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 June 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.

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must have the diagnosis chronic granulomatous disease OR severe malignant osteopetrosis.</td>
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<tr>
<td>If approved, the PA is good for 12 months.</td>
</tr>
</tbody>
</table>

**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/m² administered 3 times per week. For pediatric patients the dosing is:
  - BSA <0.5m²: 1.5mcg/kg/dose TIW, max of 50mcg/m²
  - BSA >0.5m²: 50mcg/m² (1 million units/m²) TIW, max 50mcg/m²
- For malignant osteopetrosis, the dose is 50mcg/m² SC TIW, max 50mcg/m²

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

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<tbody>
<tr>
<td>1.</td>
<td>Patient must be 18 years old or older.</td>
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<tr>
<td>2.</td>
<td>Patient must have received the diagnosis of migraine onset before age 50.</td>
</tr>
</tbody>
</table>
| 3. | Patient must have tried and had an inadequate response to a trial of TWO preventative therapies:  
a. beta blocker - propranolol 80-240mg/day or metoprolol, nadolol, or atenolol  
b. divalproex 500-1000mg/day, topiramate 100-200mg/day  
c. botulinum toxin A (prevention of chronic migraine only), at a minimum of 2 quarterly injections (6 months). |
| A trial consists of 2 or more months of claims per drug. |
| 4. | The prescriber must be a neurologist or headache specialist or be working with one regarding the prescribing for this patient. |
| 5. | If criteria are fulfilled. Approve erenumab 70 mg once monthly.  
In order for 140 mg/month approval, pt must have had inadequate response to 3 months of claims for the 70 mg/mo dose. |
|   |   |
|   | If the above criteria are satisfied, the PA is good for 3 months. |
|   | It will be imperative for the call pharmacist to record the number of stated migraine days per month in order to assess response and subsequent access to the drug. |

Continuation Criteria for Migraine Users:

1. To continue access to erenumab, the patient must have filled at least 2-30 day fills in the last 90 days and less rescue medication.

If both of the continuation criteria were achieved, allow access for 6 months. After 6 months, the patient must have shown at least 5 erenumab fills in the previous 6 months (since it is prophylactic) and less consumption of rescue medication as evidenced by fewer triptan fills than before erenumab was accessed by the patient.

Dosing: 70 mg once a month, up to 140 mg once monthly.

Ref:
5. 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 peds patients weighting \( \geq 10 \) kg.
- Recurrent pericarditis, to reduce risk of recurrence in adults and peds 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 \( 12 \) y+) |
| 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 twe, 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 \( 12 \) y+ 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.
Avelumab (Bavencio) 200 mg/10 ml solution
EBRx PA Criteria

FDA-approved for:

Merkel Cell Carcinoma (MCC)
• 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):
  o 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:
  o 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)
  o 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:

1This 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)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>1.</td>
<td>Diagnosis of unresectable, locally advanced or metastatic urothelial (bladder) carcinoma</td>
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<tr>
<td>2.</td>
<td>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]</td>
</tr>
<tr>
<td>4.</td>
<td>Avelumab will be initiated within 10 weeks of last dose of chemotherapy.</td>
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</table>

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:

Quantity Limits: n/a
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

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<thead>
<tr>
<th>Criteria for new users with LN</th>
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<tr>
<td>1. The patient must be 18 y+.</td>
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<tr>
<td>2. The patient must have a diagnosis of autoantibody+ SLE (antinuclear antibody titers &gt;1:80, anti-double-stranded DNA antibodies, or both) that fulfilled the 1982 (updated 1997) ACR classification criteria for SLE active lupus nephritis.</td>
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<td>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)</td>
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<td>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.</td>
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<td>5. The patient must not be receiving dialysis.</td>
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<td>6. The patient must be receiving standard therapy for LN including cyclophosphamide-azathioprine, or mycophenolate mofetil. [Patients may also receive ACEi or ARB, hydroxychloroquine.]</td>
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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:
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.
- Relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL). SEE CRITERIA

### Criteria for new users

<table>
<thead>
<tr>
<th>Criteria for new users</th>
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<tbody>
<tr>
<td>1. Diagnosis of relapsed or refractory acute lymphocytic leukemia (ALL)</td>
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<tr>
<td>2. Leukemia is CD19 positive</td>
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<tr>
<td>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]</td>
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</table>

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%).

Health-related quality of life was also improved in the blinatumomab group.

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.

References:


Quantity Limits: n/a (medical benefit drug)
OnabotulinumtoxinA (Botox)—Only the urinary incontinence indication is covered by EBD Commercial plans; All Indications covered for EBD Medicare plans (only non-cosmetic uses)

EBRx PA Criteria

<table>
<thead>
<tr>
<th>Urinary incontinence indication:</th>
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<tbody>
<tr>
<td>1. The patient must have the diagnosis of urinary incontinence. OR</td>
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**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.


**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.


**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 BTX for episodic migraines.


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

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

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].


**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.”


**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.
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

<table>
<thead>
<tr>
<th>Criteria for new users</th>
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<tbody>
<tr>
<td>1. Must have diagnosis of acquired thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>2. Must have a platelet count of &lt; 150,000 currently</td>
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<tr>
<td>3. Must be receiving plasma exchange concurrently</td>
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<tr>
<td>4. Must be receiving concomitant immunosuppressive therapy (e.g. rituximab, high dose steroids)</td>
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<tr>
<td>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.</td>
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<tr>
<td>6. Prescriber must be a hematologist.</td>
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<tr>
<td>Note: Must discontinue if &gt;2 aTTP recurrences occur during treatment.</td>
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<tr>
<th>Criteria for continuation</th>
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<tr>
<td>1. Must have failed the first 30 days of caplacizumab and still be suffering from aTTP.</td>
</tr>
<tr>
<td>2. Must be receiving concurrent plasma exchange, immunosuppressive therapy, and still have a platelet count &lt;150,000.</td>
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<tr>
<td>Note: PI says it should be given for 30 days initially, with an additional course extended up to an additional maximum 28 days.</td>
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Quantity Limits: 58 days max.

References:
Aztreonam inhaled (Cayston)
EBRx PA Criteria

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

<table>
<thead>
<tr>
<th>Criteria for new users</th>
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<tbody>
<tr>
<td>1. The patient must have a diagnosis of cystic fibrosis.</td>
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<tr>
<td>2. The patient must have a known pulmonary infection with Pseudomonas aeruginosa.</td>
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<td>3. The patient must be receiving bronchodilator therapy.</td>
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<tr>
<td>4. The patient should not have overlapping days supply of inhaled tobramycin (therapeutic duplication).</td>
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</table>

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

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

**References:**
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

<table>
<thead>
<tr>
<th>Criteria for new users</th>
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<tbody>
<tr>
<td>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 &amp; 3.)</td>
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<tr>
<td>2. The patient must be symptomatic (anemia, bone disease, hepatomegaly, splenomegaly, or thrombocytopenia)</td>
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<tr>
<td>3. The patient is not receiving concurrent substrate-reduction therapy (eliglustat or miglustat).</td>
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<tr>
<td>If all the criteria are satisfied, the PA is valid for 12 months.</td>
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Note: Dose is 30-60 IU/kg q2weeks. Long term outcomes with ERT with imiglucerase at two centers using low-dose (median dose 15-30 U/gh q4w) and high-dose (median dose 80 U/kg q4w) were compared retrospectively. Improvement in hemoglobin, platelet count, and hepatosplenomegaly was not significantly different between cohorts.

For nonneuronopathic (GD1), all the ERTs are approximately equivalent in efficacy. Response to treatment varies from patient to patient, but analysis of data from the Caucher Registry and GD treatment centers demonstrates certain trends for imiglucerase and alglucerase in GD1 disease.

The alternative therpay is substrate-reduction therapy (SRT) (i.e eliglustat, miglustat). Eliglustat is approved for a broader use than miglustat. Miglustat is restricted to adults with GD who are medically unable to receive ERT. Eliglustat was non inferior to imiglucerase for the composite endpoint of decreased hematologic measurements (Hb and plt count) and increased organ volume (spleen and liver)

Quantity Limits: Dose of 60IU/kg q2w.

References:
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 ≥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 <2.8mg/dL (or a level below the lower level of normal for reference)
3. A standing height below the 50th percentile for age and sex on the basis of local normative data from the US.
4. Must have received oral phosphate plus active vitamin D therapy for:
   • >12 consecutive months (for children >3y) or
   • >6 consecutive months (for children <3y)
5. Must have an X-Ray confirming rickets @ the growth plates OR bowing of femur, tibia, or both femur and tibia.
6. Must be age 1-12 years.

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

References:
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).
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:
    - 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
- 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)
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:

### Criteria for new users (NEWLY DIAGNOSED)

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<thead>
<tr>
<th>1. Must have a diagnosis of multiple myeloma with no prior systemic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
</tr>
<tr>
<td>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).</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Treatment phase</th>
<th>Weeks</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Weeks 1 to 8</td>
<td>Weekly (total of 8 doses)</td>
</tr>
<tr>
<td></td>
<td>Weeks 9 to 16</td>
<td>Every two weeks (total of 4 doses)</td>
</tr>
<tr>
<td>Stop for high dose chemotherapy and autologous stem cell transplant (ASCT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consolidation*</td>
<td>Weeks 1 to 8</td>
<td>Every two weeks (total of 4 doses)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1 to 6</td>
<td>Weekly (total of 6 doses)</td>
</tr>
<tr>
<td>Weeks 7-54</td>
<td>Every 3 weeks (total of 16 doses)</td>
</tr>
<tr>
<td>Weeks 55 and beyond (Until progression of disease)</td>
<td>Every 4 weeks</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1 to 8</td>
<td>Weekly (total of 8 doses)</td>
</tr>
<tr>
<td>Weeks 9-24</td>
<td>Every 2 weeks (total of 8 doses)</td>
</tr>
<tr>
<td>Weeks 25 and beyond (Until progression of disease)</td>
<td>Every 4 weeks</td>
</tr>
</tbody>
</table>

Note:
- In newly-diagnosed, transplant eligible patients, daratumumab/bortezomib/thalidomide/dexamethasone (D-VTD) improved overall survival at day 100 after stem cell transplant compared with
bortezomib/thalidomide/dexamethasone alone although data are immature.¹ 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.² Improvements in Quality of life were reported.³

- 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).⁴⁵ 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).⁶⁷ 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:

D-VMP:

D-RD:

Criteria for new users (RELAPSED/REFRACTORY)

<table>
<thead>
<tr>
<th>Criteria for new users (RELAPSED/REFRACTORY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Must have a diagnosis of multiple myeloma that is progressing</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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.¹
• Daratumumab/lenalidomide/dexamethasone improved progression free survival compared with lenalidomide/dexamethasone alone. Overall survival is trending towards improvement but still considered immature at last follow up.²,³

• Daratumumab monotherapy was found have improved overall survival compared to pomalidomide/dexamethasone in a matched adjusted indirect comparison analysis.⁴

References:
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
EBRx PA Criteria
Dupilimab (Dupixent) SC injection

is FDA-approved for:
• atopic dermatitis, moderate-severe, in patients ≥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 ≥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 ≥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.

