhibitor monotherapy and BRAF/MEK inhibitor combination therapy.
  - Reference: Robert C et al. Five-year outcomes from a phase 3 METRIC study in patients with BRAF V600 E/K-mutant advanced or metastatic melanoma. Eur J Cancer 2019 Mar;109:61-69. PMID 30690294, NCT01245062

In combination with dabrafenib:

- treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. Covered in first line setting only
- adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection. Covered
- treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test. NOT COVERED: data limited to single arm trial only; no comparative data at this time (other option: platinum-based chemotherapy +/- pembrolizumab)

  -Reference: Planchard D et al. Lancet Oncol 2017; 18:1307-1316. PMID 28919011
- treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options NOT COVERED: no comparative data at this time (other option: chemotherapy)

  -Reference: Subbiah V et al. J Clin Oncol 2018; 36(1):713. PMID 29072975

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Advanced/Metastatic melanoma: criteria for new users	
	1. Patient must have histologically confirmed unresectable or metastatic cutaneous melanoma
	2. Patient must be BRAF V600E or BRAF V600K mutation
	3. Patient must be ECOG 0 or 1.
	4. The patient must not have received previous systemic therapy for advanced/metastatic melanoma.
	5. Trametinib must be used in combination with dabrafenib (Tafinlar)
	If above criteria fulfilled, approve for 6 months
	Quantity Limits: 2 mg: #30/30 days
	Note: Treatment continues until progression or unacceptable toxicity.
	Starting doses: Dabrafenib 150 mg PO bid Trametinib 2 mg PO daily **Evidence:** Dabrafenib+trametinib was superior to dabrafenib monotherapy and vemurafenib monotherapy in the Combi-d and Combi-v studies, respectively. Overall survival for combination therapy was 25 mo versus 17-18 months in the monotherapy arms[1,2]. References: 3. Long GV et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol. 2017 Jul 1;28(7):1631-1639. PMID 28475671 NCT01584648 4. Robert C et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015 Jan 1;372(1):30-9. PMID 2539951 NCT01597908

Adjuvant treatment of melanoma: criteria for new users
1. Patient must have stage III cutaneous melanoma
2. Patient must have undergone complete resection of melanoma
3. Patient must be BRAF V600E or BRAF V600K mutation

4. Patient must be ECOG 0 or 1.
5. Trametinib must be used in combination with dabrafenib (monotherapy has not been studied in the adjuvant setting)
If above criteria fulfilled, approve for 12 months. *Adjuvant therapy for melanoma should not exceed 12 months.*
Quantity limits: 2 mg capsules: #30/30 days
Starting doses: Dabrafenib 150 mg PO bid Trametinib 2 mg PO daily **Evidence:** The combination of dabrafenib+trametinib improved relapse-free survival compared with placebo in patients with resected stage III melanoma. Four-year relapse free survival was 54% (dab/tram) vs 38% (placebo). An interim analysis of overall survival showed an improvement with combination therapy (3-year OS of 86% versus 77% in the placebo group (HR, 0.57; 95% CI, 0.42 to 0.79; *P* = .0006), but this improvement did not cross the prespecified interim analysis significance threshold of *P* = 0.000019. References: 4. Long GV et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. 2017;377(19):1813. PMID 28891408 NCT01682083 5. Hauschild A et al. Longer Follow-Up Confirms Relapse-Free Survival Benefit With Adjuvant Dabrafenib Plus Trametinib in Patients With Resected BRAF V600-Mutant Stage III Melanoma. J Clin Oncol. 2018 Oct 22:JCO1801219. [Epub ahead of print] PMID 30343620 NCT01682083

Revision history:

Date	Notes	Pharmacist's initials
9/17/13	Criteria written	JJ
4/2014	We began covering dabrafenib monotherapy (after DCWG) with a PA. The criteria: dx of metastatic melanoma, V600 BRAF mutation, no previous vemurafenib, trametinib, or ipilimumab (may have had IL-2). QL is 14 ds.	JJ

1/15/15	I changed the criteria to include combination trametinib + dabrafenib since new OS data are published. Dabrafenib monotherapy is still not covered. This was discussed at DCWG	JJ
4/22/19	Criteria reviewed. For melanoma, dabrafenib is only covered in combination with trametinib. New indications added: adjuvant treatment of melanoma (covered), NSCLC (not covered), anaplastic thyroid cancer (not covered)	Sk
9/26/19	Criteria reviewed. Updated monotherapy indication as wording was slightly changed. No change in any criteria. Corrected QL for adjuvant indication. Added references for indications not covered.	SK
11/16/20	Criteria reviewed. No changes.	SK

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Treprostinil (Tyvaso®)

Solution for Inhalation

0.6mg/mL (2.9mL)

EBRx PA Criteria

Tyvaso for inhalation has the same ingredient as Remodulin for injection (covered by the medical benefit without a PA). Orenitram is also treprostinil oral XR tablet 0.125, 0.25, 1mg, 2.5mg, and 5mg and is excluded from our plans.

Tyvaso is FDA-approved for: treatment of PAH (WHO Group I) in patients with NYHA class III symptoms to improve exercise ability. Nearly all controlled clinical trial experience has been with concomitant bosentan or sildenafil.

Criteria
1. The patient must have the diagnosis of pulmonary artery hypertension (Group 1), WHO functional class III AND either still symptomatic despite taking a PDE5 inhibitor (sildenafil, tadalafil, etc.) or endothelin receptor antagonist (ambrisentan, bosentan, macitentan)
OR
2. The patient must have the diagnosis of PAH Group 5 after treating underlying causes.
If both of the above are satisfied, approve for 12 months.

Dosing is 18mcg (3 inhalations) every 4 hours 4 times/day.

Diagnostic Criteria and WHO categorization of PH						
	All Groups	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 5**
Description	**Elevated PAP**	**Pulmonary arterial hypertension**	**Pulmonary venous hypertension**	**PH due to hypoxemia**	**Chronic thromboembolic PH**	**Miscellaneous or multifactorial PH**
Estimated prevalence	**Up to 10-20% of the general population**	**15 cases/1,000,000 overall; 6 cases per 1mil for idiopathic PAH**	**>3-4 mil in US**	**20% in COPD pts w/ a prior hospitalization for COPD**	**0.5-2% (up to 3.8%) in survivors of acute PE**	**Unclear**

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Diagnostic criteria						
Mean PA pressure, mmHg	**≥25**	**≥25**	**≥25**	**≥25**	**≥25**	**≥25**
PCWP or LVEDP, mmHg		**≤15**	**>15**	**≤15**	**≤15**	**≤15**
PVR, dynes/s/cm		**>240**		>240	>240	>240

References:

1. Lexicomp. Treprostinil, inhaled. Accessed 8/31/2020.

2. Klinger, James R., et al. "Therapy for pulmonary arterial hypertension in adults: update of the CHEST guideline and expert panel report." *Chest* 155.3 (2019): 565-586.

Revision History:

Date	What changed	Pharmacist's initials
2/6/15	I wrote the criteria.	JJ
8/31/2020	I updated the criteria to include NYHA Class III symptoms and added ERAs for concomitant use.	JJ

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Trientine (Syprine®, Clovique©)

available in GENERIC

250mg capsules

EBRx PA Criteria

FDA-approved for: treatment of Wilson's disease in patients who are intolerant of penicillamine.

Criteria:
1. Must have the diagnosis of Wilson's Disease intolerant to penicillamine.
2. Must be symptomatic with either clinical hepatic symptoms or neurologic symptoms; If not symptomatic, profile must include zinc 150mg/day administered in 2-3 divided doses.
3. Must ingest a low copper diet (AVOID: lamb; pork; pheasant quail; duck; goose; squid; salmon; organ meats including liver, heart, kidney, brain; shellfish including oysters, scallops, shrimp, lobster, clams, and crab; meat gelatin; soy protein meat substitutes; tofu; nuts and seeds, vegetable juice cocktail, mushrooms, nectarine, commercially dried fruits including raisins, dates, prunes; avocado, dried beans including soy beans, lima beans, baked beans, garbanzo beans, pinto beans; dried peas; lentils; millet; barley; wheat germ; bran breads and cereals; cereals with >0.2 mg of copper per serving (check label); soy flour; soy grits; fresh sweet potatoes, chocolate milk, soy milk, cocoa, desserts that contain high amounts of ingredients rich in copper; candy with nuts, chocolate, or cocoa, instant breakfast beverages, mineral water, soy-based beverages, copper-fortified formulas, brewer's yeast, multiple vitamins with copper or minerals)

Quantity Limit: 8 tabs/day (2g max/day)

Revision History:

Date	What changed	Pharmacist's initials
10/2/15	I wrote the criteria.	JJ
8/31/2020	I reviewed the criteria. It is still listed as alternative to penicillamine in the latest review article. No trials.	JJ

References:

1. Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: An update. Hepatology. 2008;47(6): 2089-2111.

2. Dietary Special Considerations. http://gicare.com/diets/copper-restriction/

(accessed 10/2/15).

4. Weiss KH, Stremmel W. Clinical considerations for an effective medical therapy in Wilson's disease. Annals of the New York Academy of Sciences. 2014;1315:81-85. (Review Article)

5. Brewer GJ, Askari F, et al. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. Arch Neurol. 2006. 63(4):521-7.

6. Aggarwal, Annu, and Mohit Bhatt. "Advances in treatment of Wilson disease." Tremor and Other Hyperkinetic Movements 8 (2018).

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EBRx Triptan Quantity Limit Override Criteria

Quantity Limits

Agent	Strength	Quantity Limit
Amerge	1mg, 2.5mg tabs	9/31 days
Axert	6.25mg, 12.5mg tabs	6/31 days
Frova	2.5mg tabs	9/31 days
Imitrex SQ Inj	4mg, 6mg Kit 6mg Vial	2 kits/31 days 5 vials/31 days
Imitrex NS	5mg 20mg	12/31 days 6/31 days
Imitrex PO	25mg, 50mg, 100mg tabs	9/31 days
Maxalt	5mg,10mg tabs 5mg, 10mg MLT	12/31 days
Relpax	20mg, 40mg tabs	6/31 days
Sumavel DosePro SQ Inj	6mg	6 units/31 days
Treximet	85/500 mg tabs	9/31days
Zomig	2.5mg tabs & 2.5mg ZMT 5mg tabs & 5mg ZMT	6/31 days 3/31 days
Zomig NS	5mg/100µL	6 units/31 days

Revision History

Since inception	**RP statins to sumatriptan. No RP applied to rizatriptan**	**Per DD**
7/14/2020	**I removed the PA from this form on the server; left the QLs. Current strategy is to RP triptans to generic sumatriptan. The RP does not apply to rizatriptan (per the DERP reports out of Oregon). Per ICER, eletriptan performed best in a network meta-analysis for the endpoints 2 hour pain relief and 24 hour sustained pain relief. Will discuss 7/27/2020 at EBRx P&T to remove RP from eletriptan.**	**JJ**

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References

1. SD Silberstein, J Olesen, *et al***.** The International Classification of Headache Disorders, 2nd Edition (ICHD-II)—revision of criteria for 8.2 *Medication-overuse headache. Chephalalgia.* 2005; 25:460–465.

2. American Academy of Neurology. AAN guideline summary for clinicians. Migraine headache. http://www.aan.com/professionals/practice/guidelines/migraine/clinician_summary_migraine.pdf. Accessed March 13, 2010.

3. Goadsby PJ, Lipton RB, *et al*. Migraine: Current understanding and treatment. *N Engl J Med*. 2002; 346:257-270.

4. Menken M, Munsat TL, Toole JF. The global burden of disease study—implications for neurology. *Arch Neurol* 2000; 57**:** 418–20.

CONFIDENTIAL

Tucatinib (Tukysa®)

50 and 150 mg tablets

EBRx PA Criteria

FDA-approved for:

Treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting [in combination with trastuzumab and capecitabine]

Criteria for new users
1. Diagnosis of metastatic breast cancer
2. Tumor is HER2 positive
3. Patient has previously been treated with trastuzumab (Herceptin or biosimilar), pertuzumab (Perjeta), and ado-trastuzumab (Kadcyla)
4. No prior lapatinib (Tykerb)
5. Tucatinib will be used in combination with trastuzumab (Herceptin or biosimilar) and capecitabine (Xeloda)
If all criteria met, approve for 12 months.

