



Evidence-Based Prescription Drug Program  
UAMS College of Pharmacy  
Medical Benefit Medication Prior Authorization Criteria for  
**The Employee Benefits Division (EBD)**  
**of the State of Arkansas**

*Revised January 2024*

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Interferon gamma-1b (Actimmune)—Medical Benefit Drug or can be self-administered  
EBRx PA Criteria

**is FDA-approved for:**

- Chronic granulomatous disease, to reduce the frequency and severity of serious infections associated it.
- Malignant osteopetrosis (severe), to delay time to disease progression in patients with severe, malignant osteopetrosis.

**Criteria for new users**

1. The patient must have the diagnosis chronic granulomatous disease OR severe malignant osteopetrosis.

If approved, the PA is good for 12 months.

**Note:**

- For chronic granulomatous disease, interferon gamma1b may be used SC TIW prophylactically, especially for those who have had more severe recurrent infections. Maximum dose is 50mcg/m<sup>2</sup> administered 3 times per week. For pediatric patients the dosing is:  
BSA  $\leq 0.5\text{m}^2$ : 1.5mcg/kg/dose TIW, max of 50mcg/m<sup>2</sup>  
BSA  $>0.5\text{m}^2$ : 50mcg/m<sup>2</sup> (1 million units/m<sup>2</sup>) TIW, max 50mcg/m<sup>2</sup>
- For malignant osteopetrosis, the dose is 50mcg/m<sup>2</sup> SC TIW, max 50mcg/m<sup>2</sup>

**References:**

1. UpToDate. Malignant osteopetrosis. 1/31/24.
2. UpToDate. Chronic granulomatous disease. 1/31/24.
3. LexiComp. Interferon gamma 1b. 1/31/24.

**Revision History:**

Date	What changed	Pharmacist's initials
1/31/24	I wrote the criteria consistent with the FDA label.	JJ

EBRx PA Criteria  
Erenumab (Aimovig) 70 mg autoinjectors (pkg size 1 or 2 autoinjectors)

**is FDA-approved to:** preventive tx of migraine in adults (both chronic and episodic)

Criteria for access:	
1.	Patient must be 18 years old or older.
2.	Patient must have received the diagnosis of migraine onset before age 50.
3.	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.
4.	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).
5.	The prescriber must be a neurologist or headache specialist or be working with one regarding the prescribing for this patient.
6.	If criteria are fulfilled. Approve erenumab 70 mg once monthly. <b>In order for 140 mg/month approval, pt must have had inadequate response to 3 months of claims for the 70 mg/mo dose.</b>
<ul style="list-style-type: none"> <li>If the above criteria are satisfied, the PA is good for 3 months.</li> <li>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.</li> </ul>	
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 than placebo. Banzi, Rita, et al. "Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of migraine in adults." <i>Cochrane Database of Systematic Reviews</i> 2015.4 (2015): 1-56.	JJ
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." <i>Cochrane Database Syst Rev</i> 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." <i>Cochrane Database Syst Rev</i> 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." <i>Cochrane Database Syst Rev</i> 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	Applied criteria to UAS Plan.	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 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.	JJ

Ref:

- Erenumab package insert. Accessed 6/25/18
- Katsarava, Zaza, et al. "Defining the differences between episodic migraine and chronic migraine." *Current pain and headache reports* 16.1 (2012): 86-92.
- Goadsby, Peter J., et al. "A controlled trial of erenumab for episodic migraine." *New England Journal of Medicine* 377.22 (2017): 2123-2132.
- 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.
- ICER evidence report accessed 6/12/18.

Rilonacept (Arcalyst)  
EBRx PA Criteria

**is FDA-approved for:**

- Cryopyrin-associated periodic syndromes, including familial cold autoinflammatory syndrome and Muckle-Wells syndrome in adults and pediatric patients  $\geq 12$ y old.
- Deficiency of interleukin-1 receptor antagonist: maintenance of remission of deficiency of IL-1 receptor antagonist in adults and pediatric patients weighing  $\geq 10$ kg.
- Recurrent pericarditis, to reduce risk of recurrence in adults and pediatric patients  $\geq 12$ y old.

**Criteria for new users; CRYOPYRIN-ASSOCIATED PERIODIC SYNDROME**

1. The patient must have the diagnosis of cryopyrin-associated periodic syndrome, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle Wells Syndrome (MWS)

2. The patient must be the appropriate age according to the FDA label. (age 12y+)

3. The patient must not be on concomitant TNF-alpha antagonists.

4. The patient has been educated to avoid getting live vaccines while on rilonacept.

If approved, the PA will be for 12 months.

**Notes:**

Adults: LD=320mg delivered as two, 2 mL, SC injections of 160mg each; MD=160mg (2mL) injection once weekly.

Peds age 12-17y: Loading dose: 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Maintenance dose: 2.2 mg/kg, up to a maximum of 160mg, administered as a single subcutaneous injection up to 2 mL once weekly.

**Criteria for new users; DEFICIENCY OF IL-1 RECEPTOR ANTAGONIST (DIRA)**

1. The patient must have the diagnosis of deficiency of IL-1 receptor antagonist.

2. The patient must weigh 10kg or more when all the following criteria are met:

Confirmed through IL1RN mutations; AND

Is in remission from previous anakinra (Kineret) treatment.

If approved, the PA will be for 12 months.

**Notes: Adults and pediatric patients weighing 10 kg or more:**

4.4 mg/kg up to a maximum of 320 mg, delivered as 1 or 2 injections (2mL/injection) once weekly.

**Criteria for new users; RECURRENT PERICARDITIS**

1. The patient must have the diagnosis of recurrent pericarditis.

2. The patient must be age 12y+ when all the following are met:

Has additional pericarditis episodes following a symptom-free period of 4-6 weeks or longer, AND

Has failed therapy with colchicine and non-steroidal anti-inflammatory drugs (NSAIDs).

If approved, the PA will be for 12 months.

**Note: Initial dose must be injected under the supervision of a health care professional.**

**Revision History:**

Date	What changed	Pharmacist's initials
4/2/21	I wrote the criteria for UAS.	JJ
5/23/22	I updated the criteria for UAS and put it on the EBD server as well. EBD still needs to vote on whether or not they will cover it.	JJ

Avelumab (Bavencio)  
200 mg/10 ml solution  
EBRx PA Criteria

**FDA-approved for:**

**Merkel Cell Carcinoma (MCC)<sup>1</sup>**

- 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.

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 criteria for axitinib + pembrolizumab).

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

<sup>1</sup>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
9/29/2022	Removed references to pembrolizumab criteria (EBRx no longer manages pembrolizumab)	SK

## Belimumab (Benlysta)

### EBRx PA Criteria

#### is 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

Belantamab mafodotin-blmf (Blenrep)  
100 mg single dose vial for reconstitution  
EBRx PA Criteria

**NOTE: The manufacturer of Blenrep is withdrawing FDA approval due to negative phase 3 data. New users will not be allowed to enroll in the REMS program and no PA requests for new users should be approved.**

**is 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)<sup>1,2</sup>

-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)<sup>3,4</sup>

-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. U Costa et al. [https://ashpublications.org/blood/article/134/Supplement\\_1/3125/423837/Overall-Survival-of-Triple-Class-Refractory-Penta](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
8/30/2022	Criteria reviewed. No change	SK
11/22/2022	Added note about withdrawal of FDA approval	SK

## 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 (e.g. conversion of MRD status from positive to negative). Although MRD negativity is associated with a better prognosis, the long term efficacy of blinatumomab in this setting has not been established.
    - 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).

#### Note:

##### 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%).<sup>1</sup> Health-related quality of life was also improved in the blinatumomab group.<sup>2</sup>

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.<sup>3</sup>

##### 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
1/18/2023	Criteria reviewed. No change	SK

**OnabotulinumtoxinA (Botox)—Only the urinary incontinence indication is covered by EBD plans (only non-cosmetic uses)**  
**EBRx PA Criteria**

**Urinary incontinence indication:**

1. The patient must have the diagnosis of urinary incontinence. OR

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

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

**Notes:**

**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. **Benztrapine 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).

**Cervical dystonia: 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.

**Hyperhidrosis:**

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	Pharmacist
2/9/2011	Document Created	CK
7/17/12	Added migraine criteria; specified infantile esotropia as indication and requirement for 2 w of eye patching previous to botulinum	JJ
7/31/12	Added medication overuse reference, definition, hyperlink; placed article/reference in the EBRx file on the network.	JJ
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.	AM/JJ

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 for EBD plans. 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.	JJ
4/1/21	Applied Ebrx criteria to UAS Plan. They cover Myobloc and Botox (non-cosmetic).	JJ
1/10/24	I reformatted the botulinum toxin criteria, separating the agents and putting them on the server as separate drugs. Of note, the EBD subplans cover Xeomin; will cover Botox for urinary incontinence. UAS covers Myobloc and Botox.	JJ

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:**

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

Aztreonam inhaled (Cayston)  
EBRx PA Criteria

**is FDA-approved for:** 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	What changed?	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. Applied to UAS plan.	JJ

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-reduction 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/kg 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 therapy 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	Applied EBRx criteria to UAS Plan.	JJ

EBRx PA Criteria  
Coagulation Factor X, Human (Coagadex)

**is FDA-approved for:** hereditary Factor X deficiency in age  $\geq 12$  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.<sup>1</sup>
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.

<sup>1</sup>**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](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.	JJohnson

Burosumab-twza (Crysvita) SC injection  
10, 20, 30mg/mL (1mL)  
EBRx PA Criteria

**is FDA-approved for:**

- Osteomalacia, tumor-induced: Treatment of fibroblast growth factor 23 (FGF23)-related hypophosphatemia in tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in pediatric patients  $\geq 2y$  and in adults.
- treating adults and children ages 6m+ 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  $\leq 2.8$ mg/dL (or a level below the lower level of normal for reference)
3. A standing height below the 50<sup>th</sup> 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).

**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
1/8/24	I updated the uses (FDA-approvals) to include osteomalacia. The age for treating x-linked hypophosphatemia was reduced to 6 months of age.	JJ

Daratumumab (Darzalex)  
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 (SEE NEWLY-DIAGNOSED CRITERIA) and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy (SEE RELAPSED/REFRACTORY CRITERIA)
- 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)
- 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)
- 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 a statistically significant overall survival or quality of life benefit has not been demonstrated to date
  - References:
  - 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.
  - David Siegel et al. (2021) Health-related quality of life outcomes from the CANDOR study in patients with relapsed or refractory multiple myeloma, *Leukemia & Lymphoma*, 62:12, 3002-3010, DOI: [10.1080/10428194.2021.1941927](https://doi.org/10.1080/10428194.2021.1941927)
  - Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes from a randomised, multicentre, open-label, phase 3 study. *Lancet Oncol.* 2022;23(1):65-76. doi:10.1016/S1470-2045(21)00579-9
  - Usmani SZ et al. Final analysis of carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone in the CANDOR study. *Blood Adv.* 2023 Jul 25;7(14):3739-3748. doi: 10.1182/bloodadvances.2023010026. PMID: 37163358; PMCID: PMC10368773.
- 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) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent (SEE RELAPSED/REFRACTORY CRITERIA)
- In combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy including lenalidomide and a proteasome inhibitor (NOT COVERED). Benefit is limited to progression free survival at this time.

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](#))
- Bahlis NJ et al. Pomalidomide, dexamethasone, and daratumumab immediately after lenalidomide-based treatment in patients with multiple myeloma: updated efficacy, safety, and health-related quality of life results from the phase 2 MM-014 trial. *Leuk Lymphoma.* 2022 Jun;63(6):1407-1417. doi: 10.1080/10428194.2022.2030477. Epub 2022 Feb 8. PMID: 35133221.

**Darzalex Faspro is also FDA-approved for:**

- light chain (AL) amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone in newly diagnosed patients. (accelerated approval). Limitation of use: DARZALEX FASPRO is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials
  - NOT COVERED due to lack of improvement in overall survival or quality of life. There is some evidence of benefit in delaying organ deterioration but endpoints are largely based on surrogate markers.
  - Reference:
    - Kastritis E et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. N Engl J Med. 2021 Jul 1;385(1):46-58. doi: 10.1056/NEJMoa2028631. PMID: 34192431. (NCT03201965)

#### Criteria for new users (NEWLY DIAGNOSED)

1. Must have a diagnosis of multiple myeloma with no prior systemic therapy

2. 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).

3. 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) **OR** lenalidomide and dexamethasone (D-RD).

Approve x 8 months if criteria 1 and 2 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)

Weeks	Schedule
Weeks 1 to 6	Weekly (total of 6 doses)
Weeks 7-54	Every 3 weeks (total of 16 doses)
Weeks 55 and beyond (Until progression of disease)	Every 4 weeks

##### Daratumumab schedule for D-RD regimen (transplant ineligible)

Weeks	Schedule
Weeks 1 to 8	Weekly (total of 8 doses)
Weeks 9-24	Every 2 weeks (total of 8 doses)
Weeks 25 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.<sup>1</sup> Daratumumab maintenance therapy after consolidation is not FDA approved and is only associated with an improvement in PFS in patients who did not receive daratumumab during induction therapy.<sup>2</sup> Improvements in Quality of life were reported.<sup>3</sup>
- 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).<sup>4,5</sup> At 36 months, the rate of overall survival was 78% in the daratumumab group and 68% in the control group. Median was not reached in either group.
- In newly-diagnosed, transplant ineligible patients, daratumumab/lenalidomide/dexamethasone (**D-RD**) improved overall survival compared to Rd (HR 0.68 95% CI 0.53-0.86; p=0.0013).<sup>6,7</sup> At 60 months, the rate of overall survival was 66% in the daratumumab group and 53% in the control group. Median was not reached in either group.

**References:**

**D-VTD:**

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. Moreau P et al. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021 Oct;22(10):1378-1390. doi: 10.1016/S1470-2045(21)00428-9. Epub 2021 Sep 13. PMID: 34529931.
3. Roussel M et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab for transplantation-eligible patients with newly diagnosed multiple myeloma (CASSIOPEIA): health-related quality of life outcomes of a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2020 Dec;7(12):e874-e883. doi: 10.1016/S2352-3026(20)30356-2. PMID: 33242444.

**D-VMP:**

4. 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
5. Mateos MV et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *NEJM*. 2018;378(6):518-528. PMID 29231133 NCT02195479

**D-RD:**

6. 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
7. Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(11):1582-1596. doi:10.1016/S1470-2045(21)00466-6

**Criteria for new users (RELAPSED/REFRACTORY)**

1. Must have a diagnosis of multiple myeloma that is progressing
  2. If daratumumab will 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
  3. 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 criterion 1 and either 2 or 3 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.<sup>1</sup>

- 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.<sup>2,3</sup>
- Daratumumab monotherapy was found have improved overall survival compared to pomalidomide/dexamethasone in a matched adjusted indirect comparison analysis.<sup>4</sup>

#### 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
6/27/2022	Minor formatting change. No change to criteria.	SK
8/30/2022	Criteria reviewed. Add DRD to covered criteria for transplant ineligible patients.	SK
10/20/23	Criteria reviewed. Added a few references but no change in criteria.	SK

EBRx PA Criteria  
Dupilimab (Dupixent) SC injection

**is FDA-approved for:**

- atopic dermatitis, moderate-severe, in patients  $\geq 6$  months of age whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
- Asthma, moderate-severe, as add-on maintenance treatment in adults and pediatric patients  $\geq 12$  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
- Eosinophilic esophagitis, in patients age 12y+ and weighing 40kg+.
- Prurigo nodularis in adults

**MODERATE TO SEVERE ATOPIC DERMATITIS**

**Criteria for new users**

1. Patient must be  $\geq 6$  months 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); pediatric dosing is 200 or 300mg SC q4w depending on weight.

References:

1. Simpson, Eric L., et al. "Two phase 3 trials of Dupilumab versus placebo in atopic dermatitis." *NEJM* 375.24 (2016): 2335-2348.
2. Lexicomp. Dupilumab. Accessed 7/1/22.

**MODERATE TO SEVERE ASTHMA, AS ADD-ON MAINTENANCE TREATMENT**

**Criteria for new users**

1. Patient must be  $\geq 12$  years old
  2. Patient must currently have on their profile:
    - an inhaled corticosteroid (medium-high-dose, fluticasone propionate at a total daily dose of  $\geq 500$ ug 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  $\geq 50\%$  of the year)
3. The patient must have a blood eosinophil count of  $>150$  cells/mm<sup>3</sup> 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.
<b>Criteria for continuation</b>
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.
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 $\geq 18$ years old
2. Patient must have the diagnosis of bilateral nasal polyposis and chronic symptoms of sinusitis despite intranasal corticosteroid 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.
<b>Criteria for continuation</b>
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.

## **EOSINOPHILIC ESOPHAGITIS (EOE)**

### **Criteria for new users**

1. Patient must be $\geq 12$ years old
2. Patient must have the diagnosis of eosinophilic esophagitis.
3. Prescriber must be an allergist, immunologist, or pulmonologist.
4. The patient is not currently being treated with omalizumab, mepolizumab, reslizumab, or benralizumab.
5. The diagnosis should be diagnosed by an eosinophil-predominant inflammation on esophageal biopsy (physician attestation is acceptable).
6. The patient must have received at least 8 weeks of a PPI.
7. The patient must have received a topical corticosteroid for at least 4 weeks (fluticasone or budesonide, inhaled and swallowed or as a viscous slurry)
Note: The dose is 300mg SC once weekly. PA is good for 16 weeks; assessment of efficacy should occur then.
<b>Criteria for continuation</b>
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.