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

**Criteria for new users**

1. Patient must be ≥6 years old
2. Patient must currently have on their profile:
   • an inhaled corticosteroid (medium-high-dose, fluticasone propionate at a total daily dose of >500ug or equipotent equivalent, for at least 3 months and with a stable dose for at least 1 month prior to first request of dupilumab),
   • a long-acting beta agonist,
   • and an inhaled long acting muscarinic agonist (LAMA) for the previous 4 months. May have montelukast in place of LAMA.

OR

The patient must be dependent on chronic oral corticosteroids (defined as being on oral steroids ≥50% of the year)

3. The patient must have a blood eosinophil count of ≥150 cells/mm3 at baseline.
4. Prior to the first dupilumab request, the patient MUST have experienced, within 1 year prior to first request, any of the following:
   • treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once
   • Hospitalization or emergency medical care visit for worsening asthma
5. Patient must have the diagnosis: **Moderate to SEVERE** asthma with an eosinophilic phenotype and still be symptomatic.
6. Prescriber must be an allergist, immunologist, or pulmonologist.

References:
1. The patient must be a non-smoker.
2. The patient must have an FEV1 <80% of predicted (or <90% of predicted for adolescents).
3. The patient is not currently being treated with omalizumab, mepolizumab, reslizumab, or benralizumab.

Note: The first dose is up to 600mg (2-300mg syringes followed by up to 1-300mg dose every other week. PA is good for 16 weeks; assessment of efficacy should occur then.

### Criteria for continuation

1. Patient must be adherent to the q2w dosing.
2. Patient must have experienced an improvement in symptoms. The physician must have documented this improvement in the medical record. A reduction in oral corticosteroid dose would be considered an improvement.

Note: if both are satisfied, approve PA for 1 year.

### Quantity Limits

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

### References


### CHRONIC RHINOSINUSITIS WITH NASAL POLYPS, AS ADD-ON MAINTENANCE TREATMENT

#### Criteria for new users

1. Patient must be >18 years old
2. Patient must have the diagnosis of bilateral nasal polyposis and chronic symptoms of sinusitis despite intranasal 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.

#### Criteria for continuation

1. Patient must be adherent to the qw dosing.
2. Patient must have experienced an improvement in symptoms. The physician must have documented this improvement in the medical record.

Note: if both are satisfied, approve PA for 1 year.

DOSE is 600mg LD followed by 300mg every other week; the patient should be receiving concurrent intranasal steroids.

Reference:


### EOSINOPHILIC ESOPHAGITIS (EOE)

#### Criteria for new users

1. Patient must be >1 years old AND at least 15kg
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 flurry)

Note: The dose is 300mg SC once weekly.
PA is good for 16 weeks; assessment of efficacy should occur then.

#### Criteria for continuation

1. Patient must be adherent to the qw dosing.
2. Patient must have experienced an improvement in symptoms. The physician must have documented this improvement in the medical record.

Note: if both are satisfied, approve PA for 1 year.

DOSE is 600mg LD followed by 300mg every other week; the patient should be receiving concurrent intranasal steroids.

Reference:

1. 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:

---

**Prurigo nodularis**

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient must be &gt;18 years old</td>
</tr>
<tr>
<td>2. Patient must have the diagnosis of prurigo nodularis.</td>
</tr>
<tr>
<td>3. Prescriber must be an allergist or immunologist.</td>
</tr>
<tr>
<td>4. The patient is not currently being treated with omalizumab, mepolizumab, reslizumab, or benralizumab.</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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.

**Criteria for continuation**

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:
**is FDA-approved for:** Treatment of adults with confirmed Fabry disease.

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must have the diagnosis of Fabry (aka Anderson-Fabry) disease with a leukocyte alpha-galactosidase A (alpha-Gal A) activity and confirmed by genetic testing.</td>
</tr>
<tr>
<td>a. A positive diagnosis in males is virtually undetectable (&lt;3%) alpha-Gal A leukocyte activity; then, confirmation by genetic testing.</td>
</tr>
<tr>
<td>b. In males with 3-35% alpha-Gal A leukocyte activity, a diagnosis should be considered and genetic testing should take place.</td>
</tr>
<tr>
<td>c. In males with alpha-Gal A leukocyte activity &gt;35% of mean normal, the diagnosis cannot be established.</td>
</tr>
<tr>
<td>d. In females, the measurement of alpha-Gal A activity is unreliable because they are heterozygotes and have variable levels of alpha-Gal A that can overlap with levels in healthy controls; in suspected cases, genetic testing must be done. Biopsy of routinely affected organs with demonstration of elevated Gb3 by electron microscopy or mass spectroscopy may be helpful in confirming the diagnosis.</td>
</tr>
<tr>
<td>2. The patient must be 18y+.</td>
</tr>
<tr>
<td>3. The patient is not receiving concurrent pegunigalsidase with agalsidase alfa or agalsidase beta.</td>
</tr>
</tbody>
</table>

If approved, the PA is good for 1 year.

<table>
<thead>
<tr>
<th>Criteria for continuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must have complied with &gt;50% of treatments.</td>
</tr>
<tr>
<td>2. The patient has not had persistent severe infusion reactions including anaphylaxis.</td>
</tr>
<tr>
<td>3. The patient does NOT have ESKD, without an option for kidney transplantation, in combination with advanced heart failure NYHA class IV.</td>
</tr>
<tr>
<td>4. The patient must have treatment response after 1 year of treatment with pegunigalsidase.</td>
</tr>
</tbody>
</table>

**Note:** Patients may receive concurrent migalastat.

**References:**
1. UpToDate. Fabry Disease Diagnosis. Also Treatment and Prognosis. 3/11/24.
**Galcanzumab (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

<table>
<thead>
<tr>
<th><strong>Initial Criteria: MIGRAINE prophylaxis:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient must be 18 years old or older.</td>
</tr>
<tr>
<td>Patient must have received diagnosis of migraine onset before age 50.</td>
</tr>
<tr>
<td>Patient must have tried and had an inadequate response to a trial of TWO preventative therapies: beta blocker- propranolol 80-240mg/day or metoprolol, nadolol, or atenolol divalproex 500-1000mg/day, topiramate 100-200mg/day botulinum toxin A.</td>
</tr>
</tbody>
</table>

**A trial consists of 2 or more months of claims per drug.**

The prescriber must be a neurologist or headache specialist or be working with one regarding the prescribing for this patient.

If criteria 1 through 6 are fulfilled, approve galcanzumab 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.

<table>
<thead>
<tr>
<th><strong>Continuation for Migraine prophylaxis:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. To continue access to galcanzumab, the patient must have filled at least 2-30 day fills in the last 90 days and less rescue medication.</td>
</tr>
</tbody>
</table>
If both of the continuation criteria were achieved, allow access for 6 months. After 6 months, the patient must have shown at least 5 galcanzumab fills in the previous 6 months (since it is prophylactic) and less consumption of rescue medication as evidenced by fewer triptan fills than before galcanzumab was accessed by the patient.

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

<table>
<thead>
<tr>
<th><strong>CLUSTER HEADACHE prophylaxis:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>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)</td>
</tr>
<tr>
<td>If the criteria for cluster headache are satisfied, approve for 12 months.</td>
</tr>
<tr>
<td>Note: Dosing for cluster HA is 300mg SC at onset and then QM until the end of the cluster period.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>2. No concurrent eculizumab (medical), inebilizumab (medical), or rituximab (medical).</td>
</tr>
</tbody>
</table>

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

References:
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:**

epcoritamab (Epkinly) 4 mg/0.8 ml and 48 mg/0.8 ml single dose vials
EBRx PA Criteria (medical benefit)

is FDA-approved for:
treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagnosis of diffuse large B-cell lymphoma (DLBCL)</td>
</tr>
<tr>
<td>2. Disease has relapsed after prior therapy OR is refractory to prior therapy</td>
</tr>
<tr>
<td>3. Patient has been treated with at least 2 prior lines of therapy [such as RCHOP, RICE, Yescarta, Tecartus, Revlimid/rituximab, loncastuximab]</td>
</tr>
<tr>
<td>4. Disease has not progressed on glofitamab (Columvi). [glofitamab is another CD20 bispecific T cell engager]</td>
</tr>
</tbody>
</table>

If above criteria are met, approve for 12 months.

Note:
Dose Note: 24 hour hospitalization is recommended after cycle 1 day 15 dose for observation:

<table>
<thead>
<tr>
<th>Cycle of treatment</th>
<th>Day of treatment</th>
<th>Dose of EPKINLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Step-up dose 1</td>
<td>0.16 mg</td>
</tr>
<tr>
<td>8</td>
<td>Step-up dose 2</td>
<td>0.8 mg</td>
</tr>
<tr>
<td>15</td>
<td>First full dose</td>
<td>48 mg</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>48 mg</td>
</tr>
<tr>
<td>Cycles 2 and 3</td>
<td>1, 8, 15 and 22</td>
<td>48 mg</td>
</tr>
<tr>
<td>Cycles 4 to 9</td>
<td>1 and 15</td>
<td>48 mg</td>
</tr>
<tr>
<td>Cycle 10 and beyond</td>
<td>1</td>
<td>48 mg</td>
</tr>
</tbody>
</table>

Note: Cycle = 28 days

The median overall survival reported with epcoritamab compares favorably with alternative therapies. There is also evidence it improves quality of life.

References:

Quantity Limits: n/a
**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

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must be &gt;18 years of age and be diagnosed with peripheral T-cell lymphoma that has progressed after at least 1 prior treatment.</td>
</tr>
<tr>
<td>2. The patient must be ECOG 0-2.</td>
</tr>
</tbody>
</table>

If above criteria are met, approve x 1 year

**Notes:**
The dose is 30mg/m²/week for 6 weeks followed by 1 week of rest. Then the cycle is repeated until progressive disease or unacceptable toxicity. B₁₂ 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:**
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.

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.