Note:

Tucatinib/trastuzumab/capecitabine was compared to placebo/trastuzumab/capecitabine. The tucatinib group showed a significant improvement in overall survival compared with the placebo group (median OS 21.9 mo vs 17.4 mo). This study included patients with untreated brain metastasis if stable and benefit was maintained in this subgroup. Will not allow prior treatment with lapatinib as efficacy of tucatinib is not well established in patients who have received prior lapatinib.

References:

Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer [published correction appears in N Engl J Med. 2020 Feb 6;382(6):586]. N Engl J Med. 2020;382(7):597- 609. doi:10.1056/NEJMoa1914609 PMID 31825569 NCT02614794

NCCN Guidelines for Breast Cancer. www.nccn.org/profressional/physician_gls/pdf/breast.pdf

Revision History:

Date	What changed	Pharmacist's initials
5/27/20	Reviewed at 5/27/2020 EBRx P&T meeting. Criteria written	SK
8/25/2021	Removed empty quantity limit space. No effective changes.	OD

CONFIDENTIAL

Uridine triacetate (Xuriden©, Vistogard©)

Xuriden 2g oral granules packets, Vistogard 10g oral granules packets

EBRx PA Criteria

Xuriden is FDA-approved for: treatment of patients with hereditary orotic aciduria (HOA).

Vistogard is FDA-approved for: emergency treatment of adult and pediatric patients following a fluorouracil or capecitabine overdose regardless of the presence of symptoms OR who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration

Xuriden Criteria for new users
1. The patient must have a validated diagnosis of hereditary orotic aciduria (validated by the EBRx Medical Director) • Confirmed by the presence of a mutation in the uridine monophosphate synthase gene • Elevated urinary orotic acid level according to age-specific reference range
2. Uridine is being prescribed by or given in consultation with a specialist in inherited metabolic diseases.
Max dose is 120mg/kg (maximum 8 GRAMS once daily)**********PA is good for 3 months.
Continuation Criteria
1. At three months, the patient must show an improvement in baseline hematologic abnormality AND urinary excretion of orotic acid OR a decrease in nephrolithiasis. If this is shown, the patient can have the PA approved for one year renewable the next year if he/she maintains response.

Vistogard Criteria for new users
1. The patient must have received an overdose of 5-fluorouracil or capecitabine OR is showing early-onset, severe, or life-threatening toxicity due to 5-fluorouracil or capecitabine.
2. Vistogard must be started within 96 hours following the end of 5-fluorouracil or capecitabine administration.
If all criteria are met, approve PA for 20 doses TOTAL taking into account any doses given inpatient. Dose is 10g PO q6h for 20 doses TOTAL. Therapy is expected to be initiated in the inpatient setting. Quantity Limits: 20 doses total including doses given as inpatient.

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Vistogard should not be administered for non-emergent toxicities as it may interfere with the efficacy of fluoropyrimidine treatment.

Note: Vistogard is supplied as follows:

-NDC 69468-151-20 (course of therapy package): 1 carton containing 20 single-dose packets of uridine triacetate

-NDC 69468-151-04 (24-hour pack): 1 carton containing 4 single-dose packets of uridine triacetate

Revision History:

Date	What changed	Pharmacist's initials
9/19/16	I wrote the criteria.	JJ
12/14/16	I added to the criteria the coverage criteria for Xuriden for HOA including continuation criteria.	JJ
9/23/19	All criteria reviewed. Vistogard: reworded criteria to cover if fluoropyrimidine overdose OR if pt is showing early-onset, severe or life-threatening toxicity. Added that Vistogard should start within 96 hours of fluoropyrimidine discontinuation. Xuriden: changed initial approval period to 3 months	SK
12/15/20	Criteria reviewed. No change.	SK
4/1/21	Clarified requirements for accurate diagnosis.	JJ
8/25/2021	Noticed criteria were updated only in UAS folder. Copied updates to EBRx criteria folder. No effective changes.	OD

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Ustekinumab (Stelara®)

PA Criteria

45 mg/0.5mL (0.5mL), 90mg/mL (1mL)

FDA approved indications:

1. Treatment of adults with moderate-to-severe **plaque psoriasis** who are candidates for phototherapy or systemic therapy.
2. Treatment of adults with active **psoriatic arthritis** (as monotherapy or in combination with methotrexate).
3. Treatment of mod-sev active Crohn's disease in adults who failed or were intolerant to immunomodulatory or corticosteroids, but never failed TNF blocker therapy or who have failed or were intolerant to treatment w/ one or more TNF blockers.

Plaque psoriasis	
Initial request	
1. Does the patient have a diagnosis of moderate-to-severe plaque psoriasis, as indicated by a PASI score of at ≥12 (scale is 0-72) and involvement of at least 10% BSA?	☐ Yes ☐ No If yes, go on to next question. If no, stop and deny coverage.
2. Has the patient had an inadequate response despite 3 months of methotrexate 25mg per week? **OR** Has the patient experience intolerance to methotrexate? **OR** Does the patient have a contraindication to methotrexate?	☐ Yes ☐ No If yes, go on to next question. If no, stop and deny coverage.
3. Has the patient had an inadequate response despite at least 3 months of treatment with at least 1 other conventional systemic agents for psoriasis (cyclosporine, or psoralen plus ultraviolet A)? **OR** Is the patient intolerant to or have a contraindication to at least 1 of those treatments?	☐ Yes ☐ No
4. The patient must have tried and failed Humira (for a minimum of 12 weeks) AND must have tried and failed Enbrel (for a minimum of 12 weeks) prior seeking ustekinumab.	
If the answer to 1, 2, AND 3 is yes, approve coverage for 28 weeks (4 doses).	
Responders maintenance therapy	

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Did the patient achieve a reduction in PASI of <u>at least</u> 50%?	□ Yes □ No
If the answer was yes, patient is approved for therapy for 1 year (4 doses).	

References:

1. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371:1665-74.

2. Lin VW, Ringold S, Devine EB. Comparison of ustekinumab with other biological agents for the treatment of moderate to severe plaque psoriasis, A Bayesian Network Meta-analysis. Arch Dermatol. Oct 2012; E1-E8.

3. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675-84.

4. Griffiths CE, Strober BE, Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010;362:118-28.

Note: Dosing is weight based. For those weighing <100 kg, each dose is 45 mg. For those weighing >100 kg, each dose is 90 mg. Drug is dosed at weeks 0 and 4, and then every 12 weeks thereafter.

Psoriatic arthritis	
1. Does the patient have a diagnosis of active psoriatic arthritis, as defined by ≥5 swollen and ≥5 tender joints and a C-reactive protein of ≥3.0mg/L?	□ Yes □ No If yes, go on to next question. If no, stop and deny coverage.
2. Has the patient had an inadequate response to ≥3 months of disease-modifying antirheumatic drug (DMARD) therapy **<u>OR</u>** ≥4 weeks of NSAID therapy **<u>OR</u>** ≥ 8 (etanercept, adalimumab, golimumad, certolizumab-pegol) or 14 (infliximab) continuous weeks of TNF-antagonist therapy? **<u>OR</u>** Was the patient intolerant of anti-TNF therapies?	□ Yes □ No
3. The patient must have tried and failed Humira (for a minimum of 12 weeks) AND must have tried and failed Enbrel (for a minimum of 12 weeks) prior seeking ustekinumab.	
If the answer to 1 and 2 is yes, approve coverage for 1 year (6 doses).	

References:

1. McInnes IB, Kavanaugh A, Gottlieb AB, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicenter, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet 2013;382:780-89.

2. Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumor necrosis factor therapy: 6-month and 1-year results of the phase 3, multicenter, double-blind, placebo-controlled, randomized PSUMMIT 2 trial. Ann Rheum Dis 2014;73:990-999.

Note: Dose for psoriatic arthritis is 45 mg. Drug is dosed at weeks 0 and 4, then every 12 weeks thereafter.

Crohns Disease
1. The patient must have the diagnosis of Crohns disease.
2. The patient must have a Crohn's Disease Activity Index of 220-450 (out of 600).
3. The patient must have tried and failed Humira (for a minimum of 12 weeks) prior seeking ustekinumab.
If the patient satisfies the criteria above, PA is approved for 1 year.
References: 1. Feagan, Brian G., et al. "Ustekinumab as induction and maintenance therapy for Crohn's disease." *New England Journal of Medicine* 375.20 (2016): 1946-1960.

PASI	Psoriasis Area Severity Index. Used to express the severity of psoriasis based on a combination of erythema, induration, and desquamation over the percentage of affected body area. Scale ranges from 0 (no disease) to 72 (maximal disease).

Date	What changed	PharmD Initials
11.7.14	PA criteria written	GBB
3/3/17	I added the Crohn's indication and reference.	JJ
3/7/17	Corrected criteria to require failure of humira AND Enbrel for PPso and PsArth, but only Humira for Crohns	JJ

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Vedolizumab (Entyvio®)

300mg (1ea) solution for IV push or bolus
EBRx PA Criteria

Crohn's Disease	
Initial request to identify responders.	
1. Does the patient have a diagnosis of Crohn's Disease?	□ Yes □ No
2. Has the patient failed treatment with, or is dependent on corticosteroids, as defined by the following: a. Signs and symptoms of persistent, active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily, PO for two weeks or IV for 1 week ***OR*** b. 2 failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily PO on 2 separate occasions ***OR*** c. History of intolerance of corticosteroids (including, but not limited to: Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, or infection)	□ Yes □ No
3. Was the patient unresponsive or intolerant to immunosuppressive therapy, as defined by the following: a. Signs and symptoms of persistent, active disease despite a history of ≥1 8-week regimen of oral azathioprine (≥1.5mg/kg) or mercaptopurine (≥0.75mg/kg) ***OR*** b. Signs and symptoms of persistent, active disease despite a history of ≥1 8-week regimen of methotrexate (≥12.5mg/kg/wk) ***OR*** c. History of intolerance of ≥1 immunosuppressive (including, but not limited to: Nausea, vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, thiopurine methyltransferase genetic mutation, or infection)	□ Yes □ No
4. Was the patient unresponsive or intolerant to treatment with a TNF antagonist, as defined by the following: a. Signs and symptoms of persistent, active disease despite a history of ≥1 4-week induction regimen of 1 of the following: - Infliximab: 5mg/kg IV, 2 doses at least 2 weeks apart - Adalimumab: 1 80mg SC dose followed by 1 40mg dose ≥2 weeks apart	□ Yes □ No

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- Certolizumab pegol: 400mg SC, 2 doses ≥2 weeks apart ***OR*** b. Recurrence of symptoms during scheduled maintenance dosing after prior clinical benefit (discontinue despite clinical benefit does not qualify) ***OR*** c. History of intolerance of at least 1 TNF antagonist (including, but not limited to: infection-related reaction, demyelination, CHF, or infection)	
If the answers to 1, 2, and either 3 OR 4 are yes, patient is approved for 14 weeks (4 doses).	
Responders Maintenance Therapy	
Did the patient respond to and was successful on therapy?	□ Yes □ No
If the answer was yes, patient is approved for therapy for 1 year (7 doses).	
References: 1. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 369;8. Aug 22, 2013. Accessed July 17, 2014. 2. Sands BE, Feagan BG, et al. Effects of vedolizumab induction therapy for patients with CD in whom TNF treatment failed. (GEMINI3) Gastroenterology. 2014;147:618-27.	

Ulcerative Colitis	
Initial request to identify responders.	
1. Does the patient have a diagnosis of Ulcerative Colitis?	□ Yes □ No
2. Has the patient failed treatment with, or is dependent on corticosteroids, as defined by the following: a. Signs and symptoms of persistent, active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily, PO for two weeks or IV for 1 week ***OR*** b. 2 failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily PO on 2 separate occasions ***OR*** c. History of intolerance of corticosteroids (including, but not limited to: Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, or infection)	□ Yes □ No
3. Was the patient unresponsive or intolerant to immunosuppressive	□ Yes □ No

therapy, as defined by the following: a. Signs and symptoms of persistent, active disease despite a history of ≥1 8-week regimen of oral azathioprine (≥1.5mg/kg) or mercaptopurine (≥0.75mg/kg) ***OR*** b. History of intolerance of ≥1 immunosuppressive (including, but not limited to: Nausea, vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, thiopurine methyltransferase genetic mutation, or infection)	
4. Was the patient unresponsive or intolerant to treatment with a TNF antagonist, as defined by the following: a. Recurrence of symptoms during scheduled maintenance dosing after prior clinical benefit (discontinue despite clinical benefit does not qualify) ***OR*** b. History of intolerance of at least 1 TNF antagonist (including, but not limited to: infection-related reaction, demyelination, CHF, or infection)	□ Yes □ No
If the answers to 1, 2, and either 3 OR 4 are yes, patient is approved for 14 weeks (4 doses).	
Responders Maintenance Therapy	
Did the patient respond to, and was successful on therapy?	□ Yes □ No
If the answer was yes, patient is approved for therapy for 1 year (7 doses).	
References: Feagan BG, Rutgeerts P, Sands BE, Hanauer S, et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med 369;8 699-710. Aug 22, 2013. Accessed July 18, 2014.	