#### References:

1. UpToDate. Eosinophilic Esophagitis. Accessed 8/29/22.

<b><u>Prurigo nodularis</u></b>
<b><u>Criteria for new users</u></b>
1. Patient must be $\geq 18$ years old
2. Patient must have the diagnosis of prurigo nodularis.
3. Prescriber must be an allergist or immunologist.
4. The patient is not currently being treated with omalizumab, mepolizumab, reslizumab, or benralizumab.
5. The patient must have tried 10 weeks of 3 times weekly narrowband ultraviolet B phototherapy (NBUVB) in combination with topical corticosteroids. If NBUVB is not available, then the patient must have tried 10 weeks Psoralen plus ultraviolet A (PUVA) photochemotherapy.
Note: The dose is 2-300mg (600mg total), followed by 300mg every other week. PA is good for 16 weeks; assessment of efficacy should occur then.
<b><u>Criteria for continuation</u></b>
1. Patient must be adherent to the every other week 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.

#### References:

1. Yosipovitch, Gil, et al. "Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials." *Nature medicine* (2023): 1-11.

#### Revision History:

Date	What changed	PharmD
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 asthma was not included despite the FDA approval due to the evidence not showing as big an advantage.	JJ
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: <ul style="list-style-type: none"> <li>• treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once</li> <li>• Hospitalization or emergency medical care visit for worsening asthma</li> </ul>	JJ
7/2021	I changed the eosinophil count to $>150$ for Mod-sev asthma per Castro, et al. Also added the 2021 GINA Asthma update.	JJ
7/1/22	Edited age to include new FDA-approved use for AD in peds patients.	JJ
8/29/22	I added eosinophilic esophagitis criteria since dupilumab recently received the new indication.	JJ
8/30/23	I added prurigo nodularis criteria since dupilumab recently received the new indication.	JJ

**Galcanezumab (Emgality) 120 mg autoinjector or prefilled syringe (carton of 1 or 2 prefilled pen or syringe)**  
**EBRx PA Criteria**

**is FDA-approved to:**

- preventive tx of migraine in adults (both chronic and episodic)
- Cluster headache prevention in adults

**Initial Criteria: MIGRAINE prophylaxis:**

7. Patient must be 18 years old or older.
8. Patient must have received diagnosis of migraine onset before age 50.
9. 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.
10. 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).
11. The prescriber must be a neurologist or headache specialist or be working with one regarding the prescribing for this patient.
12. If criteria 1 through 6 are fulfilled, approve galcanezumab 240mg once as a single loading dose, then 120mg once monthly.
  - 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 for Migraine prophylaxis:**

1. To continue access to galcanezumab, 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 galcanezumab fills in the previous 6 months (since it is prophylactic) and less consumption of rescue medication as evidenced by fewer triptan fills than before galcanezumab was accessed by the patient.

Dose: 240mg as a single loading dose, then 120mg once monthly.

**CLUSTER HEADACHE prophylaxis:**

1. The patient must have the diagnosis of cluster headache (approximately 1 headache every other day, at least 4 total attacks, and no more than 8 attacks per day during 7 consecutive days; the cluster headache period must have lasted at least 6 weeks)
- If the criteria for cluster headache are satisfied, approve for 12 months.
- Note: Dosing for cluster HA is 300mg SC at onset and then QM until the end of the cluster period.

**Revision History:**

Date	What changed	Pharmacist's initials
1/17/19	I wrote the criteria.	JJ
4/9/21	I added the cluster headache indication, defined the diagnosis per the clinical trial.	JJ
10/12/21	I updated the criteria. 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 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.	JJ

**Ref:**

6. Emgality package insert. Accessed 1/17/19.
7. Katsarava, Zaza, et al. "Defining the differences between episodic migraine and chronic migraine." *Current pain and headache reports* 16.1 (2012): 86-92.
8. ICER evidence report accessed 6/12/18.
9. Camporeale, Angelo, et al. "A phase 3, long-term, open-label safety study of Galcanezumab in patients w/migraine." *BMC neurology* 18.1 (2018): 188.
10. Goadsby, Peter J., et al. "Trial of galcanezumab in prevention of episodic cluster headache." *New England Journal of Medicine* 381.2 (2019): 132-141.

## Satralizumab (Enspryng)

### EBRx PA Criteria

**is FDA-approved for:** treatment of neuromyelitis optica spectrum disorder (NMOSD) in adults who are anti-aquaporin-4 (AQP4) antibody positive.

#### Criteria for new users

1. The patient must have the diagnosis of neuromyelitis optica spectrum disorder and be anti-aquaporin-4 antibody positive with at least 1 relapse in the previous 2 years before starting satralizumab.
2. No concurrent eculizumab (medical), inebilizumab (medical), or rituximab (medical).

**Note:** The dose is SC 120mg day 1, then 120mg 2w later, then 120mg 2w later, then 120mg q4w.

#### References:

1. UpToDate. NMOSD. Accessed 9/9/2020.
2. Cree, Bruce AC, et al. "Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOMentum): a double-blind, randomised placebo-controlled phase 2/3 trial." *The Lancet* 394.10206 (2019): 1352-1363.
3. Traboulsee, Anthony, et al. "Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial." *The Lancet Neurology* 19.5 (2020): 402-412.
4. Yamamura, Takashi, et al. "Trial of satralizumab in neuromyelitis optica spectrum disorder." *New England Journal of Medicine* 381.22 (2019): 2114-2124.
5. 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.
6. Pittock, Sean J., et al. "Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder." *New England Journal of Medicine* 381.7 (2019): 614-625.

#### Revision History:

Date	What changed	Pharmacist's initials
6/23/21	I wrote the criteria. This was approved by EBRx 10/2020.	JJ

Vedolizumab (Entyvio) 300mg for IVP or bolus  
EBRx PA Criteria

**is FDA-approved for:**

- Crohn's disease in adults [Note: moderate-severe Crohn's is covered; mild is not covered and can be managed with less costly therapy]
- Ulcerative colitis in adults

**Crohn's Disease indication**

**Criteria for new users**

The patient must have the diagnosis of active, moderate to severe Crohn's disease.

The patient must be age 18y+.

The patient must have 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)

The patient must have tried and failed combination TNF inhibitor + immunomodulator (eg, azathioprine, 6-mercaptopurine, or methotrexate)

The patient should not be on combination biologic drugs.

**Ulcerative Colitis indication**

**Criteria for new users**

The patient must have the diagnosis of moderate to severe ulcerative colitis.

The patient must be age 18y+.

The patient must not be taking concurrent combination biologic drugs.

Note: Vedolizumab may be used for induction of remission in UC as initial therapy.

**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.
3. UpToDate. Management of moderate to severe UC in adults.

**Revision History:**

Date	What changed	Pharmacist's initials
7/22/14	Created criteria	GBB
10/30/14	A 2 <sup>nd</sup> reference was added regarding CD. NO changes in PA criteria	JJ
8/31/23	I revised the criteria. This may be a medically administered drug.	JJ

Pralatrexate (Folotyn®)  
20mg/mL (1mL); 40mg/2mL (2mL), for IV push  
EBRx PA Criteria—for Medical use only

**is 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<sup>2</sup>/week for 6 weeks followed by 1 week of rest. Then the cycle is repeated until progressive disease or unacceptable toxicity. B<sub>12</sub> 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
8/31/2021	Criteria reviewed. No changes.	SK
8/29/2023	Criteria reviewed. No changes.	SK

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 demonstrated for overall survival or quality of life yet.
  - Reference: Hiddemann W et al. Immunotherapy 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

**Other indications:**

Obinutuzumab is also FDA approved in combination with venetoclax OR acalabrutinib for patients with untreated CLL/SLL. This indication is listed in the venetoclax and acalabrutinib package inserts and not in the obinutuzumab package insert SEE CRITERIA.

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
<b>If the above criteria are met, approve coverage for 6 months.</b> 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 was delayed, and the schedule adjusted accordingly, a PA may be extended to account for that and allow the entire 6 cycles to be administered.
<b>Dosing:</b> Dosing is limited to 6 28-day 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.
<b>Evidence:</b> 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

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) in combination with VENETOCLAX or ACALABRUTINIB (first line)
1. The patient must have previously <b>untreated</b> CLL.
2. The patient must be planning to use concomitant venetoclax or acalabrutinib.

**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 was 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 limited to **SIX** 28-day 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:**

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 (5-yr rate of PFS 63% vs 27%). At a median follow up of 65 mo, the 5-yr overall survival difference did not reach significance (HR, 0.72; 95% CI, 0.48-1.09; P = 12). At 5 years, 72% of patients in the ventoclax arm had not started new treatment compared with 43% in the control arm.

The approval for first-line use of acalabrutinib in combination with obinutuzumab was based on the ELEVATE-TN study which compared acalabrutinib +/- obinutuzumab to chlorambucil + obinutuzumab. Acala+Obi improved overall survival compared to the Chlor+Obi group (HR 0.55). No difference in overall survival has been demonstrated to date between the acalabrutinib and the Chlor+Obi group.

Venetoclax + obinutuzumab 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.
- European Hematology Association Abstract: <https://library.ehaweb.org/eha/2022/eha2022-congress/357012/othman.al-sawaf.venetoclaxobinutuzumab.for.previously.untreated.chronic.html?listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Ds148>. Accessed 9/23/2022

Acalabrutinib + obinutuzumab references:

- Sharman JP et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naïve 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.
- Sharman JP et al. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Five-year follow-up of ELEVATE-TN. DOI: 10.1200/JCO.2022.40.16\_suppl.7539 Journal of Clinical Oncology 40, no. 16\_suppl (June 01, 2022) 7539-7539. [https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16\\_suppl.7539](https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.7539)

**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 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/m<sup>2</sup>/day IV on days 1 & 2.

Cycles 2-6: 1000mg IV obinutuzumab on day 1 every 28 days for 5 doses PLUS bendamustine 90mg/m<sup>2</sup>/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
10/21/2022	Added coverage of obinutuzumab+venetoclax for first line treatment of CLL per 10/20/2022 P&T meeting	SK
2/16/2023	Added coverage of obinutuzumab+acalabrutinib for first line treatment of CLL per 10/20/2022 P&T meeting	SK
3/23/2023	Criteria reviewed. For follicular lymphoma indication, omit lab and life expectancy criteria. Form updated.	SK

**Fingolimod (Gilenya®) 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. Pl. 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	What changed?	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. Ran a test claim and EBD's MedAccess said it wasn't covered. Emailed Micah. Waiting on response.	JJ
3/31/2021	Applied EBRx criteria to UAS Plan	JJ

Recombinant Human Growth Hormone (Norditropin)  
EBRx PA Criteria

Gray indicates it is NOT COVERED.

**Norditropin--EBD, Genotropin, Nutropin, Humatrope, Omnitrope--UAS, Serostim, Saizen, Tev-Tropin, Zorbitive**

Indication	Drug
<b>Pediatric: Growth failure due to inadequate endogenous growth hormone (GH) secretion</b> <ul style="list-style-type: none"> <li><input type="checkbox"/> age &lt; 18</li> <li><input type="checkbox"/> short stature (height less than -2.25 SD for age based on sex specific standards)</li> <li><input type="checkbox"/> must confirm GH deficiency with provocative GH stimulation test</li> <li><input type="checkbox"/> must have open epiphyses (confirm with x-ray of a long bone)</li> </ul> <b>Approve if patient meets above criteria</b> *If pt is >18 yrs, please see adult criteria below	<input type="checkbox"/> Norditropin--EBD <input type="checkbox"/> Genotropin <input type="checkbox"/> Humatrope <input type="checkbox"/> Nutropin <input type="checkbox"/> Omnitrope--UAS <input type="checkbox"/> Saizen <input type="checkbox"/> Tev-Tropin
<b>Pediatric: Short stature associated with Turner syndrome</b> <i>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</i>	<input type="checkbox"/> Genotropin <input type="checkbox"/> Humatrope <input type="checkbox"/> Norditropin <input type="checkbox"/> Nutropin <input type="checkbox"/> Omnitrope
<b>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)</b> <i>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.</i>	<input type="checkbox"/> Genotropin (a) <input type="checkbox"/> Humatrope (b) <input type="checkbox"/> Norditropin (b) <input type="checkbox"/> Omnitrope (a)
<b>Pediatric: Idiopathic Short Stature (ISS)</b> <i>Not a covered benefit. These children are not GHD and when health related quality of life was studied, no significant improvement was found in GH treated children, nor was there any evidence that GH treatment impacts psychological adaptation or self-perception. Results suggest that short-term height gains can range from none to approximately 0.7 SD over one year.</i>	<input type="checkbox"/> Genotropin <input type="checkbox"/> Humatrope <input type="checkbox"/> Nutropin <input type="checkbox"/> Omnitrope
<b>Pediatric: Growth failure due to chronic renal insufficiency up to time of renal transplant</b> <i>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.</i>	<input type="checkbox"/> Nutropin
<b>Pediatric: Growth failure due to Prader Willi syndrome</b> <ul style="list-style-type: none"> <li><input type="checkbox"/> Open epiphyses               <ul style="list-style-type: none"> <li>○ Confirm with x-ray of long bone upon initiation of therapy</li> <li>○ If 18-25 yrs, must have yearly x-ray to verify open epiphyses as epiphyses usually close around this time</li> </ul> </li> <li><input type="checkbox"/> Diagnosis of Prader Willi syndrome from DNA testing</li> <li><input type="checkbox"/> must NOT have h/o severe respiratory impairment or upper airway obstruction</li> <li><input type="checkbox"/> must NOT have sleep apnea</li> <li><input type="checkbox"/> must Not be severely obese (&gt;225% IBW)</li> </ul> Initial Approval: 1 year Reauthorization: Pt must continue to meet above criteria	<input type="checkbox"/> Genotropin <input type="checkbox"/> Omnitrope--UAS

<b>Pediatric: Short stature or growth failure associated with short stature homeobox gene (SHOX) deficiency</b>  <i>Not a covered benefit. While RCT have shown significant increase in height over 2 years with GH treatment vs placebo<sup>7</sup>, there are no good studies demonstrating if normal adult height is achieved.</i>	<input type="checkbox"/> Humatrope
<b>Pediatric: Short stature associated with Noonan syndrome</b> 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	<input type="checkbox"/> Norditropin
<b>Adult: GH deficiency of either childhood or adult onset etiology</b>  <b>Childhood etiology</b> 1. <u>Open epiphyses</u> (usually close between 18-25 yrs) <ul style="list-style-type: none"> <li>Confirmed GH deficiency</li> <li>X-ray of long bone shows open epiphyses (pts must have yearly x-ray to confirm epiphyses still open during this time)</li> </ul> Initial Approval: 1 year Reauthorization: must continue to provide evidence of open epiphyses 2. <u>Closed epiphyses</u> <ul style="list-style-type: none"> <li><input type="checkbox"/> must confirm GH deficiency with provocative GH stimulation test [A child's GH stim test would need to be &lt;10ng/mL to represent deficiency.]</li> <li><input type="checkbox"/> If a transition patient (receiving GH when &lt;18), pt must have been off GH at least one month before GH test to determine if true GHD persists</li> <li><input type="checkbox"/> Must score ≥ 11 on "Quality of Life Assessment of Growth Hormone Deficiency in Adults" questionnaire during GH-free period</li> </ul> Initial Approval: 1 year Reauthorization: Score on "Quality of Life Assessment of Growth Hormone Deficiency in Adults" questionnaire must have increased by ≥ 7 points.  <b>Adult onset</b> 1. <u>Idiopathic:</u> <ul style="list-style-type: none"> <li>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 &lt;5ng/mL.]</li> </ul> 2. <u>Acquired:</u> <ul style="list-style-type: none"> <li>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 &lt;5ng/mL to be positive; also a panhypopituitary patient would have other drugs representative of panhypopituitarism.]</li> </ul> Initial Approval: 1 year Reauthorization: Score on "Quality of Life Assessment of Growth Hormone Deficiency in Adults" questionnaire must have increased by ≥ 7 points.	<input type="checkbox"/> Norditropin--EBD <input type="checkbox"/> Genotropin <input type="checkbox"/> Humatrope <input type="checkbox"/> Nutropin <input type="checkbox"/> Omnitrope--UAS <input type="checkbox"/> Saizen
<b>Adult: Short Bowel Syndrome</b> <ul style="list-style-type: none"> <li><input type="checkbox"/> Must be receiving parenteral nutrition and have an optimized diet</li> <li><input type="checkbox"/> Must be receiving glutamine concurrently</li> </ul> Initial Approval: 3 months	<input type="checkbox"/> Zorbtive