<table>
<thead>
<tr>
<th>CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) in combination with CHLORAMBUCIL (first line)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must have previously untreated CD20-positive CLL.</td>
</tr>
<tr>
<td>2. The patient must be planning to use concomitant chlorambucil.</td>
</tr>
<tr>
<td>3. The patient must have Binet stage C or symptomatic disease</td>
</tr>
<tr>
<td><strong>If the above criteria are met, approve coverage for 6 months.</strong></td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

**Dosing:**
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.

**Evidence:**
Obinutuzumab+chlorambucil (OC) or rituximab+chlorambucil (RC) was compared to chlorambucil (C) alone in CLL patients with coexisting conditions. Progression free survival was improved with OC and RC compared to chlorambucil. Treatment with OC prolonged overall survival compared with chlorambucil. RC did not improve overall survival compared with chlorambucil alone. There was no difference in overall survival between OC and RC.

References:

<table>
<thead>
<tr>
<th>CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) in combination with VENETOCLAX or ACALABRUTINIB (first line)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must have previously untreated CLL.</td>
</tr>
<tr>
<td>2. The patient must be planning to use concomitant venetoclax or acalabrutinib.</td>
</tr>
<tr>
<td><strong>If the above criteria are met, approve coverage for 6 months.</strong></td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>
**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:**


**Acalabrutinib + obinutuzumab references:**


**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/m2/day IV on days 1 & 2.
Cycles 2-6: 1000mg IV obinutuzumab on day 1 every 28 days for 5 doses PLUS bendamustine 90mg/m2/day IV on days 1 & 2. After combination therapy is complete (6-8 cycles), obinutuzumab may be given every 2 months for up to 2 years beginning ~2 months after the last induction phase obinutuzumab dose.

**Evidence:**
Obinutuzumab+bendamustine was compared to bendamustine alone in patients with relapsed/refractory follicular lymphoma. Overall survival was improved in the obinutuzumab+bendamustine group and time to deterioration of HRQOL was prolonged in the obinutuzumab/bendamustine group compared with bendamustine alone (8.0 mo vs 4.6 mo).

**References:**
Fingolimod (Gilenya®) tablets
EBRx PA Criteria

**is FDA-approved for:** relapsing multiple sclerosis

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient must have the diagnosis of relapsing MS with highly active disease as indicated by the prescriber (high frequency of relapses, MRI changes).</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>3. No concurrent therapy with other RRMS drug therapies.</td>
</tr>
</tbody>
</table>

**Note:** Dose is 0.5mg QD.
**QL: 30/30; specialty drug. No fills >31 ds.**

References:
<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
</tr>
</thead>
</table>
| Pediatric: Growth failure due to inadequate endogenous growth hormone (GH)secretion  
  age < 18  
  short stature (height less than -2.25 SD for age based on sex specific standards)  
  must confirm GH deficiency with provocative GH stimulation test  
  must have open epiphyses (confirm with x-ray of a long bone)  
  **Approve if patient meets above criteria**  
  *If pt is >18 yrs, please see adult criteria below** | Norditropin--EBD  
  Genotropin  
  Humatrope  
  Nutropin  
  Omnitrope--UAS  
  Saizen  
  Tev-Tropin |
| Pediatric: Short stature associated with Turner syndrome  
  *Not a covered benefit. Treatment in one trial increased final height by approximately six cm over an untreated control group. Despite this increase, the final height of treated women was still outside the normal range* | Genotropin  
  Humatrope  
  Norditropin  
  Nutropin  
  Omnitrope |
| Pediatric: Growth failure in children born small for gestational age who fail to manifest catch-up growth by either 2 years of age (a) or by 2-4 years of age (b)  
  *Not a covered benefit. These children are not GHD and treatment with GH is likely to yield only modest gains in height. Adult height will usually be below average despite therapy.* | Genotropin (a)  
  Humatrope (b)  
  Norditropin (b)  
  Omnitrope (a) |
| Pediatric: Idiopathic Short Stature (ISS)  
  *Not a covered benefit. These children are not GHD and when health related quality of life was 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.* | Genotropin  
  Humatrope  
  Nutropin  
  Omnitrope |
| Pediatric: Growth failure due to chronic renal insufficiency up to time of renal transplant  
  *Not a covered benefit. GH treatment increased height in children with CKD by about 4 cm after 1 year and by a further 2 cm after 2 years of treatment compared with no treatment. Studies were too short to determine if continuing treatment resulted in an increase in final adult height.* | Nutropin |
| Pediatric: Growth failure due to Prader Willi syndrome  
  **Open epiphyses**  
  o Confirm with x-ray of long bone upon initiation of therapy  
  o If 18-25 yrs, must have yearly x-ray to verify open epiphyses as epiphyses usually close around this time  
  Diagnosis of Prader Willi syndrome from DNA testing  
  must NOT have h/o severe respiratory impairment or upper airway obstruction  
  must NOT have sleep apnea  
  must Not be severely obese (>225% IBW)  
  **Initial Approval: 1 year**  
  **Reauthorization: Pt must continue to meet above criteria** | Genotropin  
  Omnitrope--UAS |
| Pediatric: Short stature or growth failure associated with short stature homeobox gene (SHOX) deficiency | Humatrope |
**Pediatric: Short stature associated with Noonan syndrome**
Not a covered benefit. While a clinical trial showed an initial increase in height standard deviation score, the accelerating effect of GH on bone maturation seemed to compromise the final height prognosis.

**Adult: GH deficiency of either childhood or adult onset etiology**

**Childhood etiology**
1. **Open epiphyses** (usually close between 18-25 yrs)
   - Confirmed GH deficiency
   - X-ray of long bone shows open epiphyses (pts must have yearly x-ray to confirm epiphyses still open during this time)
   
   Initial Approval: 1 year
   Reauthorization: must continue to provide evidence of open epiphyses

2. **Closed epiphyses**
   - must confirm GH deficiency with provocative GH stimulation test [A child’s GH stim test would need to be <10ng/mL to represent deficiency.]
   
   If a transition patient (receiving GH when <18), pt must have been off GH at least one month before GH test to determine if true GHD persists
   Must score ≥ 11 on “Quality of Life Assessment of Growth Hormone Deficiency in Adults” questionnaire during GH-free period
   Initial Approval: 1 year
   Reauthorization: Score on “Quality of Life Assessment of Growth Hormone Deficiency in Adults” questionnaire must have increased by ≥ 7 points.

**Adult onset**
1. **Idiopathic:**
   - Must confirm GH deficiency with TWO provocative GH stimulation tests because idiopathic GHD in adults is very rare [A positive GHD stim test would be <5ng/mL.]

2. **Acquired:**
   - If pt has a diagnosis of structural hypothalamic/pituitary disease, surgery or irradiation to pituitary, or head trauma then only one provocative GH stimulation test is necessary. A GH stim test would need to be <5ng/mL to be positive; also a panhypopituitary patient would have other drugs representative of panhypopituitaryism.]

   Initial Approval: 1 year
   Reauthorization: Score on “Quality of Life Assessment of Growth Hormone Deficiency in Adults” questionnaire must have increased by ≥ 7 points.

**Adult: Short Bowel Syndrome**
Must be receiving parenteral nutrition and have an optimized diet
Must be receiving glutamine concurrently

Initial Approval: 3 months
Reauthorization: tx must have resulted in the elimination of 1 or more days of TPN infusion

**Adult: HIV with wasting or cachexia with concomitant antiretroviral therapy**
Must be receiving concurrent HAART therapy
≥10% unintentional weight loss or low BMI (<20kg/m²) or body weight <90% of IBW

**Norditropin**
**Norditropin—EBD**
**Genotropin**
**Humatrope**
**Nutropin**
**Omnitrope—UAS**
**Saizen**

**Zorbtive**

**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 height in normal range
- Hypothalamus secretes GH-releasing hormone (GHRH), which stimulates the pituitary to secrete GH. Somatostatin is secreted by the hypothalamus to inhibit GH secretion. When GH pulses are secreted into the blood, then insulinlike growth factor (IGF)-1 is released. GHD may result from disruption of the GH axis at numerous places—in the higher brain, the hypothalamus, or the pituitary gland.
- Therapy should be discontinued when patient has reached satisfactory adult height, when epiphyses have fused, or when patient ceases to respond.
- Catch-up growth for children treated early is excellent, with a normal final height attained.11
- A final height of 30cm can be expected on average, but this is affected by variables such as birthweight, age at start of treatment, extent of deficiency, duration of treatment, frequency of GH injections, height at start of treatment, and height at the start of puberty. 11

Pediatric: Turner Syndrome (TS)
- TS is the cause of short stature in girls and primary amenorrhea in young women that is usually caused by loss of part or all of an X chromosome GH is initiated once height is below the 5th percentile for age, which usually occurs between 2-5 yrs.
- Treatment with GH is stopped once epiphyseal fusion occurs, satisfactory height is obtained, or little potential for growth remains (bone age ≥14 yr and growth velocity <2cm/year)12
- Short stature seen in TS is caused by SHOX gene haploinsufficiency, leading most children to have an avg adult stature 20cm shorter than their target height12
- Girls with TS generally have normal GH levels 12
- “Recombinant human growth hormone (hGH) doses between 0.3 to 0.375 mg/kg/wk increase short-term growth in girls with Turner syndrome by approximately three (two) cm in the first (second) year of treatment. Treatment in one trial increased final height by approximately six cm over an untreated control group. Despite this increase, the final height of treated women was still outside the normal range. Additional trials of the effects of hGH carried out with control groups until final height is achieved would allow better informed decisions about whether the benefits of hGH treatment outweigh the requirement of treatment over several years at considerable cost.” –Cochrane Review2

Pediatric: Small for Gestational Age
- The mechanism underlying postnatal growth failure in children who fail to catch up in growth by age 2 is poorly understood, but an irreversible deficit in cell number, inadequate calorie intake during the first years of life, and abnormalities in GH secretion have been hypothesized. Classic GH deficiency is rarely found.
- Most children catch up in growth during the first 6-12 months in life. If they have not caught up by age 2, they are unlikely to do so later.
- Growth hormone treatment is likely to yield only modest gains in height compared with no treatment (an increase in adult height of approximately 6 cm, provided the treatment is begun early and continued for at least seven years). Adult height will usually be below average despite therapy.
Pediatric: Growth failure due to CRI up to time of renal transplant
- Growth retardation is a common problem in children with chronic kidney disease (CKD) and is due to abnormalities in the GH-IGF axis.
- “This review of 16 studies enrolling 809 children found that rhGH increased height in children with CKD by about 4 cm after 1 year and by a further 2 cm after 2 years of treatment compared with no treatment. Studies were too short to determine if continuing treatment resulted in an increase in final adult height.” – Cochrane Review

Pediatric: Prader-Willi Syndrome (PWS)
- genetic disorder characterized by excessive appetite, severe hypotonia, emotional problems and delays in development
- Most patients have hypothalamic-pituitary dysfunction, with abnormal growth hormone secretion and hypogonadotrophic hypogonadism.
- 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
    - 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
      - 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, “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, 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 dysmorphism 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.