Revision History		
Date	**What happened**	**Pharmacist**
7/22/14	Created criteria	GBB
10/30/14	A 2nd reference was added regarding CD. NO changes in PA criteria	JJ

Vemurafenib (Zelboraf®)

240mg tabs

EBRx PA Criteria

FDA-approved for:

- treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Covered in combination with cobimetinib in first line treatment setting
- treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation NOT COVERED: data is limited to single arm trial only

  References:

  1. Diamond EL et al. Vemurafenib for BRAF V600-Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study. JAMA Oncol. 2018 Mar 1;4(3):384-388. PMID 29188284
  2. Diamond EL et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. Blood. 2014 Jul 24;124(4):483-92. doi: 10.1182/blood-2014-03-561381. Epub 2014 May 21. PMID 24850756

The following indication is not included in the vemurafenib package insert but is FDA approved per the atezolizumab (Tecentriq) package insert:

- **Melanoma**
  - in combination with atezolizumb and cobimetinib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma NOT COVERED
    - Benefit of this combination is limited to progression free survival. Overall survival nor quality of life have been shown to be improved at this time.
    - Reference: Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;395(10240):1835-1844. doi:10.1016/S0140-6736(20)30934-X PMID 32534646

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Melanoma: Criteria for new users
1. The patient must have the diagnosis of histologically confirmed unresectable or metastatic melanoma.
2. The patient must have a BRAF V600 mutation
3. The patient must be ECOG 0-1 at first request.
4. Must receive vemurafenib concurrently with cobimetinib.
5. This combination therapy must be first line. No previous treatment for melanoma is allowed prior to access to cobimetinib/vemurafenib.
If the patient meets all criteria above, PA is good for 6 months.
Quantity Limits: #224/28 days

Evidence:

Cobimetinib + vemurafenib versus placebo + vemurafenib was studied in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. Overall survival was improved in the cobimetinib+vemurafenib group with median overall survival improvement of 4.9 months (22.3 mo versus 17.4 mo). Response rate and PFS were also improved. Quality of life analysis showed similar scores between groups.[1,2]

Note:

-Vemurafenib is also FDA approved as monotherapy for treatment of advanced/metastatic melanoma and is superior to chemotherapy[3]. However, combination therapy (vemurafenib+cobimetinib) is preferred due to superiority data over monotherapy.

-Doses: Cobimetinib 60mg PO daily days 1-21 out of each 28-day cycle; vemurafenib 960mg PO BID. The combination is continued until progression of disease or unacceptable toxicity.

References:

1. Larkin J, Ascerto P, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014;371(20):1867-76. NCT01689519 PMID 25265494
2. Ascierto PA et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016 Sep;17(9):1248-60. NCT01689519 PMID 27480103
3. Chapman PB, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011.

Revision History:

Date	Notes	Pharmacist's initials
10/11/11	IB approved DUECs rec for T3PA, QL of 15 ds for 1/2 T3 copay, then 1/2 T3 copay for second 15ds.	JJ
4/22/19	Criteria reviewed. Vemurafenib combination therapy preferred over monotherapy. Added new indication of Erdheim-Chester disease (not covered). Updated references and data summary.	SK
4/23/19	Added references 4 & 5.	JJ
9/26/19	Criteria reviewed. Made some formatting changes but no change to criteria.	SK
8/7/2020	New indication reviewed (atezo+cobi+vemurafenib for melanoma). Do not cover.	SK

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Venetoclax (Venclexta®)

10mg, 50mg, 100mg Tablets

EBRx PA Criteria

FDA approved indications:

- **Chronic lymphocytic leukemia/small lymphocytic lymphoma:** Treatment of adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
  - Coverage is restricted to patients who have received at least 1 prior therapy.
  - For first line therapy, venetoclax is FDA-approved for use in combination with obinutuzumab based on data showing improved progression free survival (PFS) compared with obinutuzumab+chlorambucil (24-month rate of PFS 88% vs 64%). No overall survival data have been reported yet. Quality of life was not improved to a greater extent than the control group. See ibrutinib (Imbruvica) which does have overall survival data reported in the first-line setting.

    References:

    - Fischer K et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med. 2019 Jun 6;380(23):2225-2236. doi: 10.1056/NEJMoa1815281. Epub 2019 Jun 4. PMID 31166681 NCT02242942
    - Al-Sawaf O et al. Rapid Improvement of Patient-Reported Outcomes with Venetoclax Plus Obinutuzumab in Patients with Previously Untreated CLL and Coexisting Conditions: A Prospective Analysis from the CLL14 Trial. https://ash.confex.com/ash/2019/webprogram/Paper126542.html. Accessed 1/21/2020.
- **Acute myeloid leukemia:** in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed AML in patients who are age 75 years or older, or who have comorbities that preclude use of intensive induction chemotherapy.
  - This was an accelerated approval based on response rates only. See data below for justification of coverage. ***EBRX prefers use in combination with azaciditine or decitabine only (not low dose cytarabine).***
  - Venetoclax was granted full approval for AML indication as of 10/2020
  - ***The phase III VIALE-C (NCT03069352) showed no significant difference in overall survival with venetoclax/cytarabine as compared to placebo/cytarabine.*** https://www.targetedonc.com/news/venetoclax-plus-lowdose-cytarabine-fails-to-improve-os-in-aml.
  - Preliminary data released for azacitidine/venetoclax vs azacitidine/placebo indicates an improvement in overall survival (https://news.abbvie.com/news/press-releases/abbvie-announces-positive-topline-results-from-phase-3-trial-venclexta-venetoclax-in-combination-with-azacitidine-in-patients-with-acute-myeloid-leukemia-aml.htm?view_id=3438).
    - Full study published: DiNardo CD et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020 Aug 13;383(7):617-629. doi: 10.1056/NEJMoa2012971. PMID: 32786187.

Chronic lymphocytic leukemia (CLL) and Small lymphocytic leukemia (SLL)
9. Diagnosis of relapsed or refractory CLL or SLL
10. Must have received ≥ 1 prior therapy
11. Performance status (ECOG) 0-1 at initial request
12. Must plan to give rituximab concurrently after venetoclax ramp up period
If all of the above criteria are met, approve for 12 months; QL 120/30. May approve ONE renewal request if there is no evidence of disease progression. The maximum duration of therapy is two years from the first dose of rituximab.
Additional Notes
Per FDA labeling, use venetoclax until disease progression or up to **24 months** from day 1 cycle 1 of rituximab

Evidence:

Venetoclax + rituximab (VR) was compared to bendamustine+rituximab (BR) in patients with relapsed or refractory CLL who had received 1-3 prior therapies. Overall survival was improved in the venetoclax+rituximab group (HR 0.5 95% CI 0.30-0.85). At 3 years, the rate of overall survival was 87.9% versus 79.5% (VR vs BR). Event-free survival (no disease progression, death, or initiation of new treatment for CLL) was 85% vs 35%. Grade 3/4 toxicity was slightly higher in VR group (82% vs 70%) and was driven mostly by a higher rate of neutropenia. However, rates of infection and febrile neutropenia were lower in VR group.

Other:

- If high risk for tumor lysis syndrome, venetoclax will be initiated INPATIENT so patient can be closely monitored and given IV hydration
- Concomitant use of strong CYP3A4 inhibitors during initiation and start-up phase is contraindicated
    - If a strong 3A4 inhibitor needs to be start during the steady daily dosing phase, the dose of venetoclax should be reduced by at least 75%
    - Moderate → reduce venetoclax by at least 50%

Dosing: PO

- Week 1: 20mg QD
- Week 2: 50mg QD
- Week 3: 100mg QD
- Week 4: 200mg QD
- Week 5 and thereafter: 400mg QD
- Continue until disease progression or unacceptable toxicity for up to 24 months from day 1 cycle 1 of rituximab; begin rituximab after receiving venetoclax at the 400mg QD dose for 7 days
- Dose Modifications for toxicity

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	Dose Modification for Toxicity	
	Dose @ interruption (mg)	**Restart dose (mg)**
	400	300
	300	200
	200	100
	100	50
	50	20
	20	10

References:

1. Seymour, John F., et al. "Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia." *NEJM* 378.12 (2018): 1107-1120. PMID 29562156 NCT02005471
2. Package insert: venetoclax. Accessed 12/21/2018.

Acute myeloid leukemia
1. Diagnosis of acute myeloid leukemia
2. Ineligible for standard/intense induction chemotherapy because of presence of one of the following: age >75 years, cardiac disease or prior anthracycline use, secondary AML, high probability of treatment-related mortality
3. No prior treatment for AML (exception: patient may have received leukapheresis or hydroxyurea)
4. Venetoclax will be used in combination with either azacitidine or decitabine
If all of the above criteria are met, approve for 6 months; QL 120/30
Additional Notes
• NCCN also recommends Venetoclax with azacitidine or decitabine or low-dose cytarabine in patients >60 y/o who ARE candidates for intensive induction chemotherapy AND have high-risk cytogenetics. This use is off label and is not covered.[1] • Dosing of venetoclax with azacitidine and decitabine is 400 mg daily compared to 600 mg daily when given with low-dose cytarabine (LDAC). EBRx will cover venetoclax in combination with azacitidine/decitabine only due to increased cost when given with LDAC.

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Evidence:

- In older patients with comorbidities precluding intensive induction chemotherapy, venetoclax was studied in combination with hypomethylating agents (HMAs, decitabine or azacitidine) and low-dose cytarabine (LDAC). Response rates and overall survival were generally higher than have been seen with other therapies recommended in this population. Although venetoclax has not been compared head-to-head to other regimens, indirect comparisons between trials show possible benefit over other therapies (see table below). Therefore, we will cover for now.
- Venetoclax + azacitidine improved overall survival compared to azacitidine alone.[7]
- No overall survival benefit has been demonstrated to date for venetoclax+decitabine vs decitabine OR venetoclax+cytarabine vs cytarabine.

Studies of older patients with AML (all untreated)					
	Azacitidine[2]	Decitabine[3]	Glasdegib + LDAC[4]	Venetoclax + azacitidine or decitabine[5]	Venetoclax + LDAC[6]
CR	18%	16%	17.9%	37%	26%
CRi	NR	9.9%	6.4%	30%	28%
OS	25 mo^	8 mo^^	8 mo*	17.5 mo	10 mo
Selected baseline characteristics					
Age	≥65y: 73% ≥75y: 22%	≥65y: 99% ≥70y: 82%	≥65y: 98% ≥75y: 60%	≥65y: 100% ≥75y: 36%	≥65y: 98% ≥75y:50%
Poor cytogenetic risk	24%	36%	41%	49%	32%~
Blasts <30%	98%	27%	NR (Median blast count 41%)	24%	33%
Key inc/exc criteria	Age ≥18y; excluded therapy-related disease	≥65y, de novo or secondary AML, poor/intermediate cytogenetics	≥55y AND not suitable for intensive chemo due to age ≥75y, cr>1.3, severe cardiac	≥65 y/o AND ineligible for intensive chemo due to age >75, cardiac dz, prior anthracycline use, secondary AML, or high probability of treatment-related	≥60y AND ineligible for intensive chemo; prior azacitidine/decitabine allowed

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			disease or ECOG PS = 2	mortality; no prior azacitidine/decitabine	

CR: complete response (absence of leukemic blasts in BM, ANC>1k, Plt>100k, PRBC transfusion independence, BM blasts <5%)

CRi: meets criteria for CR but with incomplete recovery of platelet or neutrophil count

OS: overall survival

LDAC: low dose ara-c (cytarabine)
NR: not reported
^superior to group receiving best supportive care, LDAC, or intensive chemo

^^trended toward superiority compared with group receiving supportive care or LDAC

*superior to LDAC alone

~Venetoclax/LDAC study enrolled more patients with secondary AML than ventoclax+aza/dec study (49% vs 25%). Secondary AML is associated with worse prognosis