Reauthorization: tx must have resulted in the elimination of 1 or more days of TPN infusion	
<b>Adult: HIV with wasting or cachexia with concomitant antiretroviral therapy</b> <ul style="list-style-type: none"> <li><input type="checkbox"/> Must be receiving concurrent HAART therapy</li> <li><input type="checkbox"/> <math>\geq 10\%</math> unintentional weight loss or low BMI (<math>&lt; 20 \text{ kg/m}^2</math>) or body weight <math>&lt; 90\%</math> of IBW</li> <li><input type="checkbox"/> Exclude if fasting blood glucose <math>&gt; 121 \text{ mg/dL}</math>, malignancy, or active AIDS-defining opportunistic infection</li> </ul> Initial Approval: 3 months Reauthorization: pt must have $\geq 3 \text{ kg}$ weight gain or increased exercise capacity	<input type="checkbox"/> Serostim

**GH will not be approved for the following uses:**

1. Kids: Idiopathic short stature (nonGH deficient short stature)
2. Enhancement of athletic performance
3. Aging or age-related conditions
4. Down's Syndrome
5. Fanconi's syndrome
6. Bloom syndrome

**DENY if any of the following:**

- Active malignancy OR malignancy in the past year
- Age  $> 65$  yrs

**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.<sup>11</sup>
- 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.<sup>11</sup>

**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 5<sup>th</sup> 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  $\geq 14$  yr and growth velocity  $< 2 \text{ cm/year}$ )<sup>12</sup>
- 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<sup>12</sup>
- Girls with TS generally have normal GH levels<sup>12</sup>
- "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<sup>2</sup>

### **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 hypogonadotropic hypogonadism.<sup>4</sup>
- 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<sup>13</sup>
    - 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<sup>14</sup>
    - 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<sup>1</sup>, “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.
- While RCT have shown significant increase in height over 2 years with GH treatment vs placebo<sup>7</sup>, 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. <sup>15</sup>

**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, whilst another found no significant evidence that GH treatment impacts psychological adaptation or self-perception in children with ISS.” - Cochrane Review<sup>5</sup>

**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. <sup>11</sup>
- 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. <sup>11</sup>
- 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 treatment and be evaluated 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 rationale 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.<sup>16</sup>
- One RCT looked at the effect of GH on parenteral nutrition requirements<sup>8</sup>
  - 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 infusion 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<sup>17</sup>

#### **Adult : HIV with wasting or cachexia with concomitant antiretroviral therapy**

- Wasting is defined as a  $\geq 10\%$  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.<sup>18</sup>
  - 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 3<sup>rd</sup> 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 correlation 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

- 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  $\geq 3$  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  $\geq 3$  pituitary axes ([ES Grade 1+++](#))
  - this situation strongly suggests GHD
  - presence of  $\geq 3$  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

## References

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**Revision History:**

<b>Date</b>	<b>Changes</b>	<b>Pharmacist</b>
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
3/10/2021	I reformatted to be clear Norditropin is the exclusive GH product for EBD. No other changes.	JJ
3/30/21	I applied these criteria to UAS Plan (Omnitropin).	JJ

**C-1 esterase inhibitor (Haegarda is the only covered product.)****EBRx PA Criteria**

**\*\*\*Haegarda is the covered product for EBD as of 2/2018. 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.**

<b>1. The patient must have a diagnosis* of hereditary angioedema. (see diagnosis criteria below)</b>
<b>2. The drug must be used as chronic prophylactic medication.</b>
<b>3. The patient must have had <math>\geq 2</math> 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.</b>
<b>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.</b>
<b>5. If "no" to having contraindication or adverse effect to androgens, the patient must have failed androgen treatment.</b>
<b>6. The patient must remain off angiotensin-converting enzyme inhibitors (ACE-I's).</b>
<b>7. The patient must remain off any type of estrogen-containing medication.</b>

**Note doses:**

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

<b><math>\leq 41</math></b>	<b>0-2460</b>	<b>2000</b>
<b>42-58</b>	<b>2520-3480</b>	<b>3000</b>
<b>59-74</b>	<b>3540-4440</b>	<b>4000</b>
<b>75-91</b>	<b>4500-5460</b>	<b>5000</b>
<b>92-108</b>	<b>5520-6480</b>	<b>6000</b>
<b>109-124</b>	<b>6540-7440</b>	<b>7000</b>

**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.\*\*\***

**Physician signature: \_\_\_\_\_ Date: \_\_\_\_\_**

**\*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 hereditary 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).

#### Criteria History:

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

Eribulin (Halaven)  
1 mg/2ml vial  
EBRx PA Criteria

**is 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).<sup>1</sup>

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.<sup>2,3</sup>

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).<sup>4</sup> 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).<sup>5</sup>

Dose: 1.4 mg/m<sup>2</sup> 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. 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. 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). No overall survival difference was observed in leiomyosarcoma subgroup.

### **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	What Changed?	Pharmacist's initials
12/6/19	Reviewed at DCWG, criteria written	SK
3/29/2021	Criteria reviewed. No change.	SK
3/31/2021	Applied to UAS plan.	JJ
9/2/2022	Criteria reviewed. No change.	SK
9/28/2023	Criteria reviewed. No changes. Could consider removing requirement for anthracycline in breast cancer indication.	SK

## Adalimumab (Humira)

### EBRx PA Criteria

#### **Is FDA approved for:**

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for:

- **Rheumatoid Arthritis (RA):** reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- **Juvenile Idiopathic Arthritis (JIA):** reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older.
- **Psoriatic Arthritis (PsA):** reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- **Ankylosing Spondylitis (AS):** reducing signs and symptoms in adult patients with active AS.
- **Crohn's Disease (CD):** treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.
- **Ulcerative Colitis (UC):** treatment of moderately to severely active ulcerative colitis in adults and pediatric patients 5 years of age and older. Limitations of Use: Effectiveness has not been established in patients who have lost response to or were intolerant to TNF blockers.
- **Plaque Psoriasis (Ps):** treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
- **Hidradenitis Suppurativa (HS):** treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.
- **Uveitis (UV):** treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 years of age and older.

#### **Rheumatoid Arthritis**

##### **1. The patient must have the diagnosis of rheumatoid arthritis PLUS one of the following:**

###### **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.

##### **If criteria met, approve for 12 months.**

###### **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.

#### References:

- 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.
- 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.
- O'Dell JR, Mikuls TR, et al. Therapies for active RA after methotrexate failure. *N Engl J Med*. 2013;369:307-18.
- 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.
- 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.
- Bathon JM, McMahon DJ. Making rational treatment decisions in RA when methotrexate fails. *N Engl J Med*. 2013;369:4384-85.
- Singh, Jasvinder A., et al. "2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis." *Arthritis & rheumatology* 68.1 (2016): 1-26.
- Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol*. 2021;73(7):1108-1123. doi:10.1002/art.41752

## Juvenile Idiopathic Arthritis (previously known as Juvenile Rheumatoid Arthritis)

- The patient has a diagnosis of juvenile idiopathic arthritis.
- The patient has received glucocorticoid joint injections and at least 3 months of methotrexate or leflunomide at the maximum tolerated typical dose  
**OR**  
If the patient has enthesitis-related arthritis (enthesitis is inflammation where tendons or ligaments connect with the bone), he/she has received glucocorticoid joint injections and an adequate trial of sulfasalazine  
**OR**  
If the patient has sacroiliac arthritis, he/she patient has received an adequate trial of NSAIDS

If criteria met, approve for 12 months.

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

- The patient has the diagnosis of active ankylosing spondylitis.
- The patient failed a trial of 2 NSAIDS. Sequential NSAID trials should be 1 month in length and be optimally dosed.

**Note:** Initial PA should be good for 3 months. After physician confirms the patient's positive response, defined as a reduction of the BASDAI<sup>‡</sup> to 50% of the pre-treatment value, or a reduction of  $\geq 2$  units, together with a reduction of the spinal pain VAS by 2 cm or more, the patient would be eligible for re-approval.

<sup>‡</sup>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  $\geq 4$  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:

- 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>
- €DERP. Report on Targeted Immune Modulators Update 3/8/12.

## Psoriatic Arthritis

- The patient must have a diagnosis of psoriatic arthritis.
- The patient must have failed a trial of 2 NSAIDS. Each trial should be 1 month in length.
- The patient must have failed 3 months of a DMARD therapy (examples: methotrexate, sulfasalazine, penicillamine, azathioprine, leflunomide).

If criteria met, approve for 12 months.

#### References:

- DERP. Report on Targeted Immune Modulators Update 3/8/12.

## Plaque Psoriasis

1. If the patient ALSO HAS the diagnosis of psoriatic arthritis, approve Humira without requiring "fail first therapy".
2. The patient must have a diagnosis of moderate to severe (affecting  $\geq 5\%$  BSA) plaque psoriasis.
3. The patient must have failed 3 consecutive months of systemic or topical, non-biologic therapy including these options:
  - 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 retinoid: tazarotene)

If yes to 1, then approve. If yes to 2 & 3 above, approve for 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](https://icer-review.org/wp-content/uploads/2017/11/ICER_Psoriasis_Update_Draft_Report_04272018.pdf)

## Crohn's Disease

1. The patient must have a diagnosis of Crohn's disease.
2. The patient meet one of the following criteria:  
Corticosteroid-dependent (with CDAI score  $>220$ )  
**OR**  
Be 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  $\geq 2.4\text{g/d}$ ) or budesonide (at a dose of  $\geq 6\text{ mg/day}$ ).

If criteria met, approve for 12 months.

### 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

1. The patient must have a diagnosis of Ulcerative Colitis.
2. Disease is classified as moderate to severe (Mayo score 6 to 12 on a 12 point scale, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP
3. Age is 5 years or older

If criteria met, approve for 12 months.

## Hidradenitis suppurativa

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 $\geq 90$ days continuous duration of an oral antibiotic for the treatment of their HS in the past 180 days.
3. The patient must have tried chlorhexidine gluconate, triclosan, benzoyl peroxide, and dilute bleach in bathwater.
If approved, PA is good for 3 months, then the patient must satisfy continuation criteria.
<b>*Hurley Staging:</b> <ul style="list-style-type: none"> <li>• Stage I: abscess formation, single or multiple, without sinus tracts and cicatrization (scarring).</li> <li>• Stage II: One or more widely separated recurrent abscesses with tract formation and cicatrization (scars).</li> <li>• Stage III: Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement.</li> </ul>
<b>Continuation Criteria</b>
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." <i>New England Journal of Medicine</i> 375.5 (2016): 422-434.

<b>Noninfectious Uveitis</b>
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.
<b>Continuation Criteria</b>
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.

Quantity Limits: 30 day supply

Revision History:

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
6/28/2022	Created separate Humira criteria from TIMS criteria. Removed references to other drugs.	SK
8/4/2022	Add UC criteria	SK

**Durvalumab (Imfinzi)**  
**120mg/2.4mL, 500mg/10mL IV solution**  
**EBRx PA Criteria**

**FDA-approved for:**

- treatment of adult patients with 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 tremelimumab-actl and platinum-based chemotherapy, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations
- 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)
- in combination with gemcitabine and cisplatin, as treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC)
  - Note: biliary tract cancers include intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer
- in combination with tremelimumab-actl, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC)

**Non-Small Cell Lung Cancer (STAGE III; MONOTHERAPY)**

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, approve 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

<sup>1</sup>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).

**Non-Small Cell Lung Cancer (STAGE IV; WITH TREMELIMUMAB AND CHEMO)**

1. Diagnosis of stage IV non-small cell lung cancer (NSCLC)
  2. No ALK or EGFR mutation
  3. No prior therapy for stage IV NSCLC
  4. Durvalumab will be given in combination with tremelimumab and carboplatin/cisplatin-based chemotherapy.
- If all criteria are met, approve x 1 year.

Notes:

Dose: 1500 mg every 3 weeks x 4 cycles then every 4 weeks until disease progression.

Reference:

Johnson ML et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. J Clin Oncol. 2023 Feb 20;41(6):1213-1227. doi: 10.1200/JCO.22.00975. Epub 2022 Nov 3. PMID: 36327426; PMCID: PMC9937097.

### 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

### Biliary Tract Cancer

1. Diagnosis of an advanced or metastatic biliary tract cancer (e.g. intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer)

2. The patient has received no prior therapy for advanced/metastatic biliary tract cancer **OR** experienced disease recurrence at least 6 months after surgery with curative intent and/or after completion of adjuvant chemotherapy

3. Durvalumab will be used in combination with gemcitabine and cisplatin

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: 12.8 months versus 11.5 months (HR 0.8, 95% CI 0.66-0.97; p=0.021)

-18-month overall survival: 35.1% versus 25.6%

-24-month overall survival: 24.9% versus 10.4%

-ESMO magnitude of clinical benefit score is 4 due to >10% improvement in OS at 2 years.

Grade 3/4 toxicities were similar between groups.

References:

1. Oh D et al. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. DOI: 10.1200/JCO.2022.40.4\_suppl.378 Journal of Clinical Oncology 40, no. 4\_suppl (February 01, 2022) 378-378. NCT03875235
2. Oh D et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evid 2022; 1 (8) DOI:https://doi.org/10.1056/EVIDoa2200015. NCT03875235
3. NCCN Guidelines for Hepatobiliary Cancers. [https://www.nccn.org/professionals/physician\\_gls/pdf/hepatobiliary.pdf](https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf)

### Hepatocellular Carcinoma

1. Diagnosis of hepatocellular carcinoma

2. No prior systemic therapy

4. Durvalumab will be used in combination with tremelimumab.
If all criteria are met, approve x 1 year.
Notes:
Dose: 1500 mg every 4 weeks until disease progression.
Reference:
1. Abou-Alfa, G et al. (2022, June 6). Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma. New England Journal of Medicine Evid. Retrieved May 1, 2023, from <a href="https://evidence.nejm.org/doi/full/10.1056/EVIDoa2100070">https://evidence.nejm.org/doi/full/10.1056/EVIDoa2100070</a>

#### 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.	JJohnson
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
10/11/2022	Added criteria for biliary tract cancers	SK
10/19/2023	Added criteria for the tremelimumab indications as reviewed at 12/2022 P&T	SK

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 a statistically significant overall survival or quality of life benefit has not been demonstrated to date
- References:
  - 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.
  - David Siegel et al. (2021) Health-related quality of life outcomes from the CANDOR study in patients with relapsed or refractory multiple myeloma, Leukemia & Lymphoma, 62:12, 3002-3010, DOI: 10.1080/10428194.2021.1941927
  - Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes from a randomised, multicentre, open-label, phase 3 study. Lancet Oncol. 2022;23(1):65-76. doi:10.1016/S1470-2045(21)00579-9
  - Usmani SZ et al. Final analysis of carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone in the CANDOR study. Blood Adv. 2023 Jul 25;7(14):3739-3748. doi: 10.1182/bloodadvances.2023010026. PMID: 37163358; PMCID: PMC10368773.
- Isatuximab and dexamethasone 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.
    - Martin T et al. Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized Phase 3 study. Blood Cancer J. 2023 May 9;13(1):72. doi: 10.1038/s41408-023-00797-8. Erratum in: Blood Cancer J. 2023 Sep 27;13(1):152. PMID: 37156782; PMCID: PMC10166682.
- 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

**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 **with or without** lenalidomide
4. Must be ECOG Performance status 0-2 upon initial request for carfilzomib.

If all above criteria met, approve for 12 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.<sup>1</sup>
- Carfilzomib/lenalidomide/dexamethasone improved OS compared with lenalidomide/dexamethasone (median 48 mo vs 40 mo). 20% of subjects received previous lenalidomide.<sup>2</sup>
- 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).<sup>3</sup>

Regimen	Dose	Infusion time
Carfilzomib + dexamethasone	20/70 mg/m <sup>2</sup> once weekly	30 minutes
Carfilzomib + dexamethasone, or monotherapy	20/56 mg/m <sup>2</sup> twice weekly	30 minutes
Carfilzomib, Lenalidomide, and dexamethasone, or monotherapy	20/27 mg/m <sup>2</sup> 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
8/26/2022	Criteria reviewed: no change. Added new study for cfz/dara/dex.	SK
10/20/23	Criteria reviewed; no change	SK

**EBRx Medical PA Criteria**  
**Alemtuzumab (Lemtrada) 12mg/1.2mL, 1.2mL**

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.

**is FDA-approved for: relapsing forms of multiple sclerosis (RRMS)**

<b>Criteria</b>
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.<sup>2, figure 1</sup>

Quantity Limits: 5 doses/365 days for the first year, 3 doses/365 subsequent years after the 1<sup>st</sup> year. The patient should be approved for renewal once in a lifetime (max).

**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](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 of 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\\_mscpedi\\_phar&uac=126299PK&spon=30&impID=1938647&faf=1](https://www.medscape.com/viewarticle/911741?nlid=129300_4822&src=WNL_mdplsfeat_190416_mscpedi_phar&uac=126299PK&spon=30&impID=1938647&faf=1)

**Revision History:**

Date	What changed	Pharmacist's initials
2/5/15	I wrote the criteria.	Jill Johnson
3-10-15	Discussed at DCWG. QL of 5doses 1 <sup>st</sup> 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	JJ

	being treated w/ alemtuzumab who are benefiting may continue treatment in consultation with their physician.	
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.

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.

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.