Pediatric: Idiopathic Short Stature
- “Results suggest that short-term height gains can range from none to approximately 0.7 SD over one year. One study reported health related quality of life and showed no significant improvement in GH treated children
compared with those in the control group, whist another found no significant evidence that GH treatment impacts psychological adaptation or self-perception in children with ISS.” --Cochrane Review

**Adult: GH deficiency of either childhood or adult onset etiology**

- “Idiopathic GHD in adults is very rare, and stringent criteria are necessary to make this diagnosis. Because in the absence of suggestive clinical circumstances there is a significant false-positive error rate in the response to a single GH stimulation test, we suggest the use of two tests before making this diagnosis.” Endocrine Society Clinical Practice guideline 2011
- Larger doses of somatropin may be required for women taking oral estrogen replacement
- Adults with GHD may have reduced lean body mass, increased fat mass, decreased bone mass, reduced physical and cardiac performance, and an abnormal lipid profile. 11
- Short term (4 month) improvements have been seen in lean body mass, exercise capacity, and muscle strength. In some studies, QoL measures (energy, mood, physical mobility) improved with treatment. 11
- The NICE Guidelines require adults to have an impaired QoL due to the GHD. This is judged using the “Quality of Life Assessment of Growth Hormone Deficiency in Adults” questionnaire. A person should score at least 11 to initiate treated and be 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 rational for treating short bowel patients with human recombinant growth hormone and/or glutamine is the hope of reducing parenteral nutrition dependency
- Studies have shown that GH with or without glutamine appears to increase weight, lean body mass, energy absorption, and nitrogen absorption, however, the benefits of treatment don’t continue after treatment is stopped. 16
- One RCT looked at the effect of GH on parenteral nutrition requirements 8
  - Prospective, double-blind, randomized, placebo controlled trial of 41 adults randomized to either: GH + glutamine placebo, GH placebo + glutamine, or GH +glutamine . All pts had dietary optimization.
  - only patients taking human growth hormone with glutamine maintained statistically significant parenteral nutrition reductions at 3 month follow-up (p<0.005)
  - GH + glutamine + diet reduced and maintained average PN 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 17

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

- Wasting is defined as a ≥10% involuntary weight loss. It is designated an AIDS-defining condition and an independent predictor of mortality.
- Treatment options include nutritional advice, exercise, testosterone (for men, although low doses have been studied in women), appetite-stimulating drugs, and growth hormone
- A meta-analysis of 18 studies concluded that GH may have advantages over testosterone and anabolic steroids in terms of improvements in functional capacity and QOL. 18
  - Work output was reported in 2 studies
    - Improvement of 0.97KJ at 12 weeks vs. improvement of 0.20KJ in the placebo group (p=0.039)
    - Median improvement of 2.60KJ at 12 weeks vs. median decrease of 0.25KJ in placebo grp (p<0.01)
  - QOL was reported in 3 studies
    - Using BACRI scale, GH treatment group reported significant increase in QOL at week 12 (p=0.029 for QOD dosing and 0.039 for QD dosing)
    - Using HIV-PARSE in another study, no significant difference was found in QOL
    - In the 3rd study, 4 treatment groups were compared (GH + IGF, GH alone, IGF alone, or placebo)
      The MOS-HIV scale detected a significant increase in total QOL at 12 weeks in the GH group
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 ≥ 3 hours due to delayed release
        - monitor for delayed hypoglycemia due to secondary stimulation of endogenous insulin release
        - obesity may blunt GH response
    - growth hormone stimulation tests optional if deficiencies in ≥ 3 pituitary axes (ES Grade 1+++)
      - this situation strongly suggests GHD
      - presence of ≥ 3 other pituitary hormone deficiencies with low serum insulin-like growth factor I level may be as specific as any GH stimulation test
      - some insurers may require results of GH stimulation test

References
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.

1. The patient must have a diagnosis* of hereditary angioedema. (see diagnosis criteria below)

2. The drug must be used as chronic prophylactic medication.

3. The patient must have had >2 severe (with abdominal or upper airway involvement that requires hospitalization) or life threatening HAE attacks per month that require acute treatment, medical attention in an ED, or caused significant functional impairment (must be documented in the medical record), in the past year.

4. The patient must have a contraindication or adverse event to attenuated androgen (Danazol 200mg QD or methyltestosterone, stanozolol, or oxandrolone) prophylaxis. Please state the contraindication.

5. If “no” to having contraindication or adverse effect to androgens, the patient must have failed androgen treatment.

6. The patient must remain off angiotensin-converting enzyme inhibitors (ACE-I’s).

7. The patient must remain off any type of estrogen-containing medication.

Note doses:

<table>
<thead>
<tr>
<th>Weight</th>
<th>Haegarda Dose Range</th>
<th>Haegarda Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;41</td>
<td>0-2460</td>
<td>2000</td>
</tr>
<tr>
<td>42-58</td>
<td>2520-3480</td>
<td>3000</td>
</tr>
<tr>
<td>59-74</td>
<td>3540-4440</td>
<td>4000</td>
</tr>
<tr>
<td>75-91</td>
<td>4500-5460</td>
<td>5000</td>
</tr>
<tr>
<td>92-108</td>
<td>5520-6480</td>
<td>6000</td>
</tr>
<tr>
<td>109-124</td>
<td>6540-7440</td>
<td>7000</td>
</tr>
</tbody>
</table>

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).

*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:
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**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Diagnosis of metastatic or unresectable breast cancer</td>
</tr>
<tr>
<td>2.</td>
<td>Previously treated with at least 2 chemotherapeutic regimens for treatment of metastatic or unresectable breast cancer</td>
</tr>
<tr>
<td>3.</td>
<td>Prior treatment for metastatic or unresectable disease included an anthracycline, a taxane, and capecitabine, unless contraindicated</td>
</tr>
</tbody>
</table>

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:**


**Liposarcoma**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Diagnosis of metastatic or unresectable liposarcoma</td>
</tr>
</tbody>
</table>
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:
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:

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

1. The patient has a 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
   - 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 has received an adequate trial of NSAIDs

If criteria met, approve for 12 months.


### Ankylosing Spondylitis

1. The patient has the diagnosis of active ankylosing spondylitis.
2. 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‡ 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-appraisal.

‡BASDAI is **Bath Ankylosing Spondylitis Disease Activity Index**, a scale of measuring discomfort, pain, and fatigue (1 being no problem and 10 being the worst problem) in response to 6 questions asked of the patient pertaining to the 5 major symptoms of AS, Fatigue, Spinal pain, Arthralgia, Enthesitis, or inflammation of tendons and ligaments, Morning stiffness duration, Morning stiffness severity. To give each symptom equal weighting, the average of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of ≥4 suggest suboptimal control of disease, and those patients are usually good candidates for a change in medical therapy, may benefit by treatment with biologic therapies.

References:

### Psoriatic Arthritis

1. The patient must have a diagnosis of psoriatic arthritis.
2. The patient must have failed a trial of 2 NSAIDS. Each trial should be 1 month in length.
3. 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:

### 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 >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.]

### 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 ≥2.4g/d) or budesonide (at a dose of ≥6 mg/day).

If criteria met, approve for 12 months.

References:

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 ≥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.

*Hurley Staging:
- Stage I: abscess formation, single or multiple, without sinus tracts and cicatrization (scarring).
- Stage II: One or more widely separated recurrent abscesses with tract formation and cicatrization (scars).
- Stage III: Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement.

**Continuation Criteria**

1. After 3 months of therapy the patient must have at least a 50% reduction from baseline in the total abscess and inflammation-nodule count, and with no increase in the abscess or draining-fistula count.

If approved, PA is good for 12 months.

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### Noninfectious Uveitis

1. The patient must have the diagnosis of noninfectious uveitis.

2. The patient must also have had an inadequate response to locally administered ophthalmic corticosteroid drops (prednisolone acetate 1% or difluprednate 0.05%, or periocular inj of glucocorticoid such as triamcinolone or dexamethasone).

3. The patient must have had an inadequate response to systemic glucocorticoid therapy.

4. The patient must have had an inadequate response to cyclosporine and methotrexate, combined.

If approved, PA is good for 12 months.

**Continuation Criteria**

1. After 3 months of therapy the patient must have at least a 50% reduction from baseline in the total abscess and inflammation-nodule count, and with no increase in the abscess or draining-fistula count.

If approved, PA is good for 12 months.

Ref for uveitis:


**Quantity Limits:** 30 day supply
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)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagnosis of stage III, unresectable non-small cell lung cancer (NSCLC)</td>
<td></td>
</tr>
<tr>
<td>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).</td>
<td></td>
</tr>
<tr>
<td>3. Must NOT have had progression after platinum-based, concurrent chemoradiotherapy (verified with imaging such as CT or MRI done after completion of radiation)</td>
<td></td>
</tr>
<tr>
<td>4. Last chemoradiation session must have been no more than 42 days ago, from first request of durvalumab.</td>
<td></td>
</tr>
</tbody>
</table>

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

1PACIFIC 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
<th>12 m OS rate (95% CI)</th>
<th>24m OS rate (95% CI)</th>
<th>Harms Grade 3/4 AEs</th>
<th>Harms: DC 2` AEs</th>
<th>Harms: SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab NR</td>
<td>83.1% (79.4-86.2)</td>
<td>66.3 (61.7-70.4)</td>
<td>30.5%</td>
<td>15.4%</td>
<td>29.1%</td>
<td></td>
</tr>
<tr>
<td>Placebo 28.7</td>
<td>75.3 (69.2-80.4)</td>
<td>55.6 (48.9-61.8)</td>
<td>26.1%</td>
<td>9.8%</td>
<td>23.1%</td>
<td></td>
</tr>
<tr>
<td>HR for death 0.68</td>
<td>99.73%CI, 0.47-0.997</td>
<td>p=0.0025</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References:


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

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagnosis of stage IV non-small cell lung cancer (NSCLC)</td>
<td></td>
</tr>
<tr>
<td>2. No ALK or EGFR mutation</td>
<td></td>
</tr>
<tr>
<td>3. No prior therapy for stage IV NSCLC</td>
<td></td>
</tr>
<tr>
<td>4. Durvalumab will be given in combination with tremelimumab and carboplatin/cisplatin-based chemotherapy.</td>
<td></td>
</tr>
</tbody>
</table>
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:

### 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)
- 1-year overall survival: 54% versus 40%
- 18-month overall survival: 34% versus 25%

Reference:

### 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:

### Hepatocellular Carcinoma

1. Diagnosis of hepatocellular carcinoma
2. No prior systemic therapy
3. 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:

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:
- 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
- Isatuximab and dexamethasone NOT COVERED
  - Benefit is limited to progression free survival only compared to carfilzomib plus dexamethasone
- 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.