Dosing (with azacitidine or decitabine):

- Do not start Venetoclax until WBC is <25 x 10^9/L. Cytoreduction may be required (with hyroxyurea, for example)
- Venetoclax likely will be started INPATIENT
- Day 1: 100 mg QD
- Day 2: 200 mg QD
- Day 3 and beyond: 400 mg QD
- Continue until disease progression or unacceptable toxicity

References:

1. *Guidelines for AML – NCCN.* www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed 3/21/19
2. Fenaux, Pierre, et al. “Azacitidine Prolongs Overall Survival Compared With Conventional Care Regimens in Elderly Patients With Low Bone Marrow Blast Count Acute Myeloid Leukemia.” *Journal of Clinical Oncology*, vol. 28, no. 4, 2010, pp. 562–569., doi:10.1200/jco.2009.23.8329. PMID 20026804
3. Kantarjian, Hagop M., et al. “Multicenter, Randomized, Open-Label, Phase III Trial of Decitabine Versus Patient Choice, With Physician Advice, of Either Supportive Care or Low-Dose Cytarabine for the Treatment of Older Patients With Newly Diagnosed Acute Myeloid Leukemia.” *Journal of Clinical Oncology*, vol. 30, no. 21, 2012, pp. 2670–2677., doi:10.1200/jco.2011.38.9429. PMID 22689805
4. Cortes, Jorge E., et al. “Randomized Comparison of Low Dose Cytarabine with or without Glasdegib in Patients with Newly Diagnosed Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome.” *Leukemia*, 2018, doi:10.1038/s41375-018-0312-9. PMID

30555165
5. Dinardo, Courtney D., et al. “Venetoclax Combined with Decitabine or Azacitidine in Treatment-Naive, Elderly Patients with Acute Myeloid Leukemia.” *Blood*, vol. 133, no. 1, 2018, pp. 7–17., doi:10.1182/blood-2018-08-868752. PMID 30361262 NCT02203773
6. Wei AH et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. J Clin Oncol. 2019 Mar 20:JCO1801600. PMID: 30892988
7. DiNardo CD et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020 Aug 13;383(7):617-629. doi: 10.1056/NEJMoa2012971. PMID: 32786187.

Revision Table:

Date	What changed?	Pharmacist’s initials
12-19-18	Wrote criteria for venetoclax for RR CLL/SLL	ALM
1/29/19	I reviewed the criteria. I removed pregnancy/contraception requirement; it is implied. We expect prescribers to practice medicine. Although median OS had not been met for either the venetoclax/Rituxan or the placebo group, the 24 month survival was 91.9% vs 86.6%, respectively, HR 0.48, 95%CI 0.25 to 0.90.	JJ
2/7/19	Added second FDA approval for AML (not covered at this time)	Sk
4/18/19	Added new covered indication of AML in older patients or patients with comorbidities who cannot undergo standard induction chemotherapy	Sk
7/18/19	Criteria reviewed in light of new indication for use of venetoclax in combination with obinutuzumab in untreated patients. This indication will not be covered (see above).	SK
1/29/20	Clarified duration of therapy for relapsed/refractory CLL (24 months). Updated survival data from MURANO study (CLL). For first line CLL indication (with obinutuzumab), could not locate additional survival data. No indication of improvement in QOL data compared to control per an ASH abstract (reference added above).	Sk
3/16/20	Added note about phase III data for venetoclax/cytarabine (negative trial). No change to criteria.	SK
3/25/20	Added statement about preliminary data for azacitidine/venetoclax showing improvement in overall survival compared with azacitidine alone.	SK
11/16/2020	Added note that venetoclax now has full approval for AML indication. Added reference for trial showing improvement in OS when pt are treated with azacitidine+Veneto vs azacitidine alone.	SK

CONFIDENTIAL

Vigabatrin (Sabril©)

[generic available]

EBRx PA Criteria

FDA-approved for:

- infantile spasms.
- Refractory complex partial seizures as adjunctive therapy for adults and pediatric patients ≥10 yo who inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss.

Criteria for new users
1. Patient must be diagnosed with infantile spasms.
2. Patient must be either unable to take hormonal therapy for infantile spasms (high dose prednisolone) OR ELSE be planning to take it concurrently with vigabatrin.
3. The drug must be prescribed by a pediatric neurologist.
Note: The FDA requires patients to undergo visual field examinations every 3 months due to the potential irreversible retinopathies resulting in bilateral concentric constriction of visual fields.
Evidence
1. Kanner, Andres M., et al. "Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy." *Epilepsy currents* 18.4 (2018): 269-278.
2. Kanner, Andres M., et al. "Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy." *Epilepsy currents* 18.4 (2018): 260-268.
3. Hancock, Eleanor C., John P. Osborne, and Stuart W. Edwards. "Treatment of infantile spasms." *Cochrane Database of Systematic Reviews* 6 (2013).
4. O'Callaghan, Finbar JK, et al. "Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial." *The Lancet Neurology* 16.1 (2017): 33-42.

Revision History:

Date	What changed	Pharmacist's initials
4/26/19	I wrote the criteria.	JJ
7/10/19	I added the criteria requiring a pediatric neurologist to be the prescriber (per Dr. Bill Golden's recommendation at DUEC 7/8/19).	JJ

Vorinostat (Zolinza®)

100 mg capsules

EBRx PA Criteria

FDA approved for:

Cutaneous T-cell lymphoma (CTCL) with progressive, persistent, or recurrent disease on or following 2 systemic treatments

Criteria for new users
Does the patient have a diagnosis of cutaneous T-cell lymphoma with progressive, persistent, or recurrent disease on or following at least 2 systemic treatments that included methotrexate, a retinoid (isotretinoin or acitretin), interferon, or extracorporeal photopheresis?
If above criterion is met, approve x 1 year

Note:

Dose is 400 mg PO once daily

Vorinostat was associated with a 29.7% response rate and improved pruritus significantly in 32.3% of patients.

Ref: Zolinza PI. Accessed online 6/19/2019.

Quantity limits: #120 capsules/30 days

Reference:

Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007;25(21):3109-3115. doi:10.1200/JCO.2006.10.2434 PMID 17577020 NCT00091559

Revision History:

Date	Notes	Pharmacist's initials
2/20/07	IB approved DUECs recommendation to place the drug on T3PA.	JJ

2/7/07	Criteria were written	JJ
5/17/12	Revision history table added	JJ
5/13/15	I added a more specific diagnosis requirement. The FDA approval is for pts following 2 systemic therapies. After DCWG 5/12/15, discussion indicated they wanted 3 prior therapies which have better response rates and cost less than vorinostat.	JJ
6/19/19	Criteria reviewed. Allow 2 prior therapies before approved rather than 3. Allow prior use of interferon.	SK
6/16/2020	Reviewed at DCWG 6-2020. Criteria reviewed. No change.	SK

CONFIDENTIAL

Pretomanid

200mg tablets

EBRx PA Criteria

is FDA-approved for: Treatment of treatment-intolerant or nonresponsive MDR or extensively drug resistant pulmonary tuberculosis

Criteria for new users
1. Patient must have the diagnosis of pulmonary tuberculosis that is either non-responsive, multi-drug resistant or extensively drug resistant.
2. Patient must be receiving concurrent linezolid and bedaquiline.
3. The prescriber must attest to prescribing pretomanid in coordination with the state Department of Health.

Note: If approved, allow a 4 weeks supply at each dispensing. If all three drugs are not tolerated, one (possibly pretomanid) may be discontinued if later than the initial 4 weeks of treatment

Quantity Limits: 1/1

References:

1. FDA website: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212862Orig1s000MultidisciplineR.pdf

Revision History:

Date	What changed	Pharmacist's initials
12/3/19	I wrote the criteria.	JJ
10/28/2020	I reviewed the criteria.	JJ
3/10/21	Criteria reviewed; no changes.	JJ

CONFIDENTIAL

Isatuximab (Sarclisa®)

100mg/5ml and 500mg/25 ml vial

EBRx PA Criteria

is FDA-approved for:

treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (use in combination with pomalidomide and dexamethasone)

Criteria for new users
1. Diagnosis of multiple myeloma
2. Age is 75 years or older
3. Patient has been treated with at least two prior therapies, which included lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, ixazomib).
4. If patient received prior anti-CD38 monoclonal antibody therapy (e.g. daratumumab), disease was not refractory to this therapy (e.g. disease did not progress ON or within 60 days of this therapy*)
5. Patient has not experienced disease progression on pomalidomide
6. Isatuximab will be given in combination with pomalidomide and dexamethasone
If all criteria met, approve for 12 months.

*Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009 Jan;23(1):3-9. doi: 10.1038/leu.2008.291. Epub 2008 Oct 30. Erratum in: Leukemia. 2014 Apr;28(4):980. PMID: 18971951; PMCID: PMC2627786.

Note:

Isatuximab/pomalidomide/dexamethasone was compared to pomalidomide/dexamethasone in patients who were previously treated with at least two prior therapies including lenalidomide and

a proteasome inhibitor. The triplet therapy improved progression free survival (median 11.53 mo vs 6.47 mo). In the overall population, a statistically significant overall survival benefit has not been demonstrated at this time. However, in the subset of patients who were age ≥75 y, a statistically significant improvement in overall survival was demonstrated (median not reached in triplet group versus 10.25 mo in the control group (HR 0.404 95% CI 0.171- 0.956).[1,2]

Dose:

Cycle 1: 10 mg/kg IV on days 1, 8, 15, and 22 of a 28-day cycle (in combination with pomalidomide and dexamethasone.

Cycle 2 and beyond: 10 mg/kg IV on days 1 and 15 of a 28-day cycle (in combination with pomalidomide and dexamethasone), continue until disease progression or unacceptable toxicity.

References:

1. Attal M et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019 Dec 7;394(10214):2096-2107. doi: 10.1016/S0140-6736(19)32556-5. Epub 2019 Nov 14. PMID 31735560 NCT02990338
2. Schjesvold FH et al. Efficacy of Isatuximab with Pomalidomide and Dexamethasone in Elderly Patients with Relapsed/Refractory Multiple Myeloma: Icaria-MM Subgroup Analysis. Blood (2019) 134 (Supplement_1): 1893. https://ashpublications.org/blood/article/134/Supplement_1/1893/427649/Efficacy-of-Isatuximab-with-Pomalidomide

Revision History:

Date	What changed	Pharmacist's initials
8/25/2021	Changed formatting of the current criteria. No effective changes. Still looking for author of the original criteria.	OD

Talazoparib (Talzenna®)

0.25, 1 mg capsules

EBRx PA Criteria

FDA-approved for:

- treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (*gBRCAm*) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for talazoparib

Criteria for new users
1. Diagnosis of unresectable or metastatic breast cancer
2. Disease is progressing or has recurred after previous therapy
3. Germline BRCA mutation is documented
4. Tumor is HER2 negative
5. Patient has received a taxane (docetaxel, paclitaxel) and an anthracycline (epirubicin, doxorubicin) in the adjuvant or metastatic setting, unless contraindicated.
6. If platinum-based chemotherapy was previously given (e.g. cisplatin, carboplatin), tumor did not progress during platinum-based therapy
7. If tumor is hormone receptor (e.g. estrogen and/or progesterone receptor) positive, patient has received at least one hormonal therapy for treatment of metastatic disease (e.g. tamoxifen, letrozole, anastrozole, exemestane, fulvestrant)
8. No prior PARP inhibitor has been used for treatment of breast cancer (e.g. talazoparib, olaparib, rucaparib)
If all of the above criteria are met, approve for 6 months

Note:

Talazoparib was compared to physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in the above patient population. Progression free survival was improved in the talazoparib group (median 7 mo vs 4.2 mo). The overall survival analysis is immature and has not reached significance at the first follow up (median 22.3 vs 19.5 mo; HR 0.76, 95% CI, 0.55-1.06). There were similar rates of severe and serious adverse events. Time to deterioration of EORTC QLQ-C30 global health status was prolonged in the talazoparib group (median 24.3 vs 6.3 mo). Time to deterioration of EORTC QLQ-BR23 was also prolonged (medians not reached).

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Though an overall survival benefit has not been demonstrated, time to deterioration of quality of life (see other notes below).

Dose:

-1 mg daily until disease progression or unacceptable toxicity

-Dose should be reduced to 0.75 mg daily when coadministered with certain P-gp inhibitors (amiodarone, carvedilol, clarithromycin, itraconazole, verapamil)

-If creatinine clearance is 30-59 ml/min, dose should be reduced to 0.75 mg daily.