## Alglucosidase Alfa (Lumizyme 50mg IV)

### EBRx PA Criteria

**is FDA-approved for:** 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.
- 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.
4. 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.
5. 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.
6. Schoser B, Hill V, and Raben N, "Therapeutic Approaches in Glycogen Storage Disease Type II/Pompe Disease," *Neurotherapeutics*, 2008, 5(4):569-78.
7. UpToDate. Pompe Disease. Accessed 9/24/19.

#### Revision history:

Date	What changed?	Pharmacist's initials
8/7/06	T2PA approved & criteria written.	Jill Johnson
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

Gemtuzumab ozogamicin (Mylotarg) 4.5 mg vials  
EBRx PA Criteria  
MEDICAL PRIOR AUTHORIZATION – EXCLUDED FROM PHARMACY

**is 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**

1. 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  $\geq 2.5 \times$  upper limit of normal (ULN), serum bilirubin  $\geq 2 \times$  ULN, OR serum creatinine  $\geq 2.5 \times$  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<sup>2</sup> (**up to one 4.5 mg vial**) on Days 1, 4, and 7 in combination with daunorubicin (60 mg/m<sup>2</sup> on Days 1, 2, and 3) and cytarabine (200 mg/m<sup>2</sup> 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<sup>2</sup> (**up to one 4.5 mg vial**) on Day 1 in combination with daunorubicin (60 mg/m<sup>2</sup> for 1 day [first course] or 2 days [second course]) and cytarabine (1000 mg/m<sup>2</sup> 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<sup>1,2</sup>

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

#### 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.	

#### 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.

**Mepolizumab (Nucala®)**  
**EBRx PA Criteria**

<b>Asthma, eosinophilic type</b>
1. The prescriber must be a pulmonologist or allergist.
2. The patient must be age $\geq 6$ 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 <sup>3</sup> ?
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.
<b>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.</b>
<b>DOSE is 100mg SC in a physician office q4w.</b>
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.
<b>Eosinophilic granulomatosis with polyangiitis (EGPA)</b>
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: <ul style="list-style-type: none"> <li>History or presence of asthma AND</li> <li>Blood eosinophil level of 10% or an absolute eosinophil count of more than 1000 cells/mm<sup>3</sup> AND</li> <li>Presence of 2+ criteria below typical of EGPA: <ul style="list-style-type: none"> <li>A biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation;</li> <li>Neuropathy, mono or poly (motor deficit or nerve conduction abnormality);</li> <li>Pulmonary infiltrates, non-fixed;</li> <li>Sino-nasal abnormality;</li> <li>Cardiomyopathy (established by echocardiography or mri);</li> <li>Glomerulonephritis (hematuria, red cell casts, proteinuria);</li> <li>Alveolar hemorrhage (by bronchoalveolar lavage);</li> <li>Palpable purpura;</li> <li>Antineutrophil cytoplasmic antibody (anca) positive (mpo or pr3)</li> </ul> </li> </ul>
3. History of <b>relapsing OR refractory disease</b>
4. The patient must have tried azathioprine, methotrexate, leflunomide, OR mycophenolate OR have a contraindication to these therapies.
5. Patients MUST NOT have diagnosis of granulomatosis with polyangiitis (aka Wegener's granulomatosis) <b>or</b> microscopic polyangiitis <b>or</b> 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 have 75% ICS adherence rate. It is prudent to follow less costly standard treatment prior to access to asthma biologics.
<b>Hypereosinophilic Syndrome</b>
1. Must be age 12y+
2. Dx of hypereosinophilic syndrome for at least 6 months
3. Has had a heme-onc workup and the diagnosis is not a heme-onc cause
<b>Rhinosinusitis w/ Nasal Polyps</b>
1. Dx of nasal polyps
2. Inadequate response to nasal corticosteroids
3. Must be age 18y+ (adult)

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	<p>I spoke with Cameron James from GSK after communicating with Erica Brumleve 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.</p> <p>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."</p>	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
6/1/23	I added the indications hypereosinophilic syndrome and rhinosinusitis w/ nasal polyps	JJ
7/12/23	I corrected the mistake of ">" to "<"80%FEV1.	JJ

Belatacept (Nulojix)  
250mg IV infusion  
EBRx PA Criteria

**is FDA-approved for:** 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 mofetil 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](http://packageinserts.bms.com/pi/pi_nulojix.pdf) Accessed 8/3/11.
2. Vincenti F, Blanco 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
4/2/21	Applied EBRx criteria to UAS Plan.	JJ

# EBRx Prior Authorization Criteria for Ocrelizumab (Ocrevus)

Ocrevus is a CD20-directed cytolytic antibody **indicated** for the treatment of patients with **relapsing or primary progressive forms of multiple sclerosis**.

<b>Primary Progressive Multiple Sclerosis (PPMS)</b>
1) The patient has a diagnosis of <b>Primary Progressive Multiple Sclerosis (PPMS)</b> 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. <b>AND</b>
3) The patient's duration of MS symptoms must be < 15 years in patients with an <b>EDSS score of &gt; 5.0</b> at the most recent screening; <b>OR</b> A duration of MS symptoms of < 10 years in patients with an <b>EDSS score of 5.0 or less during their most recent screening. AND</b>
4) A score on the pyramidal functions component of the Functional Systems Scale (see next page and ref#4 for link) of at least 2 (range, 0 to 6, with higher scores indicating greater disability). <b>AND</b>
5) The patient must be both age ≥ 51y AND without gadolinium-enhancing lesions. (If not, rituximab is the alternative treatment.)
<b>OR</b>
6) The patient has a diagnosis of <b>Primary Progressive Multiple Sclerosis (PPMS)</b> 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) <b>OR</b> all criteria in 6-7, then ocrelizumab will be approved for 1y (max of 1200mg/y. Dosing Regimen per package insert: <ul style="list-style-type: none"> <li>Start dose: 300 mg IV, followed two weeks later by a second 300 mg IV infusion.</li> <li>Subsequent doses: 600 mg IV every 6 months (beginning 6 months after the first 300 mg dose).</li> <li>After the two initial 300 mg starting doses, doses must be separated by at least 5 months.</li> </ul> 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 cladribine).

## Relapsing Remitting Multiple Sclerosis (RRMS)

1) The patient has a diagnosis of **RRMS and has failed therapy on rituximab.**

### References:

- 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.
- Montalban, Xavier, et al. "Ocrelizumab versus placebo in primary progressive multiple sclerosis." *N Eng J Med* 376.3 (2017): 209-220.
- Ocrelizumab FDA package insert.
- 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>
1. He, Dian, et al. "Rituximab for relapsing-remitting multiple sclerosis." *Cochrane Database Syst Rev*12 (2011).
- 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]
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/>
- 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.

### Revision History:

Date	Changes	Pharmacist
07/19/17	Document Created.	JK

8/6/17	<b>For PPMS:</b> 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. <b>For RRMS:</b> Although rituximab lacks the FDA indication for RRMS, we recommend coverage of rituximab for RRMS. <sup>5-8</sup>	JJ
1/8/2021	<u>I reviewed the criteria. No changes were made except I added no concurrent cladribine.</u>	JJ
5/20/21	<u>EBRx P&amp;T voted to allow use in RRMS patients who fail rituximab.</u>	JJ

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)

Nivolumab (Opdivo)  
EBRx PA Criteria

**FDA-approved for:**

- **Melanoma**
  - Adult and pediatric patients (12 y and older) with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab ([link to metastatic melanoma criteria](#))
  - Adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma ([link to adjuvant criteria](#))
- **Non-Small Cell Lung Cancer (NSCLC)**
  - Adult patients with resectable (tumors  $\geq 4$  cm or node positive) non-small cell lung cancer in the neoadjuvant setting, in combination with platinum-doublet chemotherapy ([link to criteria](#))
  - Adult patients with metastatic non-small cell lung cancer expressing PD-L1 ( $\geq 1\%$ ) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab. ([link to criteria](#))
  - 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. ([link to criteria](#))
  - 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. ([link to criteria](#))
- **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](#))
  - Patients with intermediate or poor risk advanced RCC, as first-line treatment in combination with ipilimumab
  - Patients with advanced RCC, as first-line treatment in combination with cabozantinib
  - Patients with advanced RCC who have received prior anti-angiogenic therapy
- **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<sup>a</sup>
  - CHL that has relapsed or progressed after 3 or more lines of systemic therapy that includes autologous HSCT<sup>a</sup>
- **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**
  - Adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection ([link to criteria](#))
  - Locally advanced or metastatic disease with progression during or following platinum-containing chemotherapy<sup>a</sup> 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<sup>b</sup> 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 a single agent or in combination with ipilimumab<sup>a</sup> NOT COVERED: lack of comparative data

- **Hepatocellular Carcinoma (HCC)**

- Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib in combination with ipilimumab<sup>a</sup> NOT COVERED: lack of comparative data
- NCT01658878 compared different regimens of nivolumab/ipilimumab in patients with HCC who had been treated previously with sorafenib. Overall survival was promising with one regimen (which is now FDA approved), but no comparative trials have shown it to be superior to other therapies or placebo.

Reference: Yau T, Kang YK, Kim TY, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial [published correction appears in JAMA Oncol. 2021 Jan 1;7(1):140]. JAMA Oncol. 2020;6(11):e204564. doi:10.1001/jamaoncol.2020.4564

- **Esophageal Cancer**

- Treatment of patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy ([link to criteria](#))
- Treatment of patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy. ([link to criteria](#))
- Treatment of patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with ipilimumab. ([link to criteria](#))
- Treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy. ([link to criteria](#))

- **Gastric, gastroesophageal junction, and esophageal cancer ([link to criteria](#))**

- patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing 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.

<b>Melanoma, metastatic (new users)</b>
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 <b>OR</b> in combination with ipilimumab
<b>If above criteria fulfilled, approve for 12 months</b>

#### 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<sup>a</sup>) and another showed improvement in overall survival vs. ipilimumab in untreated patients with or without BRAF mutation (36.9m vs. 19.9 mo<sup>b</sup>). 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%).<sup>b,c</sup> 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.

-Nivolumab dosing is 240 mg every 2 weeks or 480 mg every 4 weeks IV infusion until disease progression or unacceptable toxicity

#### REFERENCES:

- a. [Ascierto PA](#) et al. Survival Outcomes in Patients With Previously Untreated BRAF Wild-Type Advanced Melanoma Treated With Nivolumab Therapy: Three-Year Follow-up of a Randomized Phase 3 Trial. *JAMA Oncol.* 2018 Oct 25.
- b. 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. PMID 30361170
- c. 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. PMID 31562797 NCT01844505
- d. NCCN guidelines for cutaneous melanoma (version 2.2019). [https://www.nccn.org/professionals/physician\\_gls/pdf/cutaneous\\_melanoma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf). Accessed 8/8/19.

#### Melanoma, adjuvant (new users)

1. Diagnosis of stage IIB, IIC, III, or IV melanoma that has been completely surgically resected
2. 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. In this trial, the grade 3 or 4 AE rates were 14.4% Nivolumab vs 45.9% Ipilimumab.

#### 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](#)

#### EARLY STAGE Non-Small Cell Lung Cancer (NSCLC)

1. Diagnosis of non-small cell lung cancer (adenocarcinoma or squamous cell carcinoma)
2. Disease is resectable
3. Tumor is either lymph node positive or size is 4 cm or greater
4. If tested, tumor does not harbor EGFR or ALK mutations (if testing not conducted, disregard this criterion)
5. Nivolumab will be given in combination with platinum-based chemotherapy (e.g. carboplatin or cisplatin plus paclitaxel, pemetrexed, gemcitabine, or other agent)
6. Nivolumab+chemotherapy will be given neoadjuvantly (before surgery) for 3 cycles

**If criteria are fulfilled, approve for 3 months. For this indication, nivolumab is given for 3 doses only.**

#### Notes:

Dose: nivolumab 360 mg IV every 3 weeks x 3 doses (with platinum based chemotherapy) given prior to surgery.

Nivolumab + chemotherapy improved event free survival compared to chemo alone in this population.

<p>CHECKMATE-816 NCT02998528 Randomized, Open Label, Multicenter</p> <p>Platinum-based chemotherapy x 3 cycles with or without nivolumab</p> <p>N=358</p> <p>Primary endpoint: Event free survival Time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression of disease in the absence of surgery, or death from any cause.</p>	<p>Inclusion: Resectable NSCLC; resectable, histologically confirmed Stage IB (<math>\geq 4</math> cm), II, or IIIA</p> <p>Excluded: known EGFR mutations or ALK translocations (testing not required)</p>	<p><b>Event free survival:</b> Nivolumab/chemo: 31.6 Chemo: 20.8 HR 0.63 0.45-0.87; p=0.0052</p> <p><b>Interim overall survival analysis:</b> HR 0.57 (95% CI: 0.38, 0.87) Did not cross the boundary for statistical significance.</p> <p><b>Complete pathologic response:</b> Nivo/chemo: 24% Chemo: 2.2%</p> <p><b>Grade 3 or 4 adverse events:</b> Nivo/chemo: 41 Chemo: 44%</p> <p><b>Other possible benefits in nivolumab group:</b> More proceeded with surgery (83% vs 75%) Shorter duration of surgery More use of minimally invasive approaches Fewer pneumonectomies' More R0 resections</p>
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**REFERENCES:**

1. Opdivo PI. [https://packageinserts.bms.com/pi/pi\\_opdivo.pdf](https://packageinserts.bms.com/pi/pi_opdivo.pdf). Accessed 4/25/2022.
2. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer [published online ahead of print, 2022 Apr 11]. N Engl J Med. 2022;10.1056/NEJMoa2202170. doi:10.1056/NEJMoa2202170

### **METASTATIC 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).<sup>1</sup>**

**2. If no prior therapy for metastatic disease AND PD-L1 is  $\geq 1\%$ , 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**

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.<sup>2</sup>

#### 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  $\geq 1\%$ , 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).<sup>4,5</sup> FDA approved this regimen for PD-L1  $\geq 1\%$  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%).<sup>6,7</sup>

#### REFERENCES:

3. 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](https://icer-review.org/wp-content/uploads/2016/08/MWCEPAC_NSCLC_Evidence_Report_Plus_Supplement_101716.pdf)
4. 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]
5. 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
6. 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
7. 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
8. Opdivo PI. [https://packageinserts.bms.com/pi/pi\\_opdivo.pdf](https://packageinserts.bms.com/pi/pi_opdivo.pdf). Accessed 7/9/2020.
9. 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 with 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 was 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). 2-year overall survival rates were 41% in the nivolumab plus ipilimumab group and 27% in the chemotherapy group. 3-year OS rates were 23% versus 15%, respectively.

#### References:

5. Opdivo package insert
6. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial [published correction appears in *Lancet*. 2021 Feb 20;397(10275):670]. *Lancet*. 2021;397(10272):375-386. doi:10.1016/S0140-6736(20)32714-8
7. Peters S, Scherpereel A, Cornelissen R, et al. First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743. *Ann Oncol*. 2022;33(5):488-499. doi:10.1016/j.annonc.2022.01.074

## Renal Cell Carcinoma (RCC)

### FIRST LINE TREATMENT CRITERIA for use with IPILIMUMAB

1. Diagnosis of advanced RCC
2. No prior systemic therapy for advanced/metastatic/unresectable disease. [if pembrolizumab given previously as adjuvant/post-operative therapy for early stage disease in the past, do not count it as prior therapy]
3. Tumor must have clear cell component
4. Nivolumab will be used in combination with ipilimumab
5. The patient must have IMDC intermediate or poor risk disease indicated by 1 or more of the following characteristics being present:
  - Less than 1 year from time of diagnosis to systemic therapy
  - Performance status <70% (Karnofsky)
  - Hemoglobin < lower limit of normal (LLN)
  - calcium > upper limit of normal (ULN)
  - Neutrophil > ULN
  - Platelets > ULN
6. Patient must have Karnofsky performance status of  $\geq 70\%$

### FIRST LINE TREATMENT CRITERIA for use with CABOZANTINIB

1. Diagnosis of advanced RCC
2. No prior systemic therapy for advanced/metastatic/unresectable disease. [if pembrolizumab given previously as adjuvant/post-operative therapy for early stage disease in the past, do not count it as prior therapy]
3. Tumor must have clear cell component
4. Nivolumab will be used in combination with cabozantinib
5. Patient must have Karnofsky performance status of  $\geq 70\%$

### CRITERIA FOR PREVIOUSLY-TREATED PATIENTS

1. Diagnosis of advanced RCC
2. Patient has received at least one prior antiangiogenic therapy (e.g. VEGF inhibitors: sunitinib, pazopanib, cabozantinib, sorafenib, axitinib, bevacizumab, lenvatinib)
3. Disease has not progressed on another PD1 or PD-L1 inhibitor (e.g. pembrolizumab)
4. Patient must have Karnofsky performance status of  $\geq 70\%$

### If criteria fulfilled, approve for 12 months.

Notes:

#### FIRST LINE SETTING WITH IPILIMUMAB:

-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.<sup>1,2</sup>

-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.<sup>1</sup>

-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

#### FIRST LINE SETTING WITH CABOZANTINIB:<sup>3</sup>

-In patients with any IMDC risk, nivo/cabo improved overall survival compared to sunitinib: at 12 mo: 85.7% vs 75.6%; HR 0.6, 98.89% CI 0.4-0.89.