Criteria for new users

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Must have a diagnosis of multiple myeloma that is relapsed or refractory</td>
</tr>
<tr>
<td>2. Must have received 1-3 prior lines of therapy</td>
</tr>
<tr>
<td>3. Must be planning to receive carfilzomib in combination with dexamethasone <strong>with or without</strong> lenalidomide</td>
</tr>
<tr>
<td>4. Must be ECOG Performance status 0-2 upon initial request for carfilzomib.</td>
</tr>
<tr>
<td>If all above criteria met, approve for 12 months</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Infusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib + dexamethasone</td>
<td>20/70 mg/m² once weekly</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Carfilzomib + dexamethasone, or monotherapy</td>
<td>20/56 mg/m² twice weekly</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Carfilzomib, Lenalidomide, and dexamethasone, or monotherapy</td>
<td>20/27 mg/m² twice weekly</td>
<td>10 minutes</td>
</tr>
</tbody>
</table>

References:
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)**

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>2. At first request, EDSS (see bottom of page) should be 0-5.</td>
</tr>
<tr>
<td>3. At first request, disease duration should be &lt; 10 y.</td>
</tr>
<tr>
<td>4. The patient should be free of any thyroid disease.</td>
</tr>
<tr>
<td>5. The patient should have normal liver transaminases prior to and during administration of alemtuzumab.</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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

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

References:

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:
**Alglucosidase Alfa (Lumizyme 50mg IV)**

**EBRx PA Criteria**

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

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must have the diagnosis of Pompe disease.</td>
</tr>
</tbody>
</table>

**Note:** If yes, approve for 1 year.

**References:**
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).
  
- 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 ≥ 2.5 x upper limit of normal (ULN), serum bilirubin ≥ 2 x ULN, OR serum creatinine ≥ 2.5 x ULN.

If patient meets criteria above, approve medical PA for 4 months. Medication is excluded from pharmacy benefit. For patients who do not achieve an adequate response during first induction cycle, no further gemtuzumab is indicated. Medication is approved ONLY in combination with cytarabine and daunorubicin.

Dosing: IV:
- **Induction Cycle**: gemtuzumab 3 mg/m² (up to one 4.5 mg vial) on Days 1, 4, and 7 in combination with daunorubicin (60 mg/m² on Days 1, 2, and 3) and cytarabine (200 mg/m² 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/m² (up to one 4.5 mg vial) on Day 1 in combination with daunorubicin (60 mg/m² for 1 day [first course] or 2 days [second course]) and cytarabine (1000 mg/m² 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

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

**Ref:**
**Mepolizumab (Nucala®)**

**EBRx PA Criteria**

**Asthma, eosinophilic type**

1. The prescriber must be a pulmonologist or allergist.
2. The patient must be age ≥ 6 and have demonstrated an eosinophil count of >150 cells/microliter in the past 6 weeks or >300 cells/microliter in the past year.
3. The patient must have an inadequate response to standard controller despite proper adherence.
4. There must be no concurrent asthma biologic agent use. (No overlapping days supply)
5. Does the patient have FEV1 <80% at the time he/she is requesting the first prior authorization?

Patients must be 12 or older (no published data in younger) with the diagnosis of asthma not controlled by continued inhaled corticosteroids. They (arbitrarily) should have 75% ICS adherence rate.

**Note:** Nucala® (mepolizumab) is FDA approved as add-on therapy to optimal asthma therapy. Currently there is not peer-reviewed published literature to support its use as monotherapy in asthma and therefore will not be covered in this manner.

**DOSE is 100mg SC in a physician office q4w.**

If approved for coverage, PA is good for 3 months. Re-authorization for a PA will require the patient to be compliant with optimal asthma drug therapy as per the current NHLBI Asthma guidelines. Subsequent requests for PA require that the past 3 of 4 months have a paid claim for a LABA/ICS either separately or as a combination product. If this is not the case, the PA should be denied.

**Eosinophilic granulomatosis with polyangiitis (EGPA)**

1. The patient must be at least 18 years of age or older
2. The patient must have a diagnosis eosinophilic granulomatosis with polyangiitis for at least 6 months. Defined as:
   - History or presence of asthma AND
   - Blood eosinophil level of 10% or an absolute eosinophil count of more than 1000 cells/mm³ AND
   - Presence of 2+ criteria below typical of EGPA:
     - A biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation;
     - Neuropathy, mono or poly (motor deficit or nerve conduction abnormality);
     - Pulmonary infiltrates, non-fixed;
     - Sino-nasal abnormality;
     - Cardiomyopathy (established by echocardiography or mri);
     - Glomerulonephritis (hematuria, red cell casts, proteinuria);
     - Alveolar hemorrhage (by bronchoalveolar lavage);
     - Palpable purpura;
     - Antineutrophil cytoplasmic antibody (anca) positive (mpo or pr3)
3. History of relapsing OR refractory disease
4. The patient must have tried azathioprine, methotrexate, leflunomide, OR mycophenolate
   OR have a contraindication to these therapies.
5. Patients MUST NOT have diagnosis of granulomatosis with polyangiitis (aka Wegener’s granulomatosis) or microscopic polyangiitis or have had organ-threatening or life-threatening EGPA 3 months prior.

-If criteria 1-5 fulfilled for EGPA, drug approved for 300 mg q4weeks. (only formulated in 100 mg strengths, so 3 injections given per dose)
- Asthma patients should should have 75% ICS adherence rate. It is prudent to follow less costly standard treatment prior to access to asthma biologics.

**Hypereosinophilic Syndrome**

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

**Rhinosinusitis w/ Nasal Polyps**

1. Dx of nasal polyps
2. Inadequate response to nasal corticosteroids
3. Must be age 18y+ (adult)

References:
**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.

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must be status post kidney transplant and currently taking mycophenolate mofexit and corticosteroids.</td>
</tr>
<tr>
<td>2. The patient must be known to be seropositive for Epstein-Barr virus.</td>
</tr>
<tr>
<td>If approved, PA is for 1 year.</td>
</tr>
</tbody>
</table>

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:
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.

### Primary Progressive Multiple Sclerosis (PPMS)

1. The patient has a diagnosis of **Primary Progressive Multiple Sclerosis (PPMS) AND**

2. Their most recent Expanded Disability Status Scale (Range 0-10, higher scores = greater disability) (EDSS) score is 3.0 to 6.5 when prescription is requested. **AND**

3. The patient’s duration of MS symptoms must be < 15 years in patients with an **EDSS score of > 5.0** at the most recent screening; **OR**

   A duration of MS symptoms of < 10 years in patients with an **EDSS score of 5.0 or less during their most recent screening. **AND**

4. A score on the pyramidal functions component of the Functional Systems Scale (see next page and ref#4 for link) of at least 2 (range, 0 to 6, with higher scores indicating greater disability). **AND**

5. The patient must be both age ≥ 51y AND without gadolinium-enhancing lesions. (If not, rituximab is the alternative treatment.) **OR**

6. The patient has a diagnosis of **Primary Progressive Multiple Sclerosis (PPMS) AND**

7. The patient has failed treatment for PPMS with rituximab characterized by confirmed disease progression (CDP).

If the patient fulfills all criteria (1-5) **OR** all criteria in 6-7, then ocrelizumab will be approved for 1y (max of 1200mg/y).

**Dosing Regimen per package insert:**
- Start dose: 300 mg IV, followed two weeks later by a second 300 mg IV infusion.
- Subsequent doses: 600 mg IV every 6 months (beginning 6 months after the first 300 mg dose).
- After the two initial 300 mg starting doses, doses must be separated by at least 5 months.

Patients should be denied access if currently taking other MS disease modifying agents (Rituximab, Zinbryta, Copaxone, Glatopa, Interferon, Plegridy, Tecfidera, Gilenya, Aubagio, Lemtrada, Tysabri, or cladribine).

### Relapsing Remitting Multiple Sclerosis (RRMS)

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

**References:**


3. Ocrelizumab FDA package insert.


7. 3. ICER. Disease-modifying therapies for RRMS and PPMS: Effectiveness and Value. 3/6/17, prepared by California Technology Assessment Forum. [https://icer-review.org/announcements/final-ms-report/](https://icer-review.org/announcements/final-ms-report/)

8. NCT02746744. Rituximab Versus Fumarate in Newly Diagnosed Multiple Sclerosis. (RIFUND-MS). Rituximab, dimethyl fumarate or placebo. Population: N = 200, ages 18-40, both sexes. Diagnosis of RRMS or one demyelinating episode with ≥2 asymptomatic high-intensity lesions compatible with MS diagnosis No previous MS tx other than with interferon or glatiramer acetate, <5 years disease duration, ≥1 relapse, ≥ 2 T2 lesions or >Gd+ lesions in previous year, EDSS score 0-5.5. Primary outcomes: RR of relapse during study period. Est. Completion Date 8/2021.
Kurtzke Functional Systems Scores (FSS)

Pyramidal Functions:
0 - Normal
1 - Abnormal signs without disability
2 - Minimal disability
3 - Mild to moderate paraparesis or hemiparesis (detectable weakness but most function sustained for short periods, fatigue a problem); severe monoparesis (almost no function)
4 - Marked paraparesis or hemiparesis (function is difficult), moderate quadriparesis (function is decreased but can be sustained for short periods); or monoplegia
5 - Paraplegia, hemiplegia, or marked quadriparesis
6 - Quadriplegia
9 - (Unknown)
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 ≥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 (≥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
  - CHL that has relapsed or progressed after 3 or more lines of systemic therapy that includes autologous HSCT

- **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 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 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 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 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)
  - Treatment of 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.

<table>
<thead>
<tr>
<th>Melanoma, metastatic (new users)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagnosis of unresectable or metastatic melanoma.</td>
</tr>
<tr>
<td>2. The patient must be ECOG performance status 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity) at initiation</td>
</tr>
<tr>
<td>3. Patient does not have diagnosis of ocular/uveal melanoma.</td>
</tr>
<tr>
<td>4. No prior treatment for unresectable/metastatic melanoma.</td>
</tr>
<tr>
<td>5. Nivolumab will be used as single agent OR in combination with ipilimumab</td>
</tr>
</tbody>
</table>

If above criteria fulfilled, approve for 12 months
- Two trials support use of nivolumab in the first line setting in BRAF mutated and non-mutated melanoma. One showed improvement in overall survival vs chemo in untreated BRAF unmutated patients (37.5m vs 11.2 m\(a\)) and another showed improvement in overall survival vs. ipilimumab in untreated patients with or without BRAF mutation (36.9m vs. 19.9 mo\(b\)). Nivolumab also studied in second line setting after ipilimumab and showed better response rates vs chemo. Survival not improved in overall population per clinical.trials.gov (NCT01721746), so EBRx will not cover in the second line setting.