-Dose reduction for toxicity is made in 0.25 mg increments.

References:

7. Litton JK et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018 Aug 23;379(8):753-763. NCT01945775 PMID 30110579
8. Litton JK et al. Talazoparib…appendix https://www.nejm.org/doi/suppl/10.1056/NEJMoa1802905/suppl_file/nejmoa1802905_appendix.pdf. Accessed 7/12/19.
9. Litton JK et al. Talazoparib…protocol https://www.nejm.org/doi/suppl/10.1056/NEJMoa1802905/suppl_file/nejmoa1802905_protocol.pdf. Accessed 7/12/19.
10. Litton JK, Hurvitz SA, Mina LA, Rugo HS, Lee KH, Gonçalves A, Diab S, Woodward N, Goodwin A, Yerushalmi R, Roché H, Im YH, Eiermann W, Quek RGW, Usari T, Lanzalone S, Czibere A, Blum JL, Martin M, Ettl J. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol. 2020 Aug 20:S0923-7534(20)42106-4. PMID: 32828825.

Quantity Limits:

1 mg: 30/30

0.25 mg: 90/30

Revision History:

Date	What changed	Pharmacist's initials
8/26/19	Criteria written.	SK
10/13/2020	Criteria reviewed. No change in criteria. Added new reference.	SK

Differences between study inclusion/exclusion criteria (taking into account amendment 1) and EBRx criteria with rationale:

-study required prior treatment with a taxane and/or anthracycline in the neoadjuvant, adjuvant, locally advanced, or metastatic setting unless contraindicated. EBRx will require prior treatment

with a taxane AND an anthracycline to mirror olaparib criteria and to push for use of less expensive therapies first.

-study did not require previous treatment with hormonal therapy. EBRx will require prior treatment with hormonal therapy for metastatic disease to push for use of less expensive therapies first.

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Stiripentol (Diacomit®)

EBRx PA Criteria

FDA-approved for: **adjunctive** treatment of refractory generalized tonic-clonic seizures in conjunction with clobazam in patients ≥2 years **with Dravet syndrome**

Criteria for new users
1. Patient must have a diagnosis of Dravet Syndrome with refractory seizures
2. Seizures must be generalized tonic-clonic
3. Patient be currently taking clobazam AND valproic acid for seizures
4. Patient must be ≥2 years of age
5. Patient must have tried and failed cannabidiol
Approve for 6 months.

Criteria for continuation
1. Continues to meet above criteria
2. Decrease in number of seizures per month has been seen
Approve for 12 months.

Revision History:

Date	What changed	Pharmacist's initials
5/16/19	Wrote criteria.	ALM
6/6/19	Added Criteria to try and fail cannabidiol	ALM
8/31/2020	I reviewed the criteria. No changes	JJ
3/10/21	I reviewed the criteria. No changes	JJ

References:

1. Inoue, Yushi, Yoko Ohtsuka, and STP-1 Study Group. "Effectiveness of add-on stiripentol to clobazam and valproate in Japanese patients with Dravet syndrome: additional supportive evidence." *Epilepsy research* 108.4 (2014): 725-731.
2. Chiron, C., et al. "Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial." *The Lancet*356.9242 (2000): 1638-1642.
3. Package insert: Diacomit. Accessed 5/6/2019.
4. LexiComp: Diacomit. Accessed 5/6/2019.

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Tafamidis (Vyndaqel®)

20mg capsules

EBRx PA Criteria

FDA-approved for: treatment of cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.

Criteria for new users
1. Diagnosis of confirmed amyloidosis by the presence of amyloid deposits on biopsies from cardiac and noncardiac sites (e.g., fat aspirate, GI sites, salivary glands, or bone marrow).
2. In patients without ATTR mutation, they must have the presence of transthyretin precursor protein confirmed on immunohistochemical analysis, scintigraphy, or mass spectrometry.
3. Cardiac involvement must be shown by one of the following: a) echocardiography must show an end-diastolic interventricular septal wall thickness exceeding 12 mm, OR b) a history of heart failure with at least 1 prior hospitalization for heart failure or clinical evidence of heart failure without hospitalization manifested in signs or symptoms of volume overload, OR c) elevated intracardiac pressures requiring treatment with a diuretic for improvement, OR d) an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level ≥600pg/mL
4. Must have a 6MWT of >100m.
5. Tafamidis must be prescribed by or given in consultation with a cardiologist transthyretin amyloidosis specialist, or medical geneticist

Note: Dose is 80mg QD (20mg caps); however, we 80mg QD was not superior to 20mg QD. Plan covers 20mg QD.

Quantity Limits: 1/1

References:

1. FDA.gov. CDER. Application 211996ORIG1s000. Clinical Review. Tafamidis. See page 76.

2. Maurer, Mathew S., et al. "Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy." *New England Journal of Medicine* 379.11 (2018): 1007-1016.

Revision History:

Date	What changed	Pharmacist's initials
6/17/2019	I wrote the criteria.	JJ
8/31/2020	I updated the criteria to reflect our decision to limit access to 20mg (not 80mg) because mortality was not different between groups.	JJ
3/9/2021	I added reference 2. I added tafamidis must be prescribed by or given in consultation with a cardiologist transthyretin amyloidosis specialist, or medical geneticist	JJ

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Ravulizumab (Ultomiris®)

Injection [MEDICAL BENEFIT ONLY]

300mg/30mL vial

EBRx PA Criteria

Paroxysmal Nocturnal Hemoglobinuria (PNH)
1. The patient must have been diagnosed with paroxysmal nocturnal hemoglobinuria, confirmed by high-sensitivity flow cytometry of red and white blood cells with granulocyte or monocyte clone size of at least 5%
2. The patient's LDH level must be ≥1.5 X ULN.
3. The patient must be 18 years old or older.
4. The patient must be symptomatic (fatigue, hemoglobinuria, abdominal pain, shortness of breath, anemis (Hb <10g/dL), thrombosis, dysphagia, erectile dysfunction, or need for RBC transfusion due to PNH.
5. The patient should have vaccination for Neisseria meningitidis 2 weeks prior to administration with ravulizumab.

References:

1. Lee, Jong Wook, et al. "Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study." *Blood* 133.6 (2019): 530-539.

2. Kulasekararaj, Austin G., et al. "Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor–experienced adult patients with PNH: the 302 study." *Blood* 133.6 (2019): 540-549.

Date	What changed?	Pharmacist's initials
2/25/19	I wrote the criteria. I included references 1 and 2.	JJ
8/10/2020	I reviewed the criteria. I added the need for Neisseria meningitidis vaccine. At the current AWP prices, the 12 month costs at the highest maintenance doses between ravulizumab $522,960 and eculizumab $610,740, the difference is $87,780 per patient. Because RAV was noninferior to ECU for paroxysmal nocturnal hemoglobinuria for LDH levels at day 183, and because the risk of N. meningitidis was not apparently different between drugs, EBRx will continue to prefer the lower cost drug.	JJ

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Osilodrostat (Isturisa®)

1,5,10mg tablets

EBRx PA Criteria

is FDA-approved for: treating Cushing disease

Criteria for new users	
1. Diagnosis of Cushing's Disease	
2. Patient must be age 18 years or older.	
3. The patient must be unable to be treated successfully with pituitary surgery and/or radiation.	
4. The patient must be unable to be treated with bilateral adrenalectomy.	
5. The patient must have tried and either failed or not tolerated ketoconazole, metyrapone, mitotane.	
6. The prescriber must be an endocrinologist.	
If all 4 of the above criteria are yes, the PA will be approved for 6 months.	

Criteria for continuation
1. After 6 months of use, the mean urinary free cortisol concentration returned to the normal range.
After identifying the patient as a responder, the PA will be good for 12 months.

Note: The usual dose is 2-7mg BID. The max dose is 30mg BID.

Quantity Limits: 6/1 (to allow for the 30mg BID dosing)

Revision History:

Date	What changed	Pharmacist's initials
5/27/2020	I wrote the criteria.	JJ
6/11/2020	I excluded etomidate from the requirement to fail because it is a continuous infusion and therefore not feasible.	JJ
7/15/2020	I added the requirement for the prescriber to be an endocrinologist.	JJ
3/29/2021	I added the 18y age requirement.	JJ

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Glasdegib (Daurismo®)

25 mg and 100 mg tablets

EBRx PA Criteria

FDA-approved for: in combination with low-dose cytarabine, treatment of newly-diagnosed acute myeloid leukemia (AML) in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.

Criteria for new users
1. Diagnosis of acute myeloid leukemia (AML) with no prior treatment
2. Glasdegib will be used in combination with low-dose cytarabine
3. Age ≥ 75 years OR presence of comorbidities that preclude use of intensive induction therapy (e.g. renal failure, severe cardiac disease, ECOG performance status = 2)
4. Patient is not a candidate for a hypomethylating agent (azacitidine, decitabine)
If all 4 criteria fulfilled, approved for 6 months

Criteria for continuation
1. Glasdegib is being used in combination with low-dose cytarabine
2. No unacceptable toxicity
If both of the continuation criteria are fulfilled, approve for 6 months.

Note: Glasdegib+low dose cytarabine (LDAC) improved overall survival by 4 months compared with LDAC monotherapy in patients who were not candidates for intensive chemotherapy (median OS: 8.8 months vs 4.9 months) [1]. Azacitidine and decitabine are preferred agents per NCCN guidelines for this patient population and have shown improved overall survival compared with other treatments[2] therefore patients should be considered for azacitidine/decitabine first. Glasdegib has only been compared with LDAC at this time.

-Dose: 100 mg PO QD. Six months of therapy should be given to allow time for response. Dose reduction to 50 mg QD allowed for QTc prolongation and other grade 3 toxicity.

-LDAC is given SC q 12 h for 10 days each month. LDAC is typically administered in clinic or at home by patient/ caregiver/home health agency.

- Treatment is continued until relapse, progression of disease, or unacceptable toxicity.

-Glasdegib monotherapy is NOT effective[3]

Quantity Limits:

25 mg tablets: 60 tablets/30 days

100 mg tablets: 30 tablets/30 days

Revision History:

Date	What changed	Pharmacist's initials
1/28/19	Criteria written	sk
6/11/19	Criteria reviewed-no changes indicated	Sk
7/7/2020	Criteria reviewed. No change to criteria.	SK

References:

1. Cortes, Jorge E., et al. "Randomized Comparison of Low Dose Cytarabine with or without Glasdegib in Patients with Newly Diagnosed Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome." *Leukemia*, 2018, doi:10.1038/s41375-018-0312-9.
2. *Guidelines for AML – NCCN*. www.nccn.org/professionals/physician_gls/pdf/aml.pdf.
3. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210656Orig1s000MedR.pdf

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Larotrectinib (Vitrakvi®)

25, 100 mg capsules and 20 mg/ml oral solution

EBRx PA Criteria

is FDA-approved for:

• Treatment of adult and pediatric patients with solid tumors that meet **all** of the following criteria:

-have a neurotrophic receptor tyrosine kinase (NTRK) gene **fusion*** without a known acquired resistance mutation

-are metastatic or where surgical resection is likely to result in severe morbidity

-have no satisfactory alternative treatments or that have progressed following treatment.

*note: NTRK aberration must be a fusion (not point mutation or amplification).

Hong DS, et al. Abstract CT062. Presented at: AACR Annual Meeting; April 27-28, 2020 (virtual meeting). https://www.healio.com/hematology-oncology/sarcoma/news/online/%7Bd3e29cb1-e9f4-436b-8ee2-7417db795408%7D/larotrectinib-induces-durable-responses-in-trk-fusion-cancers?utm_source=selligent&utm_medium=email&utm_campaign=hematology%20oncology%20news&m_bt=19042249342&page=2. Accessed 4/20/2020.