-quality of life indicators statistically and clinically improved (FKSI-19 total scores and FDSI-DRS subscale)

#### 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)<sup>4</sup>

#### REFERENCES:

1. Motzer RJ et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. NEJM. 2018 Apr 5;378(14):1277-1290. NCT02231749 PMID 29562145
2. Cella D et al. Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial. Lancet Oncol. 2019 Feb;20(2):297-310. PMID 30658932 NCT02231749
3. Choueiri TK et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2021 Mar 4;384(9):829-841. doi: 10.1056/NEJMoa2026982. PMID: 33657295.
4. Motzer RJ et al. Nivolumab vs everolimus in advanced RCC. NEJM 2015;373:1803-13. [CHECKMATE 025, NCT01668784]

### **Classical Hodgkin Lymphoma (relapsed/refractory)**

1. Diagnosis of Classical Hodgkin Lymphoma

2. Classical Hodgkin Lymphoma has relapsed or progressed after autologous hematopoietic stem cell transplant

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:

Therapy continues until disease progression or unacceptable toxicity. 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:

- a. Lozano-Ortega G et al. Incremental Survival with Nivolumab Relative to Standard of Care in Classical Hodgkin Lymphoma: A Canadian Analysis. Blood 2018 132:5894; [http://www.bloodjournal.org/content/132/Suppl\\_1/5894](http://www.bloodjournal.org/content/132/Suppl_1/5894).

### **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  $\leq 10$ mg daily prednisone (or equivalent).

2. Deny access if receiving therapy for an autoimmune disease or taking an immunosuppressant ( $>10$ mg 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**

**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 or unacceptable toxicity

**REFERENCE:**

1. Ferris RL et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. NEJM 2016;375:1858-67. [CHECKMATE 141 NCT02105636]

**Urothelial Carcinoma**

**All of the following 3 criteria are required:**

1. Diagnosis of urothelial carcinoma
2. Patient underwent radical cystectomy within 120 days of request
3. Negative surgical margins

**In addition to 1-3, one of the following 2 sets of criteria must be met:**

4. Patient meets all of the following criteria:
  - Neoadjuvant (preoperative) cisplatin-based therapy was NOT given
  - Staging of surgical specimen (i.e. pathological stage) is pT3, pT4a, or is node positive
  - Patient is not eligible for adjuvant cisplatin chemotherapy
5. Patient meets all of the following criteria:
  - Neoadjuvant (preoperative) cisplatin-based therapy WAS given
  - Staging of surgical specimen (i.e. pathological stage) is pT2, pT3, pT4a, or is node positive

**If 1-3 and either 4 or 5 are fulfilled, approve for 12 months, maximum. The duration of nivolumab for this indication is limited to 1 year.**

**Note:**

Dose: 240 mg every 2 weeks OR 480 mg every 4 weeks for 1 year.

In this patient population, nivolumab improved disease free survival (DFS) was improved with nivolumab treatment compared to placebo. The median DFS in the intention-to-treat population was 20.8 months with nivolumab and 10.8 months with placebo (HR 0.70; 98.22% CI, 0.55 to 0.90; P<0.001). Overall survival results are pending.

**REFERENCE:**

1. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma [published correction appears in N Engl J Med. 2021 Aug 26;385(9):864]. N Engl J Med. 2021;384(22):2102-2114. doi:10.1056/NEJMoa2034442

**Completely Resected Esophageal Cancer**

1. Diagnosis of esophageal or gastroesophageal junction cancer
2. The patient has undergone complete resection of tumor with negative margins
3. The patient was treated with concurrent chemotherapy and radiation prior to surgery (neoadjuvant chemoradiotherapy/chemoradiation)

4. The patient has residual disease on surgical pathology specimen (i.e. after resection, tumor cells still remained in the resected tissue)
5. The patient does not have metastatic disease
6. Nivolumab will be used as single agent

**If above criteria fulfilled, approve x 12 months ONLY. Note: Maximum duration of therapy for this indication is 1 year.**

Notes:

Treatment was continued until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration.

In the CHECKMATE-577 (NCT02743494) trial, patients meeting the above key criteria were randomized to either 1 year of nivolumab or placebo. Nivolumab statistically improved disease free survival (DFS) regardless of PD-L1 expression and histology. The following results were taken from the package insert:

	OPDIVO (n=532)	Placebo (n=262)
<b>Disease-free Survival</b>		
Number of events, n (%)	241 (45%)	155 (59%)
Median (months) (95% CI)	22.4 (16.6, 34.0)	11.0 (8.3, 14.3)
Hazard ratio <sup>a</sup> (95% CI)	0.69 (0.56, 0.85)	
p-value <sup>b</sup>	0.0003	

<sup>a</sup> Based on a stratified proportional hazards model.

<sup>b</sup> Based on a stratified log-rank test.

#### REFERENCES:

1. Opdivo package insert. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/125554s092lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125554s092lbl.pdf) Accessed 6/17/2021.
2. Kelly RJ et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med. 2021 Apr 1;384(13):1191-1203. doi: 10.1056/NEJMoa2032125. PMID: 33789008.

#### **Advanced/Metastatic/Unresectable Esophageal Cancer (FIRST LINE)**

1. Diagnosis of esophageal squamous cell carcinoma
2. No prior therapy for advanced/metastatic/unresectable disease
3. Nivolumab will be used in combination with EITHER ipilimumab OR fluoropyrimidine/platinum-containing chemotherapy
4. Tumor PD-L1 expression is  $\geq 1\%$

**If above criteria fulfilled, approve x 12 months.**

Notes:

Treatment continues until disease progression or unacceptable toxicity.

In the KEYNOTE-648 trial, patients receiving nivolumab in combination with either chemotherapy or ipilimumab experienced a statistically superior overall survival compared to patients who received chemotherapy alone. The benefit was driven by patients whose tumors had PD-L1 expression of  $\geq 1\%$ .

PD-L1 expression	Median overall survival (Nivolumab/Ipilimumab versus chemo)	Median overall survival (Nivolumab/chemo versus chemo)
Any	12.8 mo vs 10.7 mo	13.2 mo vs 10.7 mo
PD-L1 $\geq 1\%$	13.7 mo vs 9.1 mo	15.4 vs 9.1 mo

#### REFERENCES:

1. Opdivo package insert. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/125554s092lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125554s092lbl.pdf) Accessed 6/17/2021.
2. Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med. 2022;386(5):449-462. doi:10.1056/NEJMoa2111380

### **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, cisplatin, or carboplatin)
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.

##### **REFERENCES:**

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

### **Gastric cancer, gastroesophageal cancer, esophageal adenocarcinoma**

1. Diagnosis of advanced or metastatic gastric cancer, gastroesophageal cancer, or esophageal adenocarcinoma (note: not esophageal squamous cell carcinoma)
2. Tumor is not HER2 positive
3. No prior therapy
4. Nivolumab will be used in combination with FOLFOX or CapeOX

#### **If above criteria fulfilled, approve x 12 months. May renew if no disease progression.**

##### **Notes:**

Therapy is given until disease progression or unacceptable toxicity.

In the CHECKMATE-649 (NCT02872116) trial, patients meeting the above criteria were randomized to either nivolumab+chemotherapy or chemotherapy alone. Overall survival was improved in the nivolumab group regardless of level of PD-L1 expression. See the following data summary taken from the package insert.

**Table 58: Efficacy Results - CHECKMATE-649**

	OPDIVO and mFOLFOX6 or CapeOX (n=789)	mFOLFOX6 or CapeOX (n=792)	OPDIVO and mFOLFOX6 or CapeOX (n=641)	mFOLFOX6 or CapeOX (n=655)	OPDIVO and mFOLFOX6 or CapeOX (n=473)	mFOLFOX6 or CapeOX (n=482)
	All Patients		PD-L1 CPS ≥1		PD-L1 CPS ≥5	
Overall Survival						
Deaths (%)	544 (69)	591 (75)	434 (68)	492 (75)	309 (65)	362 (75)
Median (months) (95% CI)	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)	14.0 (12.6, 15.0)	11.3 (10.6, 12.3)	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)
Hazard ratio (95% CI) <sup>a</sup>	0.80 (0.71, 0.90)		0.77 (0.68, 0.88)		0.71 (0.61, 0.83)	
p-value <sup>b</sup>	0.0002		<0.0001		<0.0001	

##### **REFERENCES:**

1. Janjigian YY et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021 Jun 4:S0140-6736(21)00797-2. doi: 10.1016/S0140-6736(21)00797-2. Epub ahead of print. PMID: 34102137.
2. Opdivo Package insert: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/125554s092lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125554s092lbl.pdf). Accessed 6/17/2021.

Date	What changed?	Pharm D 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 1 <sup>st</sup> 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	<ul style="list-style-type: none"> <li>• I revised the NSCLC criteria to reflect coverage of nivolumab for 2<sup>nd</sup> line therapy but not as monotherapy for 1<sup>st</sup> line therapy. Since CheckMate-026 showed nivolumab failed to meet the primary endpoint of superior PFS compared to chemotherapy. In pts w/ &gt;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)</li> </ul> <p><b><u>Although the press release emerged 10/9/16, the peer reviewed publication still has not been published.</u></b></p> <ul style="list-style-type: none"> <li>• I removed an FDA-approved indication for melanoma because the FDA did. Of note, we never covered this FDA-approved indication: (unresectable or metastatic melanoma and disease progression following ipilimumab and (if BRAF V600 mutation positive) a BRAF inhibitor. —<b><u>NOT a covered use</u></b>)</li> </ul>	JJ
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	<ol style="list-style-type: none"> <li>1. New FDA indication listed: SCLC (not covered)</li> <li>2. Melanoma (metastatic): expanded to cover BRAF unmutated pt (first line therapy only), added exclusion of ocular melanoma, updated notes and references</li> <li>3. Melanoma (adjuvant): Added exclusion for ocular melanoma; added emphasis of duration of 1 year only.</li> <li>4. NSCLC: updated formatting, notes, references (no change in criteria)</li> <li>5. RCC: Add new indication (in combo with ipi): cover per criteria</li> <li>6. Head and Neck: added that patient should NOT have nasopharyngeal cancer</li> </ol>	Sk
6/17/19	Focused review: cover relapsed/refractory Hodgkin lymphoma as above	Sk
8/26/2019	<p>All indications reviewed.</p> <p>Updated FDA approved indications. Changed approval period from 6 mo to 12 mo for all indications.</p> <p>Metastatic melanoma: added criterion to clarify that nivo will be covered as monotherapy only.</p>	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 <b>[Note: metastatic melanoma: watch for BRAFi/IO sequencing trials (NCT02631447 and NCT02224781).]</b>	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
4/29/2021	Added criteria for nivo/cabo indication for renal cell carcinoma	SK
6/17/2021	Added criteria for nivo+chemo for gastric cancer (first line) Added criteria for adjuvant nivolumab for esophageal/GEJ cancer	SK
7/26/2021	Removed hepatocellular carcinoma indication. Mfr voluntarily withdrew indication after ODAC voted against continued accelerated approval. For historical purposes, indication/references included below: <ul style="list-style-type: none"> <li>• <b>Hepatocellular Carcinoma (HCC)</b> <ul style="list-style-type: none"> <li>○ Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab<sup>a</sup> NOT COVERED: lack of comparative data; EBRx does not cover any immunotherapy for HCC</li> <li>○ 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: <a href="https://www.targetedonc.com/news/phase-iii-checkmate-459-trial-in-unresectable-hcc-misses-primary-endpoint">https://www.targetedonc.com/news/phase-iii-checkmate-459-trial-in-unresectable-hcc-misses-primary-endpoint</a> (accessed 2/10/2020) [CHECKMATE-459, NCT02576509]</li> </ul> </li> </ul>	SK
3/30/2022	In criteria for nivolumab/ipilimumab for first line treatment of renal cell carcinoma edited Karnofsky performance status required in IMDC risk staging from 80% to 70% as done in study protocol. I changed this in form as well.	SK
4/25/2022	Full review of criteria completed. See changes below. <ul style="list-style-type: none"> <li>• Added criteria for neoadjuvant treatment of non small cell lung cancer</li> <li>• Omitted indication for SCLC (no longer FDA approved).</li> <li>• Removed FDA indication for nivolumab monotherapy for HCC. Added reference for nivolumab/ipilimumab indication.</li> <li>• Added various references</li> </ul>	SK
3/9/2023	For urothelial indication, clarified the radical surgery would be a radical cystectomy	SK
4/20/2023	For renal cell carcinoma indications: Added clarification that prior adjuvant pembrolizumab does not count as prior therapy for first line indications. For second line indication, added criteria stating that there has been no prior disease progression on a PD-1 or PD-L1 inhibitor, such as pembrolizumab	SK
8/29/2023	Criteria reviewed. No change	SK
10/20/2023	New indication: for adjuvant treatment of melanoma, stage IIB and IIC now approved. Added coverage to criteria	SK

## 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 surgery)

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%<sup>1</sup>, the pCR rates with these pertuzumab-containing regimens were ~60%<sup>2,3,4</sup>. Attainment of pCR has been strongly associated with overall survival in multiple analyses.<sup>1,5,6</sup>

**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<sup>1</sup> (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 vs placebo): 94.1% vs 93.2% (HR 0.81, 95% CI 0.66-1.00; p=0.045)
- node-positive subgroup (pertuzumab vs placebo): 92% vs. 90.2% (HR 0.77, 95% CI 0.62-0.96; p=0.02)
- node-negative subgroup (pertuzumab vs placebo): rates not given (HR 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).<sup>2</sup>

**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	What Changed?	Pharmacist's initials
12/4/19	Drug reviewed at DCWG. Criteria written.	sk
5/25/2021	Criteria reviewed. No changes	SK
1/18/2023	Criteria reviewed. No changes	SK

Polatuzumab vedotin-piiq (Polivy)  
140 mg vial  
EBRx PA Criteria (Medical)

**is 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. SEE CRITERIA
- In combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients who have previously untreated diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) or high-grade B-cell lymphoma (HGBL) and who have an International Prognostic Index score of 2 or greater. NOT COVERED
  - Benefit of this regimen is limited to progression free survival benefit only
  - Alternative: RCHOP
  - Reference: Tilly H et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022 Jan 27;386(4):351-363. doi: 10.1056/NEJMoa2115304. Epub 2021 Dec 14. PMID: 34904799.

**Criteria for new users**

1. Diagnosis of diffuse large B-cell lymphoma (DLBCL) that is progressing
2. Lymphoma is refractory to or progressed on or after 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

1/20/2022	Clarified criteria #2. Lymphoma must have progressed on or after at least 2 prior regimens	SK
1/26/2022	Criteria reviewed. No changes	SK
6/19/2023	Criteria reviewed. No changes. Added new indication for untreated DLBCL (not covered)	

**Denosumab (Xgeva or Prolia)**  
**Xgeva 120mg/1.7mL (1.7mL) for SC injection**  
**Prolia 60mg/mL (1mL) for SC injection [[jump to criteria](#)]**

**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

**Criteria for Xgeva**

Denosumab 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)

1. Diagnosis of hypercalcemia of malignancy refractory to bisphosphonate therapy and least 7 days have lapsed since last bisphosphonate dose to allow maximum effect.

OR

2. Requested indication is prevention of skeletal-related events in patients with bone metastases from solid tumors

OR

3. 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

OR

4. 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 12 months**

**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 1<sup>st</sup> on-study skeletal related event by 18% compared to ZA (HR, 0.82;95%CI, 0.71 to 0.95; p<0.001 noninferiority; p=0.01 superiority). Median time to 1<sup>st</sup> 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 ZA (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. Denosumab was associated with similar rates of grade 3/4 adverse events.
- 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.
- NCCN gives category 2A recommendation for denosumab in this setting and states to consider it for patients with renal dysfunction. Zoledronic acid holds a category 1 recommendation.

**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
- NCCN guidelines for multiple myeloma: [https://www.nccn.org/professionals/physician\\_gls/pdf/myeloma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf)

**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**

**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 nonvertebral 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<sup>st</sup> endpoint was % change in lumbar 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 1<sup>st</sup> 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, Dubsy 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.<sup>1</sup>

-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.<sup>2</sup>

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.	Jill Johnson
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.	JJohnson
3/7/19	<ol style="list-style-type: none"> <li>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.</li> <li>2. New indication: glucocorticoid induced osteoporosis: not covered due to lack of fracture data</li> <li>3. Allow use for post-menopausal women at high risk for fracture if intolerant/ contraindication to oral AND IV BP.</li> <li>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.</li> </ol>	Sk
5/25/2021	Criteria reviewed. Change approval period for Xgeva to 12 months. Updated some evidence statements. No other changes	SK
9/1/21	Criteria reviewed. Recommending to UAS to cover denosumab following the above criteria.	JJ

Sipuleucel T (Provenge)  
EBRx PA Criteria

**is FDA-approved for:** treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer

<b>Criteria for new users</b>	
1.	Diagnosis of metastatic prostate adenocarcinoma (not small cell or neuroendocrine prostate cancer).
2.	Patient does <b>not</b> 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 less 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 therapy 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.<sup>1</sup>

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).<sup>2</sup> 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.<sup>3</sup>

Baseline PSA (ng/ml)	Median OS (sipuleucel T vs placebo; months)	HR (95% CI)
<b>≤22.1</b>	<b>41 vs. 28</b>	<b>0.51 (0.31-0.85)</b>
>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 manufactured 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](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
5/25/21	Criteria reviewed. Minor rewording but no change to criteria	SK
1/18/2023	Criteria reviewed. No change.	SK
1/18/2024	Criteria reviewed. No change.	SK

Edaravone (Radicava)  
30mg/100mL IV infusion  
EBRx PA Criteria

**is 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.

## 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  $\geq 6$  RBC transfusions per 24 weeks were randomized to luspatercept or placebo.
    - Primary endpoint: percent of patients with  $\geq 33\%$  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  $\geq 50\%$  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.
    - Risks of therapy include thromboembolic events, particularly in splenectomized patients, and extramedullary masses.