- Ocular/uveal melanoma behaves differently and is treated differently from cutaneous melanoma.
- Nivolumab+ipilimumab has been shown to improve overall survival vs ipilimumab alone. Ipilimumab/nivolumab also comes extremely close to statistically improving overall survival compared to nivolumab alone in the 5-year update of the CHECKMATE 067 trial. Due to consistency of results compared to initial release of data and strong trend to improving overall survival, EBRx recommends coverage. However, note that toxicity is also increased in the ipi/nivo arm compared to nivolumab alone (grade 3-5 toxicity incidence: 59% vs 23%).

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:


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**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

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**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.

<table>
<thead>
<tr>
<th>CHECKMATE-816</th>
<th>Inclusion: Resectable NSCLC; resectable, histologically confirmed Stage IB (≥24 cm), II, or IIIA</th>
<th>Event free survival:</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02998528</td>
<td>Excluded: known EGFR mutations or ALK translocations (testing not required)</td>
<td>Nivolumab/chemo: 31.6</td>
</tr>
<tr>
<td>Randomized, Open Label, Multicenter</td>
<td></td>
<td>Chemo: 20.8</td>
</tr>
<tr>
<td>Platinum-based chemotherapy x 3 cycles with or without nivolumab</td>
<td></td>
<td>HR 0.63 0.45-0.87; p=0.0052</td>
</tr>
<tr>
<td>N=358</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint: Event free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Event free survival:**
- Nivolumab/chemo: 31.6
- Chemo: 20.8
- HR 0.63 0.45-0.87; p=0.0052

**Interim overall survival analysis:**
- HR 0.57 (95% CI: 0.38, 0.87)
- Did not cross the boundary for statistical significance.

**Complete pathologic response:**
- Nivo/chemo: 24%
- Chemo: 2.2%

**Grade 3 or 4 adverse events:**
- Nivo/chemo: 41%
- Chemo: 44%

**Other possible benefits in nivolumab group:**
- More proceeded with surgery (83% vs 75%)
- Shorter duration of surgery
- More use of minimally invasive approaches
- Fewer pneumonectomies’
- More R0 resections

REFERENCES:

**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).  

2. If no prior therapy for metastatic disease AND PD-L1 is $>1\%$, all of the following criteria must be met:
   - Nivolumab will be given with ipilimumab with or without 2 cycles of platinum-doublet chemotherapy
   - Tumor is EGFR and ALK negative

3. If no prior therapy for metastatic disease AND PD-L1 $<1\%$, all of the following criteria must be met:
   - Nivolumab will be given with ipilimumab and 2 cycles of platinum-doublet chemotherapy
   - Tumor is EGFR and ALK negative

If all criteria fulfilled from either 1, 2, or 3, approve for 12 months

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.  

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).  

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%).

REFERENCES:
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]
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

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Diagnosis of unresectable malignant pleural mesothelioma</td>
</tr>
<tr>
<td>2.</td>
<td>No prior therapy for unresectable malignant pleural mesothelioma</td>
</tr>
<tr>
<td>3.</td>
<td>Nivolumab will be used in combination with ipilimumab</td>
</tr>
<tr>
<td>4.</td>
<td>No active autoimmune disease, interstitial lung disease, or systemic immunosuppression</td>
</tr>
<tr>
<td>5.</td>
<td>No active, untreated brain metastasis</td>
</tr>
<tr>
<td>6.</td>
<td>ECOG performance status of 0 or 1</td>
</tr>
</tbody>
</table>
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

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 >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 >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 >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.¹²

-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.³

-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:³

-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)⁴

REFERENCES:


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:


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 $\leq 10 \text{mg}$ daily prednisone (or equivalent).

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


### 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:**


### 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:

<table>
<thead>
<tr>
<th>Disease-free Survival</th>
<th>OPDIVO (n=532)</th>
<th>Placebo (n=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events, n (%)</td>
<td>241 (45%)</td>
<td>155 (59%)</td>
</tr>
<tr>
<td>Median (months)</td>
<td>22.4 (16.6, 34.0)</td>
<td>11.0 (8.3, 14.3)</td>
</tr>
<tr>
<td>Hazard ratio&lt;sup&gt;a&lt;/sup&gt; (95% CI)</td>
<td>0.69 (0.56, 0.85)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

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

REFERENCES:

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 >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 >1%.

<table>
<thead>
<tr>
<th>PD-L1 expression</th>
<th>Median overall survival (Nivolumab/Ipilimumab versus chemo)</th>
<th>Median overall survival (Nivolumab/chemo versus chemo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>12.8 mo vs 10.7 mo</td>
<td>13.2 mo vs 10.7 mo</td>
</tr>
<tr>
<td>PD-L1 &gt;1%</td>
<td>13.7 mo vs 9.1 mo</td>
<td>15.4 vs 9.1 mo</td>
</tr>
</tbody>
</table>

REFERENCES:
**Esophageal Squamous Cell Carcinoma (ESCC)**

1. Diagnosis of advanced/metastatic esophageal squamous cell carcinoma (not adenocarcinoma)
2. Previously treated with fluoropyrimidine- and platinum-based chemotherapy (treatment must have contained a fluoropyrimidine (fluorouracil or capecitabine) AND a platinum agent (oxaliplatin, 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.

**REFERENCES:**
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:

### 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]
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%, the pCR rates with these pertuzumab-containing regimens were ~60%\(^2\,3\,4\). Attainment of pCR has been strongly associated with overall survival in multiple analyses.\(^1\,5\,6\)

Dose:
840 mg IV x 1 followed 3 weeks later by 420 mg IV every 3 weeks x 3-6 cycles, then proceed to surgery. After surgery, resume pertuzumab with trastuzumab to complete one year of therapy.

REFERENCES:

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### Adjuvant Treatment of Breast Cancer (therapy begins AFTER surgery)

1. Diagnosis of breast cancer
2. Breast cancer is HER2 positive
3. Lymph node involvement is present
4. Pertuzumab will be used in combination with trastuzumab and chemotherapy

If above criteria are fulfilled, approve x 1 year [maximum duration of therapy is 1 year or 18 doses]

Notes:
Total duration of pertuzumab therapy is 1 year. Pertuzumab/trastuzumab+chemo is given x 4-6 cycles, then pertuzumab and trastuzumab are continued to complete one year of therapy.

In the APHNITY study\(^1\) (n=4804), the population described in the above criteria was given pertuzumab, trastuzumab, and chemotherapy OR placebo, trastuzumab, and chemotherapy. The primary endpoint was invasive disease free survival (IDFS). At 3 years, the rates of IDFS were as follows:
- all patients (pertuzumab 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).\(^2\)

Dose:
840 mg IV x 1 followed 3 weeks later by 420 mg IV every 3 weeks x 1 year.
REFERENCES:


Polatuzumab vedotin-piq (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

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagnosis of diffuse large B-cell lymphoma (DLBCL) that is progressing</td>
</tr>
<tr>
<td>2. Lymphoma is refractory to or progressed on or after at least two prior regimens</td>
</tr>
<tr>
<td>3. Patient is not eligible for stem cell transplant</td>
</tr>
<tr>
<td>4. Polatuzumab will be used in combination with bendamustine and rituximab</td>
</tr>
</tbody>
</table>

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:

Quantity Limits: n/a
**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 1st 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 1st on study SRE was 26.4m for ZA and not yet reached with denosumab. Denosumab reduced the risk of developing multiple SREs by 23% compared to 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**


### 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.
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, McCling MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756-65.)
- 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).

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 (RADC) 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)

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

**WOMEN RECEIVING AROMATASE INHIBITORS:**

- From the PI: The efficacy of Prolia in the treatment of bone loss was evaluated in 252 women treated with aromatase inhibitor therapy due to breast CA. The trial was 2 y, was DB, placebo-controlled. 1° endpoint was % change in lumbar spine BMD from baseline to month 12. The treatment difference was 5.5% (95%CI: 4.8, 6.3; p<0.0001). Fracture rate was not measured. There was not a bisphosphonate control arm.
- Bisphosphonates also increase lumbar spine vs placebo in women with breast CA on AIs. The % change in weighted mean difference was 5.42% at the lumbar spine and 3.03% (95%CI, 4.37-6.48) at the total hip. Su G, Xiang Y, He G, Jiang C, et al. Bisphosphonates may protect against bone loss in postmenopausal women with early breast cancer receiving adjuvant aromatase inhibitor therapy: results from a meta-analysis. Arch Med Res. 2014. Oct;45(7):570-9.
- I could not find that bisphosphonates reduce fractures in AI breast cancer patients. (JJ 7/6/15)
- Denosumab reduced the risk of clinical fractures in postmenopausal women with HER2+ breast cancer, nonmetastatic, ER+ or progesterone+, postmenopausal women, receiving AIs. They were given 60mg 2x/year SC or placebo. N=3420. HR 0.50 (95%CI 0.39-0.65) for time to 1st fracture. Also received 500mg elemental Ca and at least 400IU vit D daily. Excluded if on SERMs or received bisphosphonates. 99% were white. At 36m, 6% (95%CI 3.8-6.2) of denosumab and 9.6% (95%CI 8.0-11.2) of placebo had experienced a fracture. At 84m, 11.1% (95%CI 8.1-14.1) denosumab group and 26.2% (15.6-36.8) in the placebo group. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicenter, R, DB, PC trial.