Criteria for new users
1. Diagnosis of a solid tumor (e.g. not a lymphoma, leukemia, multiple myeloma, etc)
2. Presence of a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation
3. Tumor is metastatic OR surgical resection is likely to result in severe morbidity
4. Tumor has no satisfactory alternative treatments or has progressed following treatment
5. If oral solution is being requested, patient is unable to swallow capsules.
If all criteria met, approve x 1 year

Quantity Limits:

100 mg tablets: #60 tablets/30 days

25 mg tablets: #180 tablets/30 days

Oral solution (20 mg/ml): 300 ml/30 days

Pricing			
Generic	Brand	Adult Dose	28d AWP

			(as of 10/7/19 per FDB)
Larotrectinib	Vitrakvi	100 mg PO bid	Capsule: $36,736 Oral solution: $48,980

Dosing is as follows:

BSA $\geq$ 1 m^2 (will include most adults): 100 mg PO BID

BSA < 1 m^2: 100 mg/m^2 PO BID

Larotrectinib was approved based on a pooled analysis of 3 single-arm trials showing an overall response rate of 75%.[1,2] Additionally, a quality of life analysis was conducted showing a clinically significant improvement in over 50% of patients using several QOL scales:[3]

Pt with clinically significant improvement n (%)*:

PedsQL (total score): 10 (77)

EORTC QLQ-C30: 15 (62)

EQ-5D-5L: 14 (58)

*Improvements in QOL scores seen by cycle 3 or 5 and sustained for minimum of 2 cycles. Clinically significant improvement defined in reference.

References:

1. Drilon, A., et al. “Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children.” *New England Journal of Medicine* 378.8 (February 2018): 731-739.
2. Laetsch, Theodore W., et al. "Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study." *The Lancet* 19.5 (May 2018): 705-714.
3. Kummar S et al. Patient-reported outcomes from two global multicenter clinical trials of children and adults with tropomyosin receptor kinase (TRK) fusion cancer receiving larotrectinib. DOI: 10.1200/JCO.2019.37.15_suppl.6602 Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 6602-6602. Accessed 10/7/2019. [Abstract] https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.6602.

Revision History:

Date	What changed	Pharmacist’s initials
10/28/19	Criteria written	SK
4/30/20	Added note stressing the NTRK aberration should be a fusion and not point mutation or amplification.	SK
12/29/2020	Criteria reviewed. Verified pricing info. No change	SK
3/19/2021	Reworded criteria #4 to match FDA indication. Added clarification of fusion versus point mutation/amplification	SK

Luspatercept (Reblozyl®)

25 and 75 mg vial

EBRx PA Criteria

is FDA-approved for:

- Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions NOT COVERED
    - Not covered due to limited medical benefit. In the BELIEVE trial, patients with beta thalassemia requiring ≥6 RBC transfusions per 24 weeks were randomized to luspatercept or placebo.
        - Primary endpoint: percent of patients with ≥33% reduction from baseline in RBC transfusion burden with a minimum reduction of at least 2 units for consecutive 12 weeks. In the luspatercept group 33% of patients achieved the primary endpoint compared to 4.5% of placebo patients.
        - The percent of patients who had ≥50% reduction from baseline in RBC transfusion burden (with a minimum reduction of at least 2 units) was 7.6% in the luspatercept group compared to 1.8% in the placebo group.

    REFERENCES:
    -Reblozyl PI. https://media.celgene.com/content/uploads/reblozyl-pi.pdf. Accessed 12/10/19.
    -Cappellini MD, Viprakasit V, Taher AT, et al. A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia. N Engl J Med. 2020;382(13):1219–1231. doi:10.1056/NEJMoa1910182

- Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)

  Limitations of Use: luspatercept is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia

Criteria for new users (anemia due to myelodysplastic syndrome)
1. Diagnosis of myelodysplastic syndrome (MDS) with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RL-T)* *Must have <5% bone marrow blasts and either ≥15% of erythroid precursors with ring sideroblasts OR ≥5% ring sideroblasts if an SF3B1 mutation was present. <5% blasts
2. MDS is classified as very low, low, or intermediate risk by IPSS-R (see below)

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3. Age ≥18 years or older
4. Current requirement of at least 2 red cell transfusions per 8 weeks
5. Anemia is refractory to erythropoiesis-stimulating agents (ESAs) OR serum erythropoietin level is >500 mU/ml which predicts poor response to ESAs. (note: study used cutoff of 200 mU/mL but NCCN guidelines and UpToDate algorithm recommend a cutoff of 500 mU/mL)
If all criteria met, approved for 4 months.
Continuation criteria
After 4 months of treatment, may renew PA approval for 1 year if there is documentation of a reduction in RBC transfusion burden compared to baseline of at least 2 units over an 8 week period (see dosing recommendations below).

Evidence:

Luspatercept was compared to placebo in this patient population. More patients in the luspatercept group achieved transfusion independence for 8 weeks or longer compared to placebo (38% vs 13%).

Note:

Dose:

1 mcg/kg SQ every 3 weeks. Dose may be titrated to a maximum of 1.25 mg/kg based on response. Therapy is stopped if no reduction in transfusion burden after 3 maximized doses. Package insert and study did not define “reduction in transfusion burden.” The above criteria for continuation (≥2 unit reduction over 8 weeks) was taken from the endpoints used in beta thalassemia trial. Clinical judgment may be used.

References:

1. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. N Engl J Med. 2020;382(2):140–151. doi:10.1056/NEJMoa1908892 PMID 31914241
2. NCCN Guidelines for Myelodysplastic Syndrome Version 2.2020. Accessed 4/28/2020.
3. Treatment of lower-risk myelodysplastic syndromes (MDS). https://www.uptodate.com/contents/treatment-of-lower-risk-myelodysplastic-syndromes-mds?search=luspatercept&source=search_result&selectedTitle=3~10&usage_type=default&display_rank=2#H48. Accessed 4/28/2020.

REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R) (taken from NCCN MDS guidelines)

	Score Value						
Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetic[e]	**Very good**	**—**	**Good**	**—**		**Poor**	**Very**
Marrow blasts (%)	**≤2**	**—**	**>2-<5**	**—**	**5-10**	**>10**	**—**
Hemoglobin	**≥10**	**—**	**8-<10**	**<8**	**—**	**—**	**—**
Platelets	**≥100**	**50-<100**	**<50**	**—**	**—**	**—**	**—**
ANC	**≥0.8**	**<0.8**	**—**	**—**	**—**	**—**	**—**

Revision History:

Date	What changed	Pharmacist's initials
4/28/2020	Criteria written.	SK

CONFIDENTIAL

Givosiran (Givlaari®)

SC solution 189mg/mL

EBRx PA Criteria

Medical PA—This drug must be administered by a healthcare professional.

is FDA-approved for: Treatment of adults with acute hepatic porphyria.

Criteria for new users
1. The patient must have the diagnosis of acute hepatic porphyria.

Quantity Limits: 1 injection per claim

Revision History:

Date	What changed	Pharmacist's initials
3/18/2020	I wrote the criteria.	JJ

CONFIDENTIAL

CONFIDENTIAL

Midostaurin (Rydapt®)

25mg capsules

EBRx PA Criteria

- **is FDA-approved for** treatment of adult patients with:
  - Newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation positive as detected by an FDA-approved test, **in combination with standard cytarabine and daunorubicin** induction and cytarabine consolidation
  - Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL). –NOT A COVERED USE, data limited to single arm trial. Other data pending

AML: Criteria for new users seeking INDUCTION therapy
1. The patient must be newly diagnosed with acute myeloid leukemia with a FLT3 mutation, as detected by an FDA-approved test.
2. The patient must be planning to receive concomitant daunorubicin and cytarabine therapy.
Note: If criteria are fulfilled, approve PA for 2 months.
INDUCTION regimen is midostaurin 50mg BID on days 8-21 (given with daunorubicin+cytarabine). If the day 21 bone marrow biopsy shows residual leukemia, a repeat course of given (same regimen and schedule). **If complete remission attained, CONSOLIDATION chemotherapy consists of four cycles of midostaurin 50mg BID on days 8-21 of a 28-day cycle (with cytarabine).** **If remission, then MAINTENANCE therapy consists of 12 cycles of midostaurin 50mg BID on days 1-28 of a 28-day cycle.**
AML: Criteria for users seeking CONSOLIDATION therapy
1. The patient must have received induction therapy for AML w/ FLT3 mutations (as above).
2. The patient must be planning to receive concomitant cytarabine therapy for consolidation therapy.
3. The bone marrow biopsy at the end of a maximum of 2 induction cycles must show complete remission
Note: If criteria are fulfilled for CONSOLIDATION, approve PA for 4 months.
AML: Criteria for users seeking MAINTENANCE therapy
1. The patient must have received consolidation therapy for AML w/ FLT3 mutations (as above).
2. The patient must have bone marrow results immediately after the end of consolidation therapy that shows the bone marrow biopsy at the end of a maximum of four 28-day consolidation cycles must show complete remission
Note: If criteria fulfilled for MAINTENANCE, approve PA for 12 months.

Quantity limits:

Induction and consolidation: #56 per 28 days

Maintenance: #112 per 28 days

Revision History:

Date	What changed	Pharmacist's initials
9/8/17	We wrote the criteria. Systemic mastocytosis OS data are pending (NCT00233454Phase II Midostaurin in Aggressive Systemic Mastocytosis and Mast Cell Leukemia). Efficacy and Safety of Midostaurin in Patients With Aggressive Systemic Mastocytosis or Mast Cell Leukemia (NCT00782067)—OS data pending. Awaiting results at 5 years. 100mg BID	JJ/JK
1/29/20	Criteria reviewed. Simplified wording and approval limits for AML indication.	SK

CONFIDENTIAL

Gilteritinib (Xospata®)

40 mg tablets

EBRx PA Criteria

is FDA-approved for:

Treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test.

Criteria for new users
1. Age ≥18 y/o
2. Diagnosis of either relapsed AML (loss of complete remission induced by previous therapy) or refractory AML (did not achieve a complete remission with anthracycline-containing therapy)
3. Presence of a FLT3 mutation
4. Gilteritinib will be used as single agent
If criteria are met, approve x 1 year

Note:

Dose 120 mg once daily

Gilteritinib was compared to traditional salvage chemotherapy in adults with relapsed or refractory FLT3-mutated AML. Chemotherapy arm included high intensity and low intensity regimen. The median duration of therapy was 5 months. Overall survival was improved in the gilteritinib group (median 9.3 mo vs 5.6 mo). At 12 months, rate of overall survival was 37% vs 17%. Gilteritinib was superior to both high intensity and low intensity therapies. More patients in the gilteritinib were able to proceed to potentially curative stem cell transplant compared to chemotherapy (25.5% vs 15.3%).

Reference:

Xospata package insert. Astellas. May 2019. Accessed 6/19/19 at https://astellas.us/docs/xospata.pdf

Perl AE et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med 2019; 381:1728-1740. PMID 31665578 NCT02421939

Quantity Limits: 90 tablets/30 days

Revision History:

Date	What changed	Pharmacist's initials
6/19/19	Criteria written	SK
11/25/19	Full study released. Added reference. Added that refractory AML requires prior treatment with anthracycline-containing therapy.	SK
12/29/2020	Criteria reviewed. No change	SK

CONFIDENTIAL

Onasemnogene Abeparvovec (Zolgensma®)

EBRx PA Criteria—MEDICAL PA

1-time IV infusion

is FDA-approved for: treatment of pediatric patients <2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.

Criteria for new users
1. The patient must be 2 (two) years or younger.
2. The patient must have the confirmed diagnosis of SMA-1 by genetic testing for both symptomatic and presymptomatic patients.
3. The patient must have not more than 3 copies of SMN. (Patients with 4 or more copies of SMN2 are likely to NOT develop the most severe forms of SMA and it may be reasonable to wait and monitor for signs of disease progression.)
4. The patient must have bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.
5. No prior use of Zolgensma. Previous use of Spinraza does not preclude the one time Zolgensma gene therapy; however, after Zolgensma, no further Spinraza will be covered.
6. Prescriber must be a neuromuscular specialist.
7. At request, the patient must have NO HISTORY of the ability to walk independently (defined as the ability to walk ≥15 feet unaided.
Medication is excluded from pharmacy.

It is recommended that this medication be administered at a Center of Excellence.