#### 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  $\beta$ -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)
- Anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions NOT COVERED. Luspatercept is more likely to achieve transfusion independence compared to ESA, however, prefer ESA due to cost advantage. See criteria if patient has failed ESA or if erythropoietin level is  $>500$  mU/mL.
  - Reference: Platzbecker U et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naïve, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet. 2023 Jul 29;402(10399):373-385. doi: 10.1016/S0140-6736(23)00874-7. Epub 2023 Jun 10. PMID: 37311468.

*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  $\geq 15\%$  of erythroid precursors with ring sideroblasts OR  $\geq 5\%$  ring sideroblasts if an SF3B1 mutation was present.

2. MDS is classified as very low, low, or intermediate risk by IPSS-R (see below)

3. Age  $\geq 18$  years or older

4. Patient currently requires at least 2 red cell transfusions every 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, approve 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 by at least 2 units over an 8 week period compared to baseline (see dosing recommendations below).

**\*Per NCCN**, the usual dosing for Procrit/Epogen/Retacrit and Aranesp in MDS is 40,000-60,000 Units 1-2 x/wk and 150-300 mcg every other wk, respectively. Consider patients ESA refractory if they do not achieve a

hemoglobin level that avoids transfusion after approximately 8 weeks of the upper limits of these dosing recommendations.

**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 ( $\geq 2$  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](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 <sup>e</sup>	Very good	—	Good	—		Poor	Very
Marrow blasts (%)	$\leq 2$	—	$>2-<5$	—	5-10	$>10$	—
Hemoglobin	$\geq 10$	—	8- $<10$	$<8$	—	—	—
Platelets	$\geq 100$	50- $<100$	$<50$	—	—	—	—
ANC	$\geq 0.8$	$<0.8$	—	—	—	—	—

**Revision History:**

Date	What changed	Pharmacist's initials
4/28/2020	Criteria written.	SK
7/26/2021	Criteria reviewed. No change	SK
1/18/2023	Criteria reviewed. No change	SK
11/17/2023	Listed new indication for ESA naïve MDS patients. Do not cover per 11/16/2023 P&T meeting. Added definition for ESA refractory.	SK

**Evolocumab (Repatha) 140mg/mL (1mL)**  
**Autoinjector, solution cartridge, or prefilled syringe**

FDA-approved for:

- Homozygous familial hypercholesterolemia
- Hyperlipidemia, primary (including heterozygous familial hyperlipidemia)
- Prevention of cardiovascular events in patients with established CVD

<b>Initial</b>	
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 $\geq 70\text{mg/dL}$ or a non-HDL-C of $\geq 100\text{mg/dL}$ WHILE TAKING an optimized regimen of lipid-lowering therapy <ul style="list-style-type: none"> <li>• Must be a high-intensity statin equal to atorvastatin 20mg or higher (with or without ezetimibe) for at least 6 weeks</li> </ul>
3.	Patient must also have additional characteristics that places him/her at higher cardiovascular risk including: At least 1 of the following: <ul style="list-style-type: none"> <li>• T1 or T2DM</li> <li>• Age <math>\geq 65</math></li> <li>• MI or non-hemorrhagic stroke within the past 6 months</li> <li>• Additional diagnosis of MI or non-hemorrhagic stroke excluding the one in the original history (item 1 above)</li> <li>• Current daily cigarette smoking</li> <li>• History of symptomatic peripheral artery disease,</li> </ul> OR At least 2 of the following: <ul style="list-style-type: none"> <li>• History of non-MI related coronary revascularization</li> <li>• Residual coronary artery disease with <math>\geq 40\%</math> stenosis in <math>\geq 2</math> large vessels</li> <li>• Most recent hsCRP <math>&gt; 2.0\text{mg/L}</math></li> <li>• Most recent LDL-C <math>&gt; 130\text{mg/dL}</math> or non-HDL-C <math>&gt; 160\text{mg/dL}</math></li> <li>• Diagnosis of metabolic syndrome (At least 3 of the following: <ul style="list-style-type: none"> <li>○ waist circumference <math>&gt; 40</math> inches for men or <math>&gt; 35</math> inches for women</li> <li>○ triglycerides <math>\geq 150\text{mg/dL}</math></li> <li>○ HDL-C <math>&lt; 40\text{mg/dL}</math> for men or <math>&lt; 50</math> for women</li> <li>○ Systolic blood pressure <math>\geq 130\text{mmHg}</math> or diastolic BP <math>\geq 85\text{mmHg}</math> or hypertension treated with medication</li> <li>○ Fasting glucose <math>\geq 100\text{mg/dL}</math></li> </ul> </li> </ul>
Note: dose is 140mg every 2 weeks	

Date	What changed?	Pharmacist's initials
1/16/19	I wrote the criteria.	JJ
10/5/2020	I reviewed the criteria.	JJ
3/30/21	These criteria are the same custom PA guidelines that UAS has been using. Will use this set since it is formatted like other EBRx criteria.	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)
2. 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.
3. The primary endpoint occurred in 9.8% vs 11.3%placebo (HR 0.85; 95%CI 0.79-0.92).
4. There was no reduction in all cause death or in CV death. The mean follow up was 2.2y.
5. The patients had LDL $>70\text{mg/dL}$  or non-HDL $>100\text{mg/dL}$  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).

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

Granisetron transdermal patch (Sancuso)  
34.4 mg/patch (one patch delivers 3.1 mg/24 hours)  
EBRx PA Criteria

**is 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 starting the day after chemotherapy and continuing at least 4 days 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 chemotherapy-induced nausea and vomiting (CINV) during chemotherapy and within 24 hrs after last dose of chemotherapy.<sup>1</sup>

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.<sup>2</sup>

**References:**

1. Boccia RV et al. Efficacy 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
8/30/2022	Criteria reviewed. No changes	SK

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) SEE CRITERIA
- in combination with carfilzomib 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.
    - Martin T et al. Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized Phase 3 study. *Blood Cancer J*. 2023 May 9;13(1):72. doi: 10.1038/s41408-023-00797-8. PMID: 37156782; PMCID: PMC10166682.

**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  $\geq 75$  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)).<sup>1,2</sup>

**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:**

3. 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
4. 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](https://ashpublications.org/blood/article/134/Supplement_1/1893/427649/Efficacy-of-Isatuximab-with-Pomalidomide-and)

Revision History:

Date	What changed	Pharmacist's initials
10/22/2020	Criteria written	sk
6/17/2021	Listed new indication (with carfilzomib+dex). Not covered.	SK
1/26/2022	Criteria review. No change	SK
6/19/2023	Criteria review. No change	SK

## Golimumab (Simponi) 50mg SQ EBRx PA Criteria

### is FDA-approved for:

- **Ankylosing spondylitis**, Active; in adults for the treatment of active ankylosing spondylitis
- **Polyarticular juvenile idiopathic arthritis**, treatment of active polyarticular juvenile idiopathic arthritis in pediatric patients 2 years of age and older
- **Psoriatic arthritis**, Active; in adults and the IV injection is indicated in pediatric patients 2 years and older for the treatment of active psoriatic arthritis (PsA)
- **Rheumatoid arthritis (Mod-Severe)**, Active; in combination with methotrexate is indicated for the subQ or IV treatment of moderately to severely active rheumatoid arthritis in adults
- **Ulcerative Colitis (Mod – Severe)**, Active; in adults for the treatment of moderately to severely active ulcerative colitis in patients with corticosteroid dependence and an inadequate response or failure to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for [3]:inducing and maintaining clinical response improving endoscopic appearance of mucosa during induction inducing clinical remission achieving and sustaining clinical remission in induction responders

Ankylosing Spondylitis
<b>Med Impact: Preferred</b>
1. The patient must have the diagnosis of active ankylosing spondylitis.
2. The patient must have failed a trial of 2 different NSAIDs. Sequential NSAID trials should be 1 month in length and be optimally dosed.
<b>Note:</b> 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 <b>Bath Ankylosing Spondylitis Disease Activity Index</b> , 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, <u>Fatigue</u> , <u>Spinal pain</u> , <u>Arthralgia</u> , <u>Enthesitis</u> , or inflammation of <u>tendons and ligaments</u> , <u>Morning stiffness duration</u> , <u>Morning stiffness severity</u> . 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 <u>biologic therapies</u> .
References: 1. NICE guidelines: Adalimumab, etanercept and infliximab for ankylosing spondylitis. May 2008. <a href="http://publications.nice.org.uk/adalimumab-etanercept-and-infliximab-for-ankylosing-spondylitis-ta143/evidence-and-interpretation">http://publications.nice.org.uk/adalimumab-etanercept-and-infliximab-for-ankylosing-spondylitis-ta143/evidence-and-interpretation</a> 2. EDERP. Report on Targeted Immune Modulators Update 3/8/12.

Juvenile Idiopathic Arthritis (previously known as JRA)
<b>Med Impact: Trial of 2 preferred agents (Enbrel, Humira, Xeljanz IR, Amjevita, Cyltezo, Hyrimoz, Adalimumab-ADAZ)</b>
1. The patient must have the diagnosis of juvenile idiopathic arthritis.
2. The patient has received glucocorticoid joint injections and at least 3 months of methotrexate or leflunomide at the maximum tolerated typical dose. OR The patient, specifically with enthesitis ( <b>inflammation where tendons or ligaments connect with the bone</b> )-related arthritis, received glucocorticoid joint injections and an adequate trial of sulfasalazine OR The patient received an adequate trial of NSAIDs and have sacroiliac arthritis
3. The JIA patient received more than one TNFα sequentially and is now seeking to switch therapy due to high disease activity
4. The JIA patient received more than one TNFα sequentially, then abatacept, and still have high disease activity, AND test positive for RF
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. <i>Arthritis Care &amp; Research</i> . 2011(April);63(4):465–482.

## Psoriatic Arthritis (must be used in combo with DMARD)

### Med Impact: Preferred

4. The patient must have a diagnosis of psoriatic arthritis
5. The patient must have failed a trial of 2 NSAIDs. Each trial should be 1 month in length
6. The patient must have failed 3 months of a DMARD therapy (examples: methotrexate, sulfasalazine, penicillamine, azathioprine, leflunomide).
7. If seeking upadacitinib, the patient must have failed one of the EBRx covered TNFi

#### 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](http://www.uptodate.com/contents/treatment-of-psoriatic-arthritis?source=search_result&search=psoriatic+arthritis&selectedTitle=2%7E105#H18) . Accessed 7/3/12.

## Rheumatoid Arthritis

### Med impact: Preferred

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.

\*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.<sup>1</sup>

‡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.

## Ulcerative Colitis

### Med Impact: Preferred

1. The patient must have the diagnosis of ulcerative colitis
2. The patient must have failed  $\geq 3$  months of mesalamine or sulfasalazine or glucocorticoids.
3. The patient has moderate to severe disease (characterized by steroid dependence).

#### 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	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
1/30/24	Criteria made for individual TIM	AB

Risankizumab (Skyrizi)  
EBRx PA Criteria

**is FDA-approved for:**

- Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
- Active psoriatic arthritis in adults.
- Moderately to severely active Crohn's disease in adults

**Plaque Psoriasis**

1. Age is  $\geq 18$  years
2. The patient must have the diagnosis of plaque psoriasis that is moderate to severe defined as meeting all of the following requirements:
  - Body surface area (BSA) involvement of  $\geq 5\%$
  - Static Physician's Global Assessment (sPGA) score of  $\geq 3$  in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 4
  - Psoriasis Area and Severity Index (PASI) score  $\geq 12$
3. If the patient ALSO HAS the diagnosis of psoriatic arthritis, approve Skyrizi without requiring prior therapy.
4. The patient must have failed 3 consecutive months of systemic or topical, non-biologic therapy including these options:
  - 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 criteria met, approve for 12 months.**

**Psoriatic Arthritis**

1. Age is  $\geq 18$  years
2. The patient must have the diagnosis of psoriatic arthritis
3. The patient must have failed a trial of 2 NSAIDs. Each trial should be 1 month in length.
4. The patient must have failed 3 months of a DMARD therapy (examples: methotrexate, sulfasalazine, penicillamine, azathioprine, leflunomide).

**If criteria met, approve for 12 months.**

**Crohn's Disease**

1. Age is  $\geq 18$  years
2. The patient must have the diagnosis of active Crohn's disease
3. Crohn's Disease Activity Index (CDAI) is 220 to 450 and Simple Endoscopic Score for Crohn's disease (SES-CD) is  $\geq 6$  (or  $\geq 4$  for isolated ileal disease)
4. Inadequate response, loss of response, or intolerance to oral aminosalicylates (e.g. mesalamine, sulfasalazine), corticosteroids, or immunosuppressants (e.g. azathioprine, mercaptopurine, methotrexate)

**If criteria met, approve for 12 months.**

Quantity Limits: 30 day supply

Revision History:

Date	What changed	Pharmacist's initials
6/29/2022	Split Skyrizi criteria from TIMs criteria document. Added criteria for psoriatic arthritis and Crohn's so that all FDA approved indications are covered as required by rebate contract.	SK
8/12/2022	On plaque psoriasis, changed BSA threshold from 10% to 5% to be consistent with old criteria	SK

## Eculizumab (Soliris) injection [MEDICAL BENEFIT ONLY]

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. "Ecuzumab 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.

3. The patient must have either failed therapy with rituximab or else not be a candidate for it.

4. The patient must have impaired activities of daily living.

5. 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.

6. 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	Jill Johnson
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

EBRx PA Criteria  
Nusinersen (Spinraza) 12 mg/5 mL

**is FDA-approved for:** treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

**Criteria for new users**

2. The patient must be 12 years or younger at initial request. <sup>4</sup>
<ul style="list-style-type: none"> <li>The patient <b>must have</b> a diagnosis of Spinal Muscular Atrophy with all of the following criteria:<sup>1,4</sup> including genetic documentation of homozygous deletion or mutation in <b>SMN1 gene</b>.</li> <li>Onset of clinical signs/symptoms consist with SMA at <math>\leq 48</math> months of age.<sup>1,4</sup></li> <li>Disease duration of <math>\leq 7</math> years.<sup>4</sup></li> </ul>
3. For infantile SMA, then they must also have 2 copies of the SMN2 gene <sup>1</sup> , 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.)
4. No prior use of Zolgensma. (There are not data to support subsequent Spinraza use (benefit or detriment) in patients who were administered Zolgensma.)
5. Prescriber must be a neuromuscular specialist.
6. At the initial request, the patient must have NO HISTORY of the ability to walk independently (defined as the ability to walk $\geq 15$ 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 4<sup>th</sup> 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.**

7. The patient must have begun Spinraza treatment before age 12. <sup>4</sup>
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.

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.	JJohnson
7/22/19	I updated the criteria for the medical benefit after the 5/24/19 ICER update.	JJohnson

Ref:

- 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
- ICER SMA Draft Evidence Report. Accessed 1/17/19.
- 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 HFMSE to be 3 points]
- 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
- ICER Report. Spinraza and Zolgensma for SMA. [https://icer-review.org/wp-content/uploads/2018/07/ICER\\_SMA\\_Final\\_Evidence\\_Report\\_052419.pdf](https://icer-review.org/wp-content/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf)

Esketamine (Spravato)  
EBRx PA Criteria

**is 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.
3. The psychiatrist must submit a plan outlining the treatment plan for esketamine treatment.

###The continuation PA will be good for 1 month. QL will be 84mg ONCE weekly.###

**Note: Dosing is:**

- Induction: 56mg twice wkly up to 84mg twice wkly for 4 weeks total
- Maintenance: After 5 wks from the induction phase, the dosing moves to QW, then after 9wks can decrease to q2wks.
- 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.

**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 may 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

1/8/24	I adjusted the PA approval duration from 12 months to 1 month. I added that the prescriber must submit a plan outlining the treatment plan for esketamine treatment.	JJ
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**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.