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

**NOT COVERED: MEN AT HIGH RISK FOR FRACTURE**

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

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

**NOT COVERED GLUCOCORTICOID-INDUCED OSTEOPOROSIS**

- Double blind, RCT non-inferiority study of denosumab vs risedronate in patients receiving >7.5 mg prednisone daily. Denosumab was noninferior AND superior to risedronate for improvement in lumbar spine BMD. No fracture data available.1
- Guideline: For pt >40 y/o at moderate/high risk for fracture, the 2017 American College of Rheumatology Guideline for Prevention and Treatment of Glucocorticoid-Induced Osteoporosis recommends oral bisphosphonates (BP) OVER IV BP, denosumab, teriparatide, or raloxifene. If oral BP not an option, recommend the following in order of preference: IV BP, teriparatide, denosumab, raloxifene.2

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

Sipuleucel T (Provenge)
EBRx PA Criteria

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

### Criteria for new users

1. Diagnosis of metastatic prostate adenocarcinoma (not small cell or neuroendocrine prostate cancer).
2. Patient does **not** have visceral metastasis (e.g. metastasis to sites other than bone, lymph nodes, or other soft tissue. Visceral metastases include, but are not limited to, metastases to organs such as lung, brain, liver, adrenal, or peritoneum).
3. Prostate cancer is castration resistant (disease has progressed while serum testosterone level is <50 ng/dl)
4. Patient exhibits no symptoms or has minimal symptoms due to prostate cancer defined as follows:
   - No requirement for treatment of cancer-related pain with opioids
   - Average weekly pain score of 4 or 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.¹

When patients were broken into groups by PSA level, the effect on overall survival was only significant and even larger in patients with lower PSA levels (see chart below).² This indicates that therapy may be more effective when used in earlier lines of therapy when disease burden is lower. NCCN recommends sipuleucel T only in patients with mCRPC in the first or second line setting. EBRx criteria mirror this recommendation.³

<table>
<thead>
<tr>
<th>Baseline PSA (ng/ml)</th>
<th>Median OS (sipuleucel T vs placebo; months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;22.1</td>
<td>41 vs. 28</td>
<td>0.51 (0.31-0.85)</td>
</tr>
<tr>
<td>&gt;22.1 – 50.1</td>
<td>27 vs 20</td>
<td>0.74 (0.47-1.17)</td>
</tr>
<tr>
<td>&gt;50.1-134.1</td>
<td>20 vs 15</td>
<td>0.81 (0.52-1.24)</td>
</tr>
<tr>
<td>&gt;134</td>
<td>18 vs 16</td>
<td>0.84 (0.55-1.29)</td>
</tr>
</tbody>
</table>

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:
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


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

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

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient must have diagnosis of ALS</td>
</tr>
<tr>
<td>2. The patient must have recent (from the previous 3 months) pulmonary function tests showing an FVC of at least 80% predicted</td>
</tr>
<tr>
<td>3. The patient must NOT have any history of spinal symptoms</td>
</tr>
</tbody>
</table>

If all 3 criteria above are fulfilled, approve the PA for 6 months.

<table>
<thead>
<tr>
<th>Criteria for continuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must have recent (from the previous 3 months) pulmonary function tests showing an FVC of at least 80% predicted</td>
</tr>
<tr>
<td>2. The patient must maintain adherence to the 10 days out of 14 days IV infusions.</td>
</tr>
</tbody>
</table>

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.

References:
Luspatercept (Reblozyl) 25 and 75 mg vial
EBRx PA Criteria

is FDA-approved for:

- Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions **NOT COVERED**
  - Not covered due to limited medical benefit. In the BELIEVE trial, patients with beta thalassemia requiring ≥6 RBC transfusions per 24 weeks were randomized to luspatercept or placebo.
    - Primary endpoint: percent of patients with ≥33% reduction from baseline in RBC transfusion burden with a minimum reduction of at least 2 units for consecutive 12 weeks. In the luspatercept group 33% of patients achieved the primary endpoint compared to 4.5% of placebo patients.
    - The percent of patients who had ≥50% reduction from baseline in RBC transfusion burden (with a minimum reduction of at least 2 units) was 7.6% in the luspatercept group compared to 1.8% in the placebo group.
    - Risks of therapy include thromboembolic events, particularly in splenectomized patients, and extramedullary masses.

REFERENCES:

- 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.

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)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagnosis of myelodysplastic syndrome (MDS) with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)*</td>
<td>Must have &lt;5% bone marrow blasts and either ≥15% of erythroid precursors with ring sideroblasts OR ≥5% ring sideroblasts if an SF3B1 mutation was present.</td>
</tr>
<tr>
<td>2. MDS is classified as very low, low, or intermediate risk by IPSS-R (see below)</td>
<td></td>
</tr>
<tr>
<td>3. Age ≥18 years or older</td>
<td></td>
</tr>
<tr>
<td>4. Patient currently requires at least 2 red cell transfusions every 8 weeks</td>
<td></td>
</tr>
<tr>
<td>5. Anemia is refractory to erythropoiesis-stimulating agents (ESAs)* OR serum erythropoietin level is &gt;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)</td>
<td></td>
</tr>
</tbody>
</table>

**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 (>2 unit reduction over 8 weeks) was taken from the endpoints used in beta thalassemia trial. Clinical judgment may be used.

**References:**

**REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R) (taken from NCCN MDS guidelines)**

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic⁹</td>
<td>0.5 1 1.5 2 3 4</td>
</tr>
<tr>
<td>Very good</td>
<td>— Good — Poor Very</td>
</tr>
<tr>
<td>Marrow blasts (%)</td>
<td>≤2 &gt;2-&lt;5 5-10 &gt;10 —</td>
</tr>
<tr>
<td>≥10</td>
<td>— 8-&lt;10 &lt;8 — — —</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100 50-&lt;100 &lt;50 — — —</td>
</tr>
<tr>
<td>≥0.8</td>
<td>&lt;0.8 — — — — —</td>
</tr>
<tr>
<td>ANC</td>
<td>— — — — — — —</td>
</tr>
</tbody>
</table>
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

**Initial**

1. Patient must have clinically evident atherosclerotic cardiovascular disease (defined as a history of myocardial infarction, nonhemorrhagic stroke (TIA does NOT qualify), or symptomatic peripheral artery disease).

2. Patient must have fasting LDL-C of >70mg/dL or a non-HDL-C of >100mg/dL WHILE TAKING an optimized regimen of lipid-lowering therapy
   - Must be a high-intensity statin equal to atorvastatin 20mg or higher (with or without ezetimibe) for at least 6 weeks

3. Patient must also have additional characteristics that places him/her at higher cardiovascular risk including:
   - At least 1 of the following:
     - T1 or T2DM
     - Age >65
     - MI or non-hemorrhagic stroke within the past 6 months
     - Additional diagnosis of MI or non-hemorrhagic stroke excluding the one in the original history (item 1 above)
     - Current daily cigarette smoking
     - History of symptomatic peripheral artery disease,
   - OR
   - At least 2 of the following:
     - History of non-MI related coronary revascularization
     - Residual coronary artery disease with ≥40% stenosis in ≥2 large vessels
     - Most recent hsCRP>2.0mg/L
     - Most recent LDL-C >130mg/dL or non-HDL-C >160 mg/dL
     - Diagnosis of metabolic syndrome (At least 3 of the following:
       - waist circumference >40 inches for men or >35 inches for women
       - triglycerides >150 mg/dL
       - HDL-C <40 mg/dL for men or <50 for women
       - Systolic blood pressure >130mmHg or diastolic BP >85 mmHg or hypertension treated with medication
     - Fasting glucose >100 mg/dL

Note: dose is 140mg every 2 weeks

References:
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>70mg/dL or non-HDL>100mg/dL AND established cardiovascular disease. Randomized to evolocumab SC 140mg q2w or 420mg monthly plus high- or moderate-intensity effective statin dose; or placebo SC q2w or qM plus high to mod statin dose (at least atorva 20mg).
**Elapegademase-lvrl (Revcovi) IM for self-injection**

**EBRx PA Criteria**

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

<table>
<thead>
<tr>
<th>Criteria for new users</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must have the diagnosis of ADA-SCID.</td>
<td></td>
</tr>
<tr>
<td>2. The patient must be awaiting HSCT or else not be able to undergo HSCT.</td>
<td></td>
</tr>
</tbody>
</table>

**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:**

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

### 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.


**Note:**

Isatuximab/pomalidomide/dexamethasone was compared to pomalidomide/dexamethasone in patients who were previously treated with at least two prior therapies including lenalidomide and a proteasome inhibitor. The triplet therapy improved progression free survival (median 11.53 mo vs 6.47 mo). In the overall population, a statistically significant overall survival benefit has not been demonstrated at this time. However, in the subset of patients who were age ≥75 y, a statistically significant improvement in overall survival was demonstrated (median not reached in triplet group versus 10.25 mo in the control group (HR 0.404 95% CI 0.171- 0.956).¹²

**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:**


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

**Med Impact: Preferred**

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.

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

‡BASDAI is **Bath Ankylosing Spondylitis Disease Activity Index**, a scale of measuring discomfort, pain, and fatigue (1 being no problem and 10 being the worst problem) in response to 6 questions asked of the patient pertaining to the 5 major symptoms of AS, Fatigue, Spinal pain, Arthralgia, Enthesitis, or inflammation of tendons and ligaments. Morning stiffness duration, Morning stiffness severity. To give each symptom equal weighting, the average of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of >4 suggest suboptimal control of disease, and those patients are usually good candidates for a change in medical therapy, may benefit by treatment with biologic therapies.

**References:**


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

**Med Impact: Trial of 2 preferred agents (Enbrel, Humira, Xeljanz IR, Amjevita, Cyltezo, Hyrimoz, Adalimumab-ADAZ)**

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 (inflammation where tendons or ligaments connect with the bone)-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 TNFaI sequentially and is now seeking to switch therapy due to high disease activity
4. The JIA patient received more than one TNFaI sequentially, then abatacept, and still have high disease activity, AND test positive for RF


### 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:**


### 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.¹

‡Tapering is seen as either dose reduction or prolongation of intervals between applications.

§Most data are available for TNF inhibitors, but it is assumed that dose reduction or interval expansion is also pertinent to biological agents with another mode of action.