Date	What changed	Pharmacist's initials
7/22/19	I wrote the criteria for the medical benefit after the 5/24/19 ICER update.	JJ

Revision History:

Ref:

1. ICER Report. Spinraza and Zolgensma for SMA. https://icer-review.org/wp-content/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf

CONFIDENTIAL

Sacituzumab govitecan (Trodelvy©)

Vial 180 mg

EBRx PA Criteria

FDA-approved for:

Treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease

Criteria for new users
1. Diagnosis of metastatic triple negative breast cancer [i.e. <1% estrogen and progesterone receptor expression and HER2 negative]
2. Refractory to or relapsed after at least two prior treatment regimens for advanced/metastatic disease
3. Sacituzumab will be used as single agent
If criteria met, approve for 12 months

Note:

ASCENT

NCT02574455

Phase III, RCT

1:1 randomization

SG vs physicians choice single-agent chemo*

*capecitabine, eribulin, vinorelbine, OR gemcitabine

Key inclusion/exclusion criteria:

Metastatic triple-negative breast cancer

-at least 2 prior treatment for metastatic disease

-prior taxane required

Population enrolled:

N=529

Median age: 54 y/o

Median # of prior regimens: 4

Results for patients with no brain mets at baseline (n=468)

Outcome	SG	Chemo
Median progression free survival	5.6 mo	1.7 mo HR 0.41*
Median overall survival	12.1 mo	6.7 mo HR 0.48*
Overall response rate	35%	5%
Grade ≥3 adverse events		
Neutropenia	51%	33%
Febrile neutropenia	6%	2%
Diarrhea	10.5%	<1%

*p<0.0001 (SG vs chemo)

ESMO MCB grade: 4 (HR <0.65 and OS gain >3 mo)

Reference:

Bardia A, Tolaney SM, Loirat D, et al: ASCENT: A randomized phase III study of sacituzumab govitecan vs treatment of physician's choice in patients with previously treated metastatic triple-negative breast cancer. ESMO Virtual Congress 2020. Abstract LBA17. Presented September 19, 2020. https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/ascent-a-randomized-phase-iii-study-of-sacituzumab-govitecan-sg-vs-treatment-of-physician-s-choice-tpc-in-patients-pts-with-previously-treat

Quantity Limits: n/a (medical drug)

Revision History:

Date	What changed	Pharmacist's initials
11/19/2020	Criteria written	SK

CONFIDENTIAL

CONFIDENTIAL

Migalastat (Galafold©)

123mg Capsule

EBRx PA Criteria

is FDA-approved for: **Fabry disease:** Treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data.

Criteria for new users
1. Patient must have the diagnosis of Fabry Disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data.

Note: DOSING is EVERY OTHER DAY. DO NOT ADMINISTER DAILY.

Quantity Limits: #15/30days

Trial	N	Endpoints	Results
[2]ATTRACT RCT, OL, parallel assignment Migalastat vs ERT	57	Co-1° Endpoints:MIG vs ERT through 18m on eGFR (measured and estimated) Other=LVMi via echo, Composite clinical endpoints: Renal (decrease in GFR by 15mL/min OR an increase in 24h urine protein); Cardiac (MI, UA, new symptomatic arrhythmia requiring med or cardioversion or PM, CHF Class III or IV); Cerebrovascular (stroke/TIA)	• Similar change in annualized GFR o Mig -4.35mL/min ±0.93 (-2.27-1.48) o ERT -3.24±2.27 (-7.81-1.33) • LVMi -6.6 [-11.0 to -2.2] • Renal, cardiac, cerebrovascular events 29% MIG vs 44% ERT (p=0.36)
3D echo= reliable way to determine LVMi but intra- and inter-observer variability were 4.5 ± 4.2% and 5.5 ± 3.2% respectively[3]			

Although Migalastat was not superior over enzyme treatment, migalastat offers an oral alternative in patients with some working enzymes; cost is similar. Compared HTH, the eGFR was similar after 18 months and the renal/cardiac/cerebrovascular events were similar.

References:

1. LexiComp: migalastat accessed 9/5/2018, 9/16/19.
2. Hughes, Derralynn A., et al. "Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study." *Journal of medical genetics* (2016): jmedgenet-2016. 54.4 (2017): 288-296.
3. Mizukoshi, Kei, et al. "Normal values of left ventricular mass index assessed by transthoracic three-dimensional echocardiography." *Journal of the American Society of Echocardiography* 29.1 (2016): 51-61.
4. UpToDate: Fabry Disease accessed 9/5/2018.
5. Package insert (Galafold) Accessed 9/13/2018.

Revision History:

Date	What changed	Pharmacist's initials
1/14/21	I wrote the criteria.	JJ

CONFIDENTIAL

Ozanimod (Zeposia©)

Capsule 0.23mg, 0.46mg, 0.92 mg

EBRx PA Criteria

is FDA-approved for: treating relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Criteria for new users
1. The patient must have the diagnosis of relapsing MS, clinically isolated syndrome, or active secondary progressive disease.
2. The patient must be at low risk for progressive multifocal leukoencephalopathy (PML) including those who are antibody positive as long as the anti-JCV antibody index is below 0.9.
3. No concurrent therapy with other multiple sclerosis drug therapies.

Note: The dose is 0.23mg QD on days 1-4, then 0.46mg daily on days 5-7, then a maintenance dose of 0.92mg daily.

If a dose is missed during the first 2 weeks, reinitiation of titration must be done with 0.23mg QD, then increasing per above.

Quantity Limits: QL of 1/1.

References:

1. Cohen, Jeffrey A., et al. "Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial." *The Lancet Neurology* 18.11 (2019): 1021-1033.

2. Cohen, Jeffrey A., et al. "Efficacy and safety of ozanimod in multiple sclerosis: dose-blinded extension of a randomized phase II study." *Multiple Sclerosis Journal* 25.9 (2019): 1255-1262.

Revision History:

Date	What changed	Pharmacist's initials
1/29/2021	I wrote the criteria.	JJ

CONFIDENTIAL

Ivosidenib (Tibsovo®)

250 mg tablet

EBRx PA Criteria

FDA-approved for:

- Treatment of adults with relapsed or refractory acute myeloid leukemia (AML) in adult patients with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an approved test SEE CRITERIA
- Adult patients with newly-diagnosed AML with IDH1 mutation who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy NOT COVERED data limited to single arm trial without demonstration of quality of life or overall survival improvement

Criteria for new users
1. Diagnosis of acute myeloid leukemia
2. Confirmed IDH1 mutation
2. Disease is refractory to or has relapsed after prior intensive chemotherapy
3. Ivosidenib will be used as single agent
If criteria met, approve for 12 months

Notes:

Dose=500 mg PO daily. Continue for a minimum of 6 months and then until disease progression or unacceptable toxicity occurs.

Trial	N	Outcome measures	Results
[1]Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML Phase I, MC, OL, **single arm**	N=258 for safety N=125 1° efficacy pop. (relapsed or refractory that received 500mg daily with at least 6mo of f/u)	• Clinical efficacy • OS • Remission duration • Time to remission *mutation cl =clearance of IDH1 mutations from the	Survival-median f/u=14.8mo **CR: 21.6%** Median OS 8.8mo [6.7-10.2] in 1°efficacy pop. N=125) Median OS in mutation cl 14.5mo [13.9-NE] (n=7) Median OS w/o cl =10.2 [9.0-12.5] (n=66) At 23.5 month f/u:

		bone marrow mononuclear cells= mutation can no longer be detected by PCR	median OS: 12.6 mo 12-mo OS: 51%[2]
[3]American Society of Hematology abstract (2020) **<u>Ivosidenib vs matched historical controls</u>** Prior intensive chemo plus one other regimen OR ≥1 prior non-intensive regimen if not a candidate for intensive chemo	• Ivosidenib arm: N=109 • Historical controls arm: n=60 • Matching/weighting method: Inverse probability of treatment weighting (IPTW)	Overall survival Complete response rate	Overall survival (median) • Ivo: 8.1 mo • Controls: 2.9 mo • HR 0.396 (95% CI: 0.279 to 0.562) 12-month overall survival • Ivo: 35% • Controls: 10.8% Complete response rate • Ivo: 18.3% • Controls: 7%

References:

1. DiNardo, Courtney D., et al. "Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML." N Engl J Med. 2018 Jun 21;378(25):2386-2398. PMID 29860938 NCT02074839
2. Roboz GJ et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. Blood. 2020 Feb 13;135(7):463-471. doi: 10.1182/blood.2019002140. PMID: 31841594
3. Paschka P et al. Ivosidenib Improves Overall Survival Relative to Standard Therapies in Relapsed or Refractory Mutant *IDH1* AML: Results from Matched Comparisons to Historical Controls. Blood (2020) 136 (Supplement 1): 18–19. https://doi.org/10.1182/blood-2020-136957.

Quantity Limits: 60/30

Revision History:

Date	What changed	Pharmacist's initials
03/10/2021	Criteria written	SK/HG (Student)

CONFIDENTIAL

Nitrofurantoin suspension

EBRx PA Criteria

FDA-approved for: Cystitis, acute uncomplicated, treatment; Cystitis, uncomplicated, prophylaxis for recurrent infection

Criteria for new users
1. The patient must be 7 years old or younger OR be unable to tolerate swallowing pills or capsules, to access the suspension.
2. The patient must have no other pills or capsules on their profile.

Revision History:

Date	What changed	Pharmacist's initials
3/9/2021	I wrote the criteria.	JJ

CONFIDENTIAL

Trilaciclib (Cosela)

300 mg IV solution for reconstitution

EBRx PA Criteria

FDA-approved for:

- To decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer SEE CRITERIA

Criteria for new users
1.Diagnosis of extensive stage small cell lung cancer
2. Patient will be treated with either a platinum/etoposide-containing regimen or topotecan-containing regimen
3. The patient is not a candidate for G-CSF (pegfilgrastim or filgrastim).
If criteria met, approve for 12 months
Note: per PI, GCSF is contraindicated in patients with history of hypersensitivity (serious allergic reaction) to pegfilgrastim, filgrastim, or any component of the formulation. Patients also may experience severe bone pain with GCSF which may prevent further use.

Notes:

Dose: 240 mg/m2 IV within 4 hours of each dose of chemotherapy (3 doses per cycle of platinum/etoposide regimens; 5 doses per cycle in topotecan regimens).

Compared to placebo, trilaciclib reduces duration of severe neutropenia. The following secondary endpoints were numerically improved (no stats given) in the trilaciclib group: use of GCSF, dose reduction of chemotherapy, incidence of febrile neutropenia, and hospitalization due to chemo-induced myelosuppression or sepsis. Some quality of life assessments were also improved. Trilaciclib does not appear to adversely affect overall survival or progression free survival.

Trilaciclib is given without GCSF/ESA in the first cycle of chemotherapy, but GCSF and/or erythropoietin stimulating agents (ESAs) may be used in addition to trilaciclib in subsequent cycles.

For prevention of neutropenia, GCSF has more robust data compared to trilaciclib, as GCSF has been shown to improve infection-related mortality as well as duration/incidence/severity of neutropenia, incidence of febrile neutropenia, and hospitalization. Therefore, GCSF will be preferred.

Quantity Limits: n/a (medical drug)

References:

1. Trilaciclib PI. https://www.g1therapeutics.com/cosela/pi/. Accessed 3/15/2021.
2. Daniel D et al. Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed extensive-stage small cell lung cancer: A multicentre, randomised, double-blind, placebo-controlled Phase II trial. Int J Cancer. 2020 Dec 21. doi: 10.1002/ijc.33453. Epub ahead of print. PMID: 33348420.
3. Hart LL et al. Myelopreservation with Trilaciclib in Patients Receiving Topotecan for Small Cell Lung Cancer: Results from a Randomized, Double-Blind, Placebo-Controlled Phase II Study. Adv Ther. 2021 Jan;38(1):350-365. doi: 10.1007/s12325-020-01538-0. Epub 2020 Oct 29. PMID: 33123968; PMCID: PMC7854399.
4. NCCN Guidelines Hematopoietic Growth Factors Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed 3/16/2021.

Revision History:

Date	What changed	Pharmacist's initials
03/18/2021	Criteria written	SK

Ponatinib (Iclusig®)

10, 15, 30, 45 mg tablets

EBRx PA Criteria

is FDA-approved for:

- Chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors. See criteria
- Accelerated phase (AP) or blast phase (BP) CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated Not covered
- T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL See criteria

Criteria for new users
1. Diagnosis of chronic phase chronic myelogenous leukemia (CML)
2. Failure of at least 2 BCR/ABL tyrosine kinase inhibitors OR T315I mutation positive
If criteria met, approve for 12 months

Notes:

Dose=45 mg once daily. Dose may be lowered to 15 mg once daily after disease control is obtained and reescallated if disease control is lost.

Ponatinib induces deep and durable responses in above patient population, and there may be an overall survival benefit compared to allogeneic transplant. The overall survival benefit has not been demonstrated in patients with accelerated phase or blast phase CML or Philadelphia chromosome positive acute lymphocytic leukemia.