## 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.
4. Treatment of moderately to severely active **ulcerative colitis** in adults

<b>Plaque psoriasis</b>	
<b>Initial request</b>	
1. Does the patient have a diagnosis of moderate-to-severe plaque psoriasis, as indicated by a PASI score of at $\geq 12$ (scale is 0-72) and involvement of at least 10% BSA?	<input type="checkbox"/> Yes <input type="checkbox"/> 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? <b>OR</b> Has the patient experience intolerance to methotrexate? <b>OR</b> Does the patient have a contraindication to methotrexate?	<input type="checkbox"/> Yes <input type="checkbox"/> 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)? <b>OR</b> Is the patient intolerant to or have a contraindication to at least 1 of those treatments?	<input type="checkbox"/> Yes <input type="checkbox"/> 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.	
<b>If the answer to 1, 2, AND 3 is yes, approve coverage for 28 weeks (4 doses).</b>	
<b>Responders maintenance therapy</b>	
Did the patient achieve a reduction in PASI of <u>at least</u> 50%?	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>If the answer was yes, patient is approved for therapy for 1 year (4 doses).</b>	
<p>References:</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>	

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

<b>Psoriatic arthritis</b>	
1. Does the patient have a diagnosis of active psoriatic arthritis, as defined by $\geq 5$ swollen and $\geq 5$ tender joints and a C-reactive protein of $\geq 3.0$ mg/L?	<input type="checkbox"/> Yes <input type="checkbox"/> No If yes, go on to next question. If no, stop and deny coverage.
2. Has the patient had an inadequate response to $\geq 3$ months of disease-modifying antirheumatic drug (DMARD) therapy	<input type="checkbox"/> Yes <input type="checkbox"/> No

<b>OR</b> ≥4 weeks of NSAID therapy <b>OR</b> ≥ 8 (etanercept, adalimumab, golimumab, certolizumab-pegol) or 14 (infliximab) continuous weeks of TNF-antagonist therapy? <b>OR</b> Was the patient intolerant of anti-TNF therapies?	
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.	
<b>If the answer to 1 and 2 is yes, approve coverage for 1 year (6 doses).</b>	
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. <i>Lancet</i> 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. <i>Ann Rheum Dis</i> 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.

<b>Crohn's Disease</b>
1. The patient must have the diagnosis of Crohn's 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.
<b>If the patient satisfies the criteria above, PA is approved for 1 year.</b>
References: 1. Feagan, Brian G., et al. "Ustekinumab as induction and maintenance therapy for Crohn's disease." <i>New England Journal of Medicine</i> 375.20 (2016): 1946-1960.

<b>Ulcerative Colitis</b>
<input type="checkbox"/> Infliximab (Remicade®) <input type="checkbox"/> infliximab-abda (Renflexis) <input type="checkbox"/> infliximab-abda (Inflectra®)
4. The patient must have the diagnosis of ulcerative colitis
5. The patient must have failed ≥3 months of mesalamine or sulfasalazine or glucocorticoids?
6. The patient have moderate to severe disease (characterized by steroid dependence).

#### 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	PharmD Initials
11.7.14	PA criteria written	GBB
3/3/17	I added the Crohn's indication and reference.	J Johnson
3/7/17	Corrected criteria to require failure of humira AND Enbrel for PPso and PsArth, but only Humira for Crohn's	JJ
12/7/23	Added UC indication and PA criteria already in place	AB

<b>PASI</b>	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).
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Histrelin (Supprelin LA)  
EBRx PA Criteria

**is FDA-approved for:** Treatment of children with central precocious puberty

**Criteria for new users**

- |   |
|---|
| 1. Diagnosis of central precocious puberty                  |
| 2. Child must be between the ages of 4 and 12 years of age. |

Note: Dose is 1 implant every 12 months; it contains 50mg histrelin acetate. The implant in the inner aspect of the upper arm should be removed after 12 months of therapy when another implant can be inserted.

Quantity Limits: 1 implant per year.

References:

1. Supprelin LA PI. Accessed from DailyMed. 10/3/23.

Revision History:

Date	What changed	Pharmacist's initials
10/3/23	I wrote the criteria.	JJ

Granisetron sustained-release SQ injection (Sustol)  
EBRx PA Criteria

**is 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 5HT3 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.<sup>1</sup>

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.<sup>2</sup>

**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
3/29/2021	Criteria reviewed. No changes.	SK
8/30/2022	Criteria reviewed. No changes	SK

Atezolizumab (Tecentriq)  
840 mg/14 mL and 1200 mg/20 mL vials  
EBRx PA Criteria

**is FDA-approved for:**

- **Non-small cell lung cancer, metastatic (NSCLC)**
  - As adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on  $\geq 1\%$  of tumor cells, as determined by an FDA-approved test. COVERED FOR PD-L1  $>50\%$  ONLY
  - As monotherapy for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (**EITHER** PD-L1 stained  $\geq 50\%$  of tumor cells [TC  $\geq 50\%$ ] **OR** PD-L1 stained tumor-infiltrating immune cells covering  $\geq 10\%$  of the tumor area [IC  $\geq 10\%$ ]), 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
- **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.
    - References:
      - 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
      - Ascierto PA et al. Overall survival with first-line atezolizumab in combination with vemurafenib and cobimetinib in BRAFV600 mutation-positive advanced melanoma (IMspire150): second interim analysis of a multicentre, randomised, phase 3 study. Lancet Oncol. 2023 Jan;24(1):33-44. doi: 10.1016/S1470-2045(22)00687-8. Epub 2022 Nov 29. PMID: 36460017.
      - Ascierto PA et al. Overall survival with first-line atezolizumab in combination with vemurafenib and cobimetinib in BRAFV600 mutation-positive advanced melanoma (IMspire150): second interim analysis of a multicentre, randomised, phase 3 study. Lancet Oncol. 2023 Jan;24(1):33-44. doi: 10.1016/S1470-2045(22)00687-8. Epub 2022 Nov 29. PMID: 36460017.
- **Alveolar Soft Part Sarcoma (ASPS)** NOT COVERED
  - Treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic ASPS
    - Data limited to single arm trial with no QOL/OS/symptom improvement
    - Chen AP, Sharon E, O'Sullivan-Coyne G, Moore N, Foster JC, Hu JS, Van Tine BA, Conley AP, Read WL, Riedel RF, Burgess MA, Glod J, Davis EJ, Merriam P, Naqash AR, Fino KK, Miller BL, Wilsker DF, Begum A, Ferry-Galow KV, Deshpande HA, Schwartz GK, Ladle BH, Okuno SH, Beck JC, Chen JL, Takebe N, Fogli LK, Rosenberger CL, Parchment RE, Doroshow JH. Atezolizumab for Advanced Alveolar

### Early Stage (Resectable) Non-Small Cell Lung Cancer (NSCLC)

1. Patient must have diagnosis of NSCLC
2. Patient has undergone complete tumor resection
3. PD-L1 expression is at least 50%
4. Patient has completed post-operative (adjuvant) cisplatin-based chemotherapy. If fewer than 4 cycles were given, therapy was discontinued due to toxicity.
5. Tumor is stage II or IIIA per 7<sup>th</sup> edition AJCC staging

**If all criteria are met, approve for 12 months only (total duration of therapy is limited to 12 mo)**

Note:

Patients meeting above criteria were randomized to either atezolizumab or best supportive care. Patients in the atezolizumab (n=476). Among patients with PD-L1 expression  $\geq 1\%$ , the median disease free survival was not reached in the atezolizumab arm and 35.3 mo in the control arm (p=0.004). Benefit in this population was driven by patients whose tumor PD-L1 expression was at least 50% (see table).

PD-L1 expression	Median disease free survival (Atezo versus control)	Hazard ratio, 95% CI/p value
$\geq 1\%$ (n=476)	Not reached vs 35.3 mo	0.66 (0.5-0.88); p=0.004 [primary analysis]
1-49% (n=247)	32.8 mo vs 31.4 mo	0.87 (95% CI: 0.60, 1.26) [post hoc analysis]
$\geq 50\%$ (n=229)	Not reached vs 35.7 mo	0.43 (95% CI: 0.27, 0.68) [prespecified subgroup analysis]

References:

1. Tecentriq PI. [https://www.gene.com/download/pdf/tecentriq\\_prescribing.pdf](https://www.gene.com/download/pdf/tecentriq_prescribing.pdf). Accessed 6/27/2022
2. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial [published correction appears in Lancet. 2021 Sep 23;]. Lancet. 2021;398(10308):1344-1357. doi:10.1016/S0140-6736(21)02098-5

### Metastatic 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  $\geq 50\%$  or IC  $\geq 10\%$ ) [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.<sup>1</sup> 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).<sup>2</sup>

Atezolizumab/carboplatin/nab-paclitaxel also improved OS vs carboplatin/nab-paclitaxel with median OS of 18.6 mo vs. 13.9 mo.<sup>3</sup>

-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).<sup>4</sup> [data from trial Impower 110 study, NCT02409342—results published in PI only as of 6/2/2020]

#### References:

3. 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
4. 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
5. 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
6. Tecentrig PI. [https://www.gene.com/download/pdf/tecentrig\\_prescribing.pdf](https://www.gene.com/download/pdf/tecentrig_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). Median overall survival in the atezo/bev group was later reported as 19.2 mo.

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.

**References:**

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

Cheng AL et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022 Apr;76(4):862-873. doi: 10.1016/j.jhep.2021.11.030. Epub 2021 Dec 11. PMID: 34902530.

**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
7/21/2022	Added criteria for adjuvant lung cancer indication per 7/21/2022 P&T meeting	SK
9/29/2022	Removed reference to pembrolizumab criteria (EBRx no longer manages pembrolizumab)	SK
12/12/2022	Added updated reference for atezo/bev HCC indication	SK
1/17/2023	<ul style="list-style-type: none"> <li>Criteria reviewed (no changes)</li> <li>Added new reference for melanoma indication (updated OS data with no significant difference)</li> <li>Added new indication (ASPS). Not covered.</li> <li>Removed the following urothelial and breast cancer indications (were not covered by EBRx). FDA approval was withdrawn due to lack of confirmed benefit.</li> <li><b><u>Urothelial carcinoma, locally advanced or metastatic</u></b> <ul style="list-style-type: none"> <li>patients not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering <math>\geq 5\%</math> of the tumor area) NOT COVERED: single arm trial only</li> <li>patients not eligible for any platinum-containing chemotherapy regardless of PD-L1 status NOT COVERED: single arm trial only</li> <li>Patients who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy. NOT COVERED: 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</li> </ul> </li> </ul>	SK

	<p>immunotherapy). PEMBROLIZUMAB has shown overall survival benefit in this setting with fewer severe adverse effects versus chemotherapy.</p> <ul style="list-style-type: none"> <li>• <b><u>Triple-Negative Breast Cancer (TNBC)</u></b> <ul style="list-style-type: none"> <li>○ 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 <math>\geq 1\%</math> of the tumor area), as determined by an FDA approved test (<b>accelerated approval based on progression free survival</b>). NOT COVERED           <ul style="list-style-type: none"> <li>▪ As of 5/20/2021 EBRx P&amp;T meeting, TNBC indication will no longer be covered. <b><i>Current users will be grandfathered.</i></b></li> <li>▪ In IMPOWER130, benefit was limited to progression free survival only.</li> <li>▪ In confirmatory trial (IMPOWER131), PFS benefit was NOT confirmed, and an overall survival benefit was not evident.</li> <li>▪ References:               <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• IMPOWER 131: <a href="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">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</a> Accessed 4/27/2021 [NCT03125902 impassion 131]</li> </ul> </li> </ul> </li> </ul> </li> </ul>	
1/19/2024	Criteria reviewed. No change except added 2 new references for excluded indications.	SK

## Sacituzumab govitecan (Trodelvy)

180 mg vial

EBRx PA Criteria

### is FDA-approved for:

- Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease SEE CRITERIA
- Unresectable locally advanced or metastatic hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting SEE CRITERIA
- Locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PDL1) inhibitor. (Accelerated approval) NOT COVERED
  - Data limited to single arm trial with response rates reported only
    - Reference: Tagawa ST et al. TROPY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. J Clin Oncol. 2021 Apr 30;JCO2003489. doi: 10.1200/JCO.20.03489. Epub ahead of print. PMID: 33929895.

### Criteria for new users

1. Diagnosis of metastatic breast cancer
  2. Disease is HER2 negative (IHC 0, IHC 1+ or IHC 2+/ISH-)
  3. Disease is refractory to or relapsed on/after two or more prior systemic therapies, at least one of them for metastatic disease
  4. If disease is hormone receptor positive (estrogen receptor and/or progesterone receptor +), patient has received prior endocrine therapy (e.g. tamoxifen, anastrozole, letrozole, fulvestrant)
  5. Sacituzumab will be used as single agent
- If criteria met, approve for 12 months

### Note:

ASCENT NCT02574455 Phase III, RCT	Key inclusion/exclusion criteria: Metastatic triple-negative breast cancer -at least 2 prior treatment for metastatic disease -prior taxane required	Results for patients with no brain mets at baseline (n=468)		
		Outcome	SG	Chemo
1:1 randomization SG vs physician's choice single-agent chemo*	Population enrolled: N=529 Median age: 54 y/o Median # of prior regimens: 4	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*
*capecitabine, eribulin, vinorelbine, OR gemcitabine		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
6/17/2021	Listed new urothelial cancer indication. Not covered.	SK

1/27/2022	Criteria review. Updated FDA indication and criteria for breast cancer to mirror wording of current FDA approval (no major change in criteria)	SK
4/20/2023	Updated breast cancer criteria to cover HR+ tumors based on newer FDA approval	SK

Natalizumab (Tysabri) MEDICAL PA  
EBRx PA Criteria

**is FDA-approved for:**

- relapsing multiple sclerosis,
- Crohns disease

**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. 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.
6. No concurrent therapy with immunosuppressive drugs
7. 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

**Revision History:**

Date	What changed	Pharmacist's initials
9/18/19	I wrote the criteria.	JJohnson
10/28/2020	I updated the criteria.	JJohnson

**References:**

1. Lexicomp. Natalizumab. 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>
4. Sandborn, William J., et al. "Natalizumab induction and maintenance therapy for Crohn's disease." *New England Journal of Medicine* 353.18 (2005): 1912-1925.

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 (splenic flexure to rectum) derive significantly more benefit from EGFR inhibitors compared to right-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 (1°) 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](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.
<p>Notes:</p> <p>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).</p> <p>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.</p> <p>Panitumumab has not been shown to improve or be detrimental to quality of life.</p> <p>Reference:</p> <p>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</p> <p>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</p>

Revision History:

Date	What changed?	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
1/26/2022	Criteria reviewed. No change	SK
1/19/2024	Criteria reviewed. No change	SK

Iloprost (Ventavis) Solution for Inhalation  
10 or 20 mcg/mL (1mL)  
EBRx PA Criteria

**is FDA-approved for:** Treatment of pulmonary arterial hypertension (WHO group I) in patients with NYHA functional class III or IV symptoms to improve exercise tolerance, symptoms, and diminish clinical deterioration.

**Criteria for new users**

1. The patient must have the diagnosis of PAH, WHO group I, and NYHA functional class III or IV symptoms.
2. The patient must taking a PDE5 inhibitor daily (i.e. tadalafil, sildenafil) or must be unable to take one.
3. The patient must have tried and failed combination ambrisentan or bosentan, plus PDE5i.
4. The patient must not have concurrent iloprost with IV epoprostenol, IV treprostinil, or SC treprostinil.

OR

1. The patient must have the diagnosis of PAH Group 5 after treating underlying causes.

**Note:**

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.

Combination iloprost and bosentan is acceptable.

**References:**

1. Humbert, Marc, et al. "2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the 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 the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG)." *European heart journal* 43.38 (2022): 3618-3731.
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
3/20/23	I updated the criteria.	

**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/cm		>240		>240	>240	>240

Von Willebrand Factor, recombinant (Vonvendi)---Medical Benefit Drug  
EBRx PA Criteria

**is FDA-approved for: von Willebrand disease:** Treatment (on demand) and control of bleeding episodes and perioperative management of bleeding in adults with von Willebrand disease (VWD); routine prophylaxis in adult patients with severe type 3 VWD receiving on-demand therapy to reduce the frequency of bleeding episodes.

**Criteria for new users**

1. The patient must have the diagnosis of von Willebrand disease and require on demand and control of bleeding episodes and perioperative management of bleeding. OR have severe type 3 von Willebrand disease (a virtual absence of the VWF protein) and require routine prophylaxis to prevent bleeding.
2. The patient must be an adult (age 18y+)

If approved, this PA should be good for 1 year. Could be longer since diagnosis doesn't go away. Unless there is a gene therapy.

**Note:** Contraindication: hypersensitivity to hamster or mouse proteins.

May develop antibody formation, hypersensitivity, or thrombotic events.

Administration is slow IV infusion, max rate of 4mL/min. May require administration of factor VIII in which case the VWF should be infused, then the factor VIII within 10 minutes.

- 1) type 1 is a partial quantitative deficiency of VWF,
- 2) type 2 is caused by qualitative abnormalities of VWF, and
  - a) type 2A is characterized by reduced or absent high-molecular-weight VWF,
  - b) type 2B results from a gain of function in VWF that increases its affinity for platelets,
  - c) type 2M is caused by reduced VWF interactions with platelets or collagen, and
  - d) type 2N results from reduced binding of VWF to FVIII.
- 3) type 3 is a virtual absence of the VWF protein with associated very low FVIII levels.

**References:**

1. Lexicomp. Vonvendi. 1/31/24.
2. James, Paula D., et al. "ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease." *Blood advances* 5.1 (2021): 280-300.