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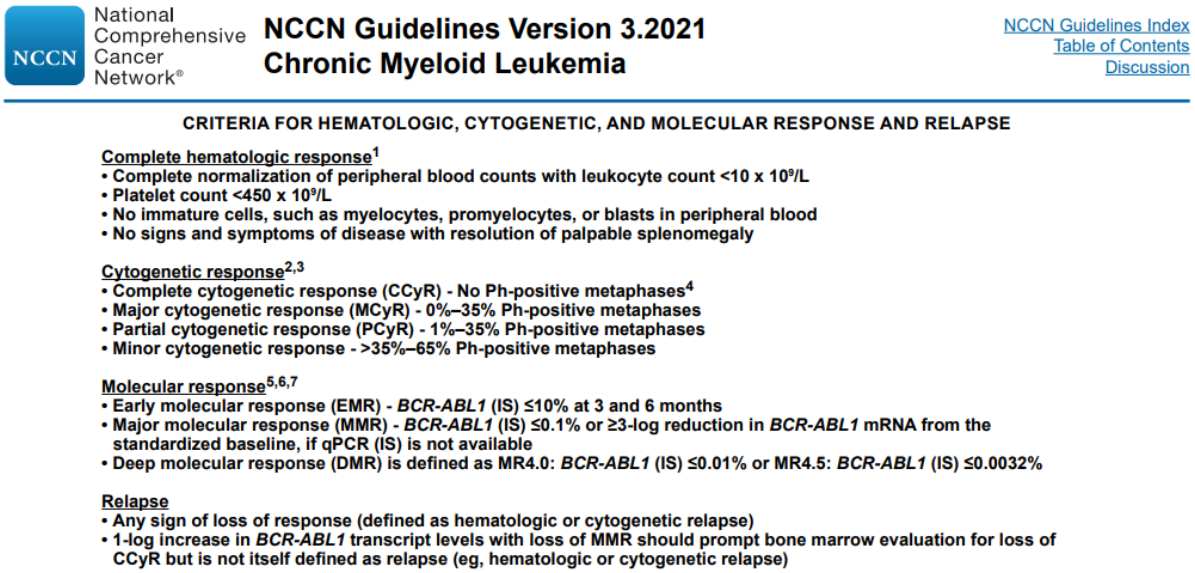
Trial	Population	Key Results	
OPTIC[1] NCT02467270 single-arm, dose optimization trial	Chronic phase CML resistant or resistant/intolerant to at least 2 prior kinase inhibitors or who have the T315I mutation N=93 27% with T315I mutation	Overall ≤1% BCR-ABL1^{IS} Rate at 12 months	42%
		Major cytogenetic response rate	49%
PACE[1,2] NCT01207440 single-arm, open-label, international, multicenter trial	CML or Ph+ ALL whose disease was considered to be resistant or intolerant to a prior kinase inhibitor All patients n=444 (29% with T315I mutation) CP-CML: n=267 AP-CML: n=83 BP-CML: n=62 PH+ ALL: n=32 <u>Median f/u</u> all patients: 37.3 mo (median duration of treatment: 16.7 mo) CP-CML patients: 56.8 mo (median duration of treatment: 32.1 mo)	CP-CML: MMR	40%
		CP-CML: Major cytogenetic response rate	60%
		CP-CML: % of responders remaining in MCyR at 5y	82%
		CP-CML: % of responders remaining in MMR at 5y	59%
		CP-CML: PFS at 5 y	53%
		CP-CML: OS at 5y	73%
		AP-CML: complete hematologic response rate	55%
		AP-CML: PFS at 5 yrs	22%
		AP-CML: OS at 5 yrs	49%
		BP-CML: complete hematologic response rate	21%
		BP-CML: median PFS	3.7 mo
		BP-CML: OS at 3 yrs	9%
		Ph+ ALL: complete hematologic response rate	34%
		Ph+ ALL: median PFS	3 mo
		Ph+ ALL: OS at 3 yrs	12%
Post hoc, retrospective, indirect comparison[3] Ponatinib versus allogeneic transplant	Included patients how received ponatinib in PACE trial and compared to patients who underwent allogeneic hematopoietic stem cell transplant as reported to the European Bone Marrow Transplant registry Stratified by CML disease phase and Ph+ ALL Adjusted for confounders Ponatinib group: n=128 Allo group: n=56	CP-CML: OS at 24 months (ponat vs. allo)	85% vs 61% *P* = 0.004
		CP-CML: OS at 48 months (ponat vs. allo)	73% vs 56% *P* = 0.013
		BP-CML: (ponat vs. allo)	HR, 2.29 [95% CI, 1.08- 4.82; *P* = .030]
		AP-CML and Ph+ ALL OS:	no difference
National observational study (French study)[4]	CML patients who had failed at least 2 lines of tyrosine kinase inhibitor therapy or one line if T315I mutation 2013-2014 compassionate program N=48 (all with CP CML) Median f/u: 26.5 mo	OS at 3 years:	80.5%
		Major molecular response rate (cumulative):	81.8%

CP-CML: chronic phase chronic myeloid leukemia

Response definitions:



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Chronic Myeloid Leukemia

NCCN Guidelines Index
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Discussion

CRITERIA FOR HEMATOLOGIC, CYTOGENETIC, AND MOLECULAR RESPONSE AND RELAPSE

Complete hematologic response[1]
- Complete normalization of peripheral blood counts with leukocyte count <10 x 10^9/L
- Platelet count <450 x 10^9/L
- No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood
- No signs and symptoms of disease with resolution of palpable splenomegaly

Cytogenetic response[2,3]
- Complete cytogenetic response (CCyR) - No Ph-positive metaphases[4]
- Major cytogenetic response (MCyR) - 0%–35% Ph-positive metaphases
- Partial cytogenetic response (PCyR) - 1%–35% Ph-positive metaphases
- Minor cytogenetic response - >35%–65% Ph-positive metaphases

Molecular response[5,6,7]
- Early molecular response (EMR) - *BCR-ABL1* (IS) ≤10% at 3 and 6 months
- Major molecular response (MMR) - *BCR-ABL1* (IS) ≤0.1% or ≥3-log reduction in *BCR-ABL1* mRNA from the standardized baseline, if qPCR (IS) is not available
- Deep molecular response (DMR) is defined as MR4.0: *BCR-ABL1* (IS) ≤0.01% or MR4.5: *BCR-ABL1* (IS) ≤0.0032%

Relapse
- Any sign of loss of response (defined as hematologic or cytogenetic relapse)
- 1-log increase in *BCR-ABL1* transcript levels with loss of MMR should prompt bone marrow evaluation for loss of CCyR but is not itself defined as relapse (eg, hematologic or cytogenetic relapse)

References:

1. Ponatinib PI. https://www.iclusig.com/pdf/ICLUSIG-Prescribing-Information.pdf. Accessed 3/17/2021.
2. Cortes JE et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood. 2018 Jul 26;132(4):393-404. doi: 10.1182/blood-2016-09-739086. Epub 2018 Mar 22. PMID: 29567798; PMCID: PMC6071555.
3. Nicolini FE et al. Overall survival with ponatinib versus allogeneic stem cell transplantation in Philadelphia chromosome-positive leukemias with the T315I mutation. Cancer. 2017 Aug 1;123(15):2875-2880. doi: 10.1002/cncr.30558. Epub 2017 Apr 7. PMID: 28387926; PMCID: PMC5573914.

Heiblig M et al. Ponatinib evaluation and safety in real-life chronic myelogenous leukemia patients failing more than two tyrosine kinase inhibitors: the PEARL observational study. Exp Hematol. 2018 Nov;67:41-48. doi: 10.1016/j.exphem.2018.08.006. Epub 2018 Sep 5. PMID: 30195076.

Quantity Limits: 1/1

Revision History:

Date	What changed	Pharmacist's initials
03/18/2021	Criteria written	SK

CONFIDENTIAL

Selinexor (Xpovio©)

20 mg, 40 mg, 50 mg, 60 mg tablets

EBRx PA Criteria

FDA-approved for:

- In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy NOT COVERED Benefit is limited to progression free survival.
    - References:
        - NCCN Multiple Myeloma Guidelines. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
        - Grosicki S et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet. 2020 Nov 14;396(10262):1563-1573. doi: 10.1016/S0140-6736(20)32292-3. PMID: 33189178.
- In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody SEE CRITERIA
- For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy. This indication is approved under ***accelerated approval*** based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s) NOT COVERED Data limited to single arm trial without overall survival or QOL benefit demonstrated.
    - Reference: Kalakonda N et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. Lancet Haematol. 2020 Jul;7(7):e511-e522. doi: 10.1016/S2352-3026(20)30120-4. PMID: 32589977.

Criteria for new users
1. Diagnosis of multiple myeloma
2. Patient has received at least four prior regimens
3. Disease is refractory* to the following: (a) **Two** proteasome inhibitors (e.g., bortezomib [Velcade], carfilzomib [Kyprolis], ixazomib [Ninlaro]) (b) **Two** immunomodulatory agents (e.g., lenalidomide [Revlimid], thalidomide [Thalomid], pomalidomide [Pomalyst]) (c) An anti-CD38 monoclonal antibody (e.g., daratumumab [Darzalex], isatuximab [Sarclisa])
4. Selinexor will be used in combination with dexamethasone
If all criteria met, approve for 12 months.

*Refractory disease is defined as ONE of the following:

- ≤ 25% response to therapy (e.g. ≤25% decrease in m-protein)
- Progression during therapy

- Progression within 60 days after completion of therapy.

Notes:

Selinexor dose: 80 mg PO twice weekly on days 1 and 3 (in combination with dexamethasone). Continue until disease progression or unacceptable toxicity. Dose reductions are common.

Selinexor+dexamethasone has not been directly compared to another agent and exhibited a low response rates in the STORM2 trial (~25%). However, two formal indirect comparisons have demonstrated an improvement in overall survival compared to usual care.

STORM trial (single arm trial)[1]

-response rate: 25.3%

-median overall survival: 8.6 mo

-dose reduction required: 53%

STORM trial versus MAMMOTH data (formal indirect comparison)[2,3]

-Selinexor median overall survival: 10.4 mo

-Usual care median overall survival: 6.9 mo

Adjusted HR 0.55, 95% CI 0.36-0.84

STORM trial versus Flatiron database (formal indirect comparison)[4]

-Selinexor median overall survival: 10.4 mo

-Usual care median overall survival: 5.2 mo

Adjusted HR 0.49, p=0.0241

References:

1. Chari A et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. N Engl J Med. 2019 Aug 22;381(8):727-738. doi: 10.1056/NEJMoa1903455. PMID: 31433920.
2. LJ Costa et al. https://ashpublications.org/blood/article/134/Supplement_1/3125/423837/Overall-Survival-of-Triple-Class-Refractory-Penta. Accessed 11/18/19 [mammoth]
3. Cornell R et al. Overall survival of patients with triple-class refractory multiple myeloma treated with selinexor plus dexamethasone vs standard of care in MAMMOTH. Am J Hematol. 2021 Jan;96(1):E5-E8. doi: 10.1002/ajh.26010. Epub 2020 Oct 21. PMID: 32974944.
4. Richardson PG, Jagannath S, Chari A, et al. Overall survival (OS) with oral selinexor plus low dose dexamethasone (Sd) in patients with triple class refractory multiple myeloma (TCR-MM). J Clin Oncol. 2019; 37(suppl):8014. https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.8014. Accessed 11/18/19. [Flatiron]

Quantity Limits: 28 day supply

Revision History:

Date	What changed	Pharmacist's initials
5/21/2021	Criteria written	sk

Belumosudil (Rezurock®)

200 mg Tablet

EBRx PA Criteria

FDA-approved for:

Treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.\

Criteria for new users
1. Diagnosis of chronic graft versus host disease (cGVHD)
2. Patient has been treated with at least two prior lines of systemic therapy with persistent manifestations of cGVHD
3. Patient's age is 12 years or older
Approve for 12 months if all criteria met.

Dose: 200 mg PO once daily. Treatment continues until progression of GVHD or unacceptable toxicity.

References:

4. Cutler, Corey, et al. "Belumosudil for Chronic Graft-versus-Host Disease (cGVHD) After 2 or More Prior Lines of Therapy: The ROCKstar Study." Blood (2021).
5. NIH response criteria for cGVHD: https://www.sciencedirect.com/science/article/pii/S108387911500155X
6. Rezurock PI: https://www.rezurock.com/full-prescribing-information.pdf

Quantity Limits: 1/1

Revision History:

Date	What changed	Pharmacist's initials
9/21/21	Criteria written	SK

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