**Revision History:**

Date	What changed	Pharmacist's initials
1/31/24	I wrote the criteria consistent with the FDA approval.	JJ

EBRx PA Criteria  
Pazopanib (Votrient®)  
200 mg tablets

**FDA-approved for:**

- Advanced renal cell carcinoma See criteria
- 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<sup>st</sup> 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<sup>st</sup> outcome was PFS, 2<sup>nd</sup> 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).<sup>1</sup>

Pazopanib may also be cost effective compared with sunitinib in the first-line setting.<sup>2</sup>

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	What changed?	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	Clay said the PBM has already programmed a 2 w supply limit for pazopanib.	JJ

7/5/17	James Barr 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
4/7/21	Applied EBRx criteria to UAS. No current users	JJ
10/2021	Criteria reviewed. No change.	SK
3/23/2023	Criteria reviewed. No change.	SK

# 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  $\geq 30$  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<sup>2</sup>.
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<sup>3</sup>.

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 6 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<sup>4</sup>.

### Continuation Criteria for Asthma

1. The patient may not miss more than 33% of scheduled omalizumab doses. (must receive at least 4 of the last 6 scheduled doses) on time.
2. The patient must meet ONE of the following criteria:
  - A 25% reduction in asthma exacerbations (i.e. hospitalizations, urgent or emergent care visits, use of rescue medications) compared to their baseline prior to omalizumab
  - The patient has been able to reduce their oral corticosteroid dose from their pre-omalizumab baseline dose

If so, may approve a 12 month PA.

### CHRONIC IDIOPATHIC URTICARIA

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 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 4 weeks.
8. If still not controlled, first generation antihistamines hydroxyzine 100mg-200mg, or doxepin 100-150mg, must be tried at bedtime.

Usual dose is 150-300mg q4 weeks regardless of IgE or body weight. Don't exceed 300mg q4w.

If approved, the PA may be approved for 12m.

**Continuation Criteria for Chronic Idiopathic Urticaria**

**1. The patient must not have missed more than 33% of scheduled omalizumab doses. (must receive at least 4 of the last 6 scheduled doses) on time.**

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:

<sup>1</sup>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.

<sup>2</sup>Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.

<sup>3</sup>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.

<sup>4</sup>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
12/11/20	I added continuation criteria to the asthma and CIU indications.	JJ
3/9/2021	I reviewed the criteria. No changes.	JJ

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)
- Treatment of adult patients with unresectable or metastatic melanoma, in combination with nivolumab
- 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 NOT COVERED

- **Renal Cell Carcinoma (RCC)**

- Intermediate or poor risk advanced RCC, as first line treatment 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<sup>a</sup> 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.<sup>a</sup> NOT COVERED:
- NCT01658878 compared different regimens of nivolumab/ipilimumab in patients with HCC who had been treated previously with sorafenib. Overall survival was promising with one regimen (which is now FDA approved), but no comparative trials have shown it to be superior to other therapies or placebo.

Reference: Yau T, Kang YK, Kim TY, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial [published correction appears in JAMA Oncol. 2021 Jan 1;7(1):140]. JAMA Oncol. 2020;6(11):e204564. doi:10.1001/jamaoncol.2020.4564

- **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.

- **Malignant Pleural Mesothelioma**

- Adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab

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.

### **Melanoma, metastatic**

6. Diagnosis of unresectable or metastatic melanoma.
7. If the patient has received no prior therapy, ipilimumab will be used in combination with nivolumab
8. If the patient has received prior therapy for advanced/metastatic, tumor is progressing.
9. The patient must be ECOG performance status 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity) at initiation
10. Patient does not have diagnosis of ocular/uveal melanoma.

**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 as indicated 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%).<sup>1,2</sup>
  - Ipilimumab does have activity after nivolumab or pembrolizumab though this is based on a retrospective review<sup>3</sup>
  - 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.<sup>4</sup>
- 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)**

7. See nivolumab (Opdivo) FIRST LINE TREATMENT CRITERIA for use with IPILIMUMAB. If criteria met, approve ipilimumab (Yervoy) for 4 months (maximum of 4 doses total).

NOTE: Continuation not allowed if 4 doses already given. If doses were delayed due to toxicity or other reason and reapproval is needed, approve as indicated if no disease progression and no unacceptable toxicity.

### **Non-Small Cell Lung Cancer (NSCLC)**

If patient meets criteria for use of nivolumab (Opdivo) in combination with ipilimumab for first-line treatment (no prior therapy for advanced/metastatic disease) of NSCLC, approve x 12 months.

NOTE: Ipilimumab is continued until disease progression or unacceptable toxicity for this indication

### **Malignant Pleural Mesothelioma**

If patient meets criteria for use of nivolumab (Opdivo) in combination with ipilimumab for treatment of malignant pleural mesothelioma, approve x 12 months.

NOTE: Ipilimumab is continued until disease progression or unacceptable toxicity for this indication

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	What changed?	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 continuation criteria Renal cell: allow use in combination with nivo for untreated, intermediate/poor risk patients for max of 4 doses only	Sk
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
11/16/2020	Added new indication for mesothelioma (covered—see nivolumab criteria); all criteria reviewed—no changes	SK
3/30/2022	In criteria for nivolumab/ipilimumab for first line treatment of renal cell carcinoma edited Karnofsky performance status required in IMDC risk staging from 80% to 70% as done in study protocol. I changed this in form as well.	SK
4/25/2022	Criteria review completed. Did not change criteria. Made notes to refer to nivolumab criteria for NSCLC, RCC, and mesothelioma indications (ipilimumab and nivolumab criteria are identical).	SK

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
- treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation NOT COVERED: data is limited to single arm trial only. One case series demonstrated symptom improvement in 3 patients (low quality data).

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
3. Haroche J et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation *Blood (2013) 121 (9): 1495–1500.*

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 atezolizumab 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

**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. Must receive vemurafenib concurrently with cobimetinib.
4. Tumor has not previously progressed on a BRAF or MEK inhibitor (e.g. encorafenib, vemurafenib, dabrafenib, binimetinib, trametinib, cobimetinib).

**If the patient meets all criteria above, approve for 12 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.<sup>1,2</sup>

**Note:**

-Vemurafenib is also FDA approved as monotherapy for treatment of advanced/metastatic melanoma and is superior to chemotherapy<sup>3</sup>. 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, Ascarto 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	What changed?	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
12/15/2020	Criteria reviewed. No change. Added reference for case series (n=3) for use of vemurafenib in Erdheim Chester. Patient experienced symptom improvement. Since this is low quality evidence, no change to criteria.	SK
3/31/2021	Applied to UAS plan	JJ
4/25/2022	Criteria reviewed. No change.	SK
8/1/2023	Criteria reviewed. For melanoma indication, allow use for 2 <sup>nd</sup> line setting	SK

EBRx PA Criteria—MEDICAL PA  
Onasemnogene Abeparvovec (Zolgensma Kit) for 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 $\geq$ 15 feet unaided).
Medication is excluded from pharmacy.	

It is recommended that this medication be administered at a Center of Excellence.

Revision History:

Date	What changed	Pharmacist's initials
7/22/19	I wrote the criteria for the medical benefit after the 5/24/19 ICER update.	JJohnson

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](https://icer-review.org/wp-content/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf)

**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 baricitinib 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>

<b>Rheumatoid Arthritis—PA updated 4/22/21JJ</b>				
	<b>csDMARD (conventional synthetic)</b>	<b>tsDMARD (targeted synthetic)</b>	<b>boDMARD (biologic originator)</b>	
	<b>Methotrexate Sulfasalazine Leflunomide</b>	<b>Tofacitinib Baricitinib (targets JAK)</b>	<b>Adalimumab Certolizumab Etanercept Golimumab Upadacitinib Sarilumab</b>	<b>Infliximab Abatacept Rituximab* Tocilizumab Anakinra</b>
1. The patient must have the diagnosis of rheumatoid arthritis.				
<b>Early RA (diagnosis less than 6 months ago and still symptomatic):</b>				
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.				
<b>Established RA:</b>				
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.				
<b>*FOR RITUXIMAB</b>				
<b>NOTE:</b> 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. <sup>1</sup>				
‡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*. 2012;369:4384-85.
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

Date	Update	Pharmacist's initials
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## Juvenile Idiopathic Arthritis (previously known as JRA)

☐ AFS Etanercept (Enbrel®)-TNFα, ☐ AFS Adalimumab (Humira®)-TNFα, ☐ AFS \*Infliximab (Remicade®)-TNFα --must be used w/ methotrexate, ☐ AFS anakinra (Kineret), ☐ AFS infliximab-abda (Renflexis)

Does the patient have the diagnosis of juvenile idiopathic arthritis?	<input type="checkbox"/> AFS Yes <input type="checkbox"/> AFS No
3. 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?	<input type="checkbox"/> AFS Yes <input type="checkbox"/> AFS No
Abatacept (Orencia®) Criteria (should apply the above criteria as well as the following:)	
3. Has the JIA patient received more than one TNFα sequentially and is now seeking to switch therapy due to high disease activity?	<input type="checkbox"/> AFS Yes <input type="checkbox"/> AFS No
Rituximab (Rituxan®) Criteria (should have fulfilled the above criteria 1-3 and the following:)	
Has the JIA patient received more than one TNFα sequentially, then abatacept, and still have high disease activity, AND test positive for RF?	<input type="checkbox"/> AFS Yes <input type="checkbox"/> AFS 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. <i>Arthritis Care &amp; Research</i> . 2011(April);63(4):465-482.	

## Ankylosing Spondylitis

<input type="checkbox"/> AFS Adalimumab (Humira®) <input type="checkbox"/> AFS Etanercept (Enbrel®) <input type="checkbox"/> AFS Golimumab (Simponi®)€ <input type="checkbox"/> AFS Certolizumab (Cimzia®) <input type="checkbox"/> AFS Secukinumab (Cosentyx®) <input type="checkbox"/> AFS Ixekizumab (Taltz®) <input type="checkbox"/> AFS Infliximab (Remicade®)—no new starts; only allow if currently receiving.	
Does the patient have the diagnosis of active ankylosing spondylitis?	<input type="checkbox"/> AFS Yes <input type="checkbox"/> AFS No
Has the patient failed a trial of 2 NSAIDS? Sequential NSAID trials should be 1 month in length and be optimally dosed.	<input type="checkbox"/> AFS Yes <input type="checkbox"/> AFS 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  $\geq 2$  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  $\geq 4$  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

[A][AFS] Adalimumab (Humira®) [A][AFS] Etanercept (Enbrel®) [A][AFS] Infliximab (Remicade®) [A][AFS] infliximab-abda (Renflexis) [A][AFS] Golimumab (Simponi®) [A][AFS] Certolizumab (Cimzia®) [A][AFS] Abatacept (Orencia) [A][AFS] Secukinumab (Cosentyx®) [A][AFS] Ixekizumab (Taltz)

\*\*\*Ustekinumab (Stelara)—Please go to the EBD PA criteria “Ustekinumab” for criteria  
Upadacitinib (Rinvoq)—FDA-approved 12/15/21 as 2<sup>nd</sup> line to TNFi.

The patient must have a diagnosis of psoriatic arthritis.

The patient must have failed a trial of 2 NSAIDs. Each trial should be 1 month in length.

The patient must have failed 3 months of a DMARD therapy (examples: methotrexate, sulfasalazine, penicillamine, azathioprine, leflunomide).

If seeking upadacitinib, the patient must have failed one of the EBRx covered TNFi.

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](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

TNF inhibitors:	IL-17 inhibitors:	IL-12/23 inhibitors:	IL-23 inhibitor:
<span>[A]</span> <span>[AFS]</span> Adalimumab (Humira®)	<span>[A]</span> <span>[AFS]</span> Secukinumab (Cosentyx®)	*** Ustekinumab	<span>[A]</span> <span>[AFS]</span> Guselkumab
<span>[A]</span> <span>[AFS]</span> Etanercept (Enbrel®)	<span>[A]</span> <span>[AFS]</span> Ixekizumab (Taltz®)	(Stelara®)—Please go to	(Tremfya®)
<span>[A]</span> <span>[AFS]</span> Infliximab (Remicade®)	<span>[A]</span> <span>[AFS]</span> Brodalumab (Siliq®)	EBD PA criteria for	<span>[A]</span> <span>[AFS]</span> Risankizumab
<span>[A]</span> <span>[AFS]</span> infliximab-abda (Renflexis)		“Ustekinumab” for criteria	(Skyrizi®)

1. If the patient ALSO HAS the diagnosis of psoriatic arthritis, approve the biologic without requiring “fail first therapy”.

2. Otherwise, the patient must have a diagnosis of moderate to severe (affecting  $\geq 5\%$  BSA) plaque psoriasis.

3. The patient must have failed 3 consecutive months of systemic or topical, non-biologic therapy including these options:

- 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](https://icer-review.org/wp-content/uploads/2017/11/ICER_Psoriasis_Update_Draft_Report_04272018.pdf)

## Crohn's Disease

[A][AFS] Adalimumab (Humira®) [A][AFS] upadacitinib (Rinvoq®)—after TNF failure or intolerance  
[A][AFS] Certolizumab pegol (Cimzia®)  
[A][AFS] Infliximab (Remicade®)

<b>A</b> <b>AFS</b>	<b>infliximab-abda (Renflexis®)</b>
<b>A</b> <b>AFS</b>	<b>infliximab-abda (Inflectra®)</b>
	3. The patient must have a diagnosis of Crohn's disease.
	4. The patient must either be corticosteroid-dependent (with CDAI score >220) OR be 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 $\geq 2.4\text{g/d}$ ) or budesonide (at a dose of $\geq 6\text{ mg/day}$ ).
	5. 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.
	6. 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.
<b>A</b> <b>AFS</b>	<b>Natalizumab (Tysabri) (Patient should satisfy the above criteria as well as the one below.)</b>
	7. The patient must have a diagnosis of Crohn's disease AND an inadequate response to or unable to tolerate conventional CD therapies and anti-TNF therapy.
<p>References:</p> <ol style="list-style-type: none"> <li>1. Lichtenstein GR, Hanauer SB, Sandborn WJ. ACG Practice Guidelines. Management of Crohn's Disease in Adults. <i>Am J Gastroenterol</i>. 2009. <i>Am J Gastroenterol</i> advance online publication, 6 January 2009; doi: 10.1038/ajg.2008.168.</li> <li>2. Colombel JF, Sandborn WJ, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. <i>N Engl J Med</i>. 2010;362:1383-95.</li> <li>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. <i>Gastroenterology</i>. 2013;145:1459-63.</li> <li>4. Garnett WR, Yunker N. Treatment of Crohn's Disease with Infliximab. <i>Am J Health Syst Pharm</i>. 2001;58(4).</li> </ol> <p>Note: CDAI is Crohn's Disease Activity Index. &gt;450 is severe. 200-449 is moderate. 150-199 is quiescent disease. &lt;150 is in remission.</p>	

## Ulcerative Colitis

<b>A</b> <b>AFS</b>	<b>Infliximab (Remicade®)</b>
<b>A</b> <b>AFS</b>	<b>infliximab-abda (Renflexis)</b>
<b>A</b> <b>AFS</b>	<b>infliximab-abda (Inflectra®)</b>
	1. The patient must have the diagnosis of ulcerative colitis
	2. The patient must have failed $\geq 3$ months of mesalamine or sulfasalazine or glucocorticoids?
	3. The patient have moderate to severe disease (characterized by steroid dependence).
<p>General References:</p> <ol style="list-style-type: none"> <li>1. Drug Effectiveness Review Project. Targeted Immune Modulators Update 3/8/12.</li> <li>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. <i>Am J Gastroenterol</i> 2010; 105:501–523.</li> </ol>	

## Hidradenitis suppurativa

<b>A</b> <b>AFS</b>	<b>Adalimumab (Humira®)</b>
	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 $\geq 90$ days continuous duration of an oral antibiotic for the treatment of their HS in the past 180 days.
	3. The patient must have tried chlorhexidine gluconate, triclosan, benzoyl peroxide, and dilute bleach in bathwater.
	If approved, PA is good for 3 months, then the patient must satisfy continuation criteria.
<p>*Hurley Staging:</p> <ul style="list-style-type: none"> <li>• Stage I: abscess formation, single or multiple, without sinus tracts and cicatrization (scarring).</li> <li>• Stage II: One or more widely separated recurrent abscesses with tract formation and cicatrization (scars).</li> </ul>	

<ul style="list-style-type: none"> <li>• Stage III: Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement.</li> </ul>
<b>Continuation Criteria</b>
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." <i>New England Journal of Medicine</i> 375.5 (2016): 422-434.

<b>Noninfectious uveitis</b>
<b>Adalimumab (Humira®), etanercept (Enbrel)</b>
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.
<b>Continuation Criteria</b>
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." <i>New England Journal of Medicine</i> 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 Criteria" on the EBRx, EBD PA Criteria Folder	JJ
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 (Olmiant) 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
12/16/21	Added upadacitinib (Rinvoq) as a treatment option (2 <sup>nd</sup> line) after at least 1 TNFi. FDA-approved 12/15/21.	JJ

2/8/23	Added ixekizumab (Taltz) as a treatment option after trying 2 NSAIDs. Also added ixekizumab as a treatment option for psoriatic arthritis after 2 NSAIDs and 3 months of DMARD therapy.	JJ
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