DMARD, disease-modifying antirheumatic drug; EMA, European Medical Agency; EULAR, European League against Rheumatism; FDA, Food and Drug Administration; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

**References:**

**Ulcerative Colitis**

**Med Impact: Preferred**

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

**General References:**
**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

<table>
<thead>
<tr>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age is &gt;18 years</td>
</tr>
<tr>
<td>2. The patient must have the diagnosis of plaque psoriasis that is moderate to severe defined as meeting all of the following requirements:</td>
</tr>
<tr>
<td>- Body surface area (BSA) involvement of ≥5%</td>
</tr>
<tr>
<td>- Static Physician’s Global Assessment (sPGA) score of ≥3 in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 4</td>
</tr>
<tr>
<td>- Psoriasis Area and Severity Index (PASI) score ≥12</td>
</tr>
<tr>
<td>3. If the patient ALSO HAS the diagnosis of psoriatic arthritis, approve Skyrizi without requiring prior therapy.</td>
</tr>
<tr>
<td>4. The patient must have failed 3 consecutive months of systemic or topical, non-biologic therapy including these options:</td>
</tr>
<tr>
<td>- systemic therapy: methotrexate or cyclosporine or acitretin systemic therapy</td>
</tr>
<tr>
<td>- phototherapy (broadband ultraviolet B (UVB), narrowband UVB, and psoralen with ultraviolet A (PUVA)</td>
</tr>
<tr>
<td>- topical treatments (calcineurin inhibitors (tacrolimus or pimecrolimus), topical corticosteroids, vitamin D analogs (calcipotriene), topical retinoids (tazarotene))</td>
</tr>
</tbody>
</table>

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

### Psoriatic Arthritis

<table>
<thead>
<tr>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age is &gt;18 years</td>
</tr>
<tr>
<td>2. The patient must have the diagnosis of psoriatic arthritis</td>
</tr>
<tr>
<td>3. The patient must have failed a trial of 2 NSAIDS. Each trial should be 1 month in length.</td>
</tr>
<tr>
<td>4. The patient must have failed 3 months of a DMARD therapy (examples: methotrexate, sulfasalazine, penicillamine, azathioprine, leflunomide).</td>
</tr>
</tbody>
</table>

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

### Crohn’s Disease

<table>
<thead>
<tr>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age is &gt;18 years</td>
</tr>
<tr>
<td>2. The patient must have the diagnosis of active Crohn’s disease</td>
</tr>
<tr>
<td>3. Crohn’s Disease Activity Index (CDAI) is 220 to 450 and Simple Endoscopic Score for Crohn’s disease (SES-CD) is ≥6 (or ≥4 for isolated ileal disease)</td>
</tr>
<tr>
<td>4. Inadequate response, loss of response, or intolerance to oral aminosalicylates (e.g. mesalamine, sulfasalazine), corticosteroids, or immunosuppressants (e.g. azathioprine, mercaptopurine, methotrexate)</td>
</tr>
</tbody>
</table>

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

Quantity Limits: 30 day supply
Eculizumab (Soliris) injection 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.

<table>
<thead>
<tr>
<th>Paroxysmal Nocturnal Hemoglobinuria (PNH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Although FDA-approved for this indication, ravulizumab is EBRx's preferred drug. Please see the PA for Ultomiris.</td>
</tr>
</tbody>
</table>

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

References:

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:

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:
### FDA approved for:

- the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy
- the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival
- the treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy

#### Acromegaly

1. The patient has a diagnosis of acromegaly
2. The patient had an inadequate response to or has a contraindication to surgery and/or radiotherapy

**If all criteria fulfilled, approve for 12 months.**

**Initial Somatuline Depot dosing is 90 mg given via deep subcutaneous injection every 4 weeks for 3 months. The dose is then adjusted according to growth hormone levels, insulin-like growth factor-1 levels, and clinical symptoms.**

#### Gastroenteropancreatic Neuroendocrine Tumors

1. The patient has a diagnosis unresectable, locally advanced, or metastatic gastroenteropancreatic neuroendocrine tumor (GEP-NET; pancreatic, small or large intestine, appendix, rectum, anal canal, anus)
2. Tumor is well or moderately differentiated
3. Somatostatin-receptor scintigraphy is grade 2 or higher (e.g. positive OctreoScan)

**If all criteria fulfilled, approve for 12 months.**

**Dose is 120 mcg SQ every 4 weeks given until disease progression or unacceptable toxicity.**

Lanreotide markedly improved progression free survival over placebo in this patient population (2-year PFS: 65% vs 33%). Overall survival was confounded by high rate (~85%) of crossover from placebo to active treatment.

**References:**


#### Carcinoid Syndrome

1. Diagnosis of carcinoid syndrome with presence of symptoms (e.g. flushing, diarrhea)
2. Diagnosis of neuroendocrine or carcinoid tumor
3. Somatostatin-receptor scintigraphy is grade 2 or higher (e.g. positive OctreoScan)

**If all criteria fulfilled, approve for 12 months.**

**Dose is 120 mcg SQ every 4 weeks given until disease progression or unacceptable toxicity.**

Lanreotide improves symptoms in patients with carcinoid syndrome to a greater extent than placebo.

**Reference:**

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.¹
   - The patient **must have** a diagnosis of Spinal Muscular Atrophy with all of the following criteria:¹,⁴ including genetic documentation of homozygous deletion or mutation in **SMN1 gene**.
   - Onset of clinical signs/symptoms consist with SMA at ≤ 48 months of age.¹,⁴
   - Disease duration of ≤ 7 years.⁴

3. For infantile SMA, then they must also have 2 copies of the SMN2 gene¹, 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 >15 feet unaided.

If patient meets criteria above approve medical PA for 1 year. Medication is excluded from pharmacy.

### Dosing:
**Intrathecal:**
- **Loading dose:** 12 mg once q14 days for 3 doses; then the 4th dose is 12 mg administered once 30 days after the third dose.
- **Maintenance:** 12 mg once q4 months. Year 1 maximum doses is 6 doses. Year 2 and beyond, maximum doses are 3 per year.

### Criteria for CONTINUATION.

1. The patient must have begun Spinraza treatment before age 12.⁴

2. 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.

Ref:
**Esketamine (Spravato)**

**EBRx PA Criteria**

**is FDA-approved for:** treatment resistant depression in adults in conjunction with PO antidepressants

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient must be between ages 18 and 75 years old.</td>
</tr>
<tr>
<td>2. Patient must have the diagnosis of treatment-resistant depression.</td>
</tr>
<tr>
<td>3. Patient must show treatment-resistance in the following ways:</td>
</tr>
<tr>
<td>a. have on their profile, in the past 2 years, at least 3 different antidepressant strategies (2 previous and 1 concomitant) nonconcurrent antidepressant therapies.</td>
</tr>
<tr>
<td>i. either 3 from different classes (SSRIs, or SNRIs, or bupropion monotherapies).</td>
</tr>
<tr>
<td>ii. 2 monotherapies plus one augmentation strategy</td>
</tr>
<tr>
<td>iii. 1 monotherapy, 1 augmentation strategy, ECT/Repetitive transcranial magnetic stimulation (rTMS)</td>
</tr>
<tr>
<td>iv. other combination of the above</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>6. The prescriber must be a psychiatrist.</td>
</tr>
<tr>
<td>7. The prescriber must have checked the AR PMP to rule out substance abuse.</td>
</tr>
<tr>
<td>8. The prescriber must, in good conscience, attest to the patient NOT being a current, active substance abuser.</td>
</tr>
</tbody>
</table>

***The initial PA is good for 4 weeks. QL is 84mg **TWICE** weekly.***

<table>
<thead>
<tr>
<th>Criteria for continuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must be currently adherent with receiving esketamine nasal.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>3. The psychiatrist must submit a plan outlining the treatment plan for esketamine treatment.</td>
</tr>
</tbody>
</table>

###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.

**References:**
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
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

### Plaque psoriasis

**Initial request**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the patient have a diagnosis of moderate-to-severe plaque psoriasis, as indicated by a PASI score of at ≥12 (scale is 0-72) and involvement of at least 10% BSA?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Has the patient had an inadequate response despite 3 months of methotrexate 25mg per week?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR Has the patient experience intolerance to methotrexate?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR Does the patient have a contraindication to methotrexate?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR Is the patient intolerant to or have a contraindication to at least 1 of those treatments?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**If the answer to 1, 2, AND 3 is yes, approve coverage for 28 weeks (4 doses).**

**Responders maintenance therapy**

Did the patient achieve a reduction in PASI of at least 50%?

**If the answer was yes, patient is approved for therapy for 1 year (4 doses).**

References:

Note: Dosing is weight based. For those weighing <100 kg, each dose is 45 mg. For those weighing >100 kg, each dose is 90 mg. Drug is dosed at weeks 0 and 4, and then every 12 weeks thereafter

### Psoriatic arthritis

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the patient have a diagnosis of active psoriatic arthritis, as defined by ≥5 swollen and ≥5 tender joints and a C-reactive protein of ≥3.0mg/L?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Has the patient had an inadequate response to ≥3 months of disease-modifying antirheumatic drug (DMARD) therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR ≥4 weeks of NSAID therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Crohn's Disease**

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 to seeking ustekinumab.

**Ulcerative Colitis**

1. Infliximab (Remicade®)
2. Infliximab-abda (Renflexis)
3. 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 must have moderate to severe disease (characterized by steroid dependence).

General References:

**PASI**

Psoriasis Area Severity Index. Used to express the severity of psoriasis based on a combination of erythema, induration, and desquamation over the percentage of affected body area. Scale ranges from 0 (no disease) to 72 (maximal disease).
Histrelin (Supprelin LA)
EBRx PA Criteria

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

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagnosis of central precocious puberty</td>
</tr>
<tr>
<td>2. Child must be between the ages of 4 and 12 years of age.</td>
</tr>
</tbody>
</table>

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:
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**

<table>
<thead>
<tr>
<th>Criteria for new users</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient must have a cancer diagnosis</td>
<td></td>
</tr>
<tr>
<td>2. Patient must be receiving moderately emetogenic chemotherapy or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>4. Creatinine clearance must be &gt;30 ml/min</td>
<td></td>
</tr>
</tbody>
</table>

If above criteria met, approve for 6 months maximum. Use of Sustol with successive chemotherapy cycles for more than 6 months is not recommended per package insert.

**Dose:**

- 10 mg SQ at least 30 minutes before the start of emetogenic chemotherapy on day 1.
- Do not administer more frequently than once every 7 days
- Use with successive emetogenic chemotherapy cycles for more than 6 months is not recommended as safety and efficacy have not been verified beyond this time frame.

**Evidence:**

A randomized, double-blind study compared Sustol to palonosetron in patients receiving moderately emetogenic chemotherapy or an anthracycline+cyclophosphamide regimen. Dexamethasone was also given and neurokinin 1 antagonists were NOT given. Sustol was non-inferior to palonosetron for prevention of acute and delayed chemotherapy-induced nausea/vomiting.\(^1\)

Another randomized, double-blind, double dummy trial compared Sustol/Emend/dexamethasone to ondansetron IV/Emend/dexamethasone in patients receiving highly emetogenic chemotherapy. Dexamethasone was also given on days 2-4 at standard doses. The Sustol group was superior for prevention of delayed n/v (24 to 120h after chemotherapy was given; complete response 65% vs 57%; p=0.014). However, a major limitation of this study is that Sustol has a longer half-life than ondansetron (24h vs 3-6h) so coverage in the delayed phase was different between groups and explains the superior effect of Sustol for prevention of n/v in the delayed phase.\(^2\)

**References:**


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)**
  o 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 ≥ 1% of tumor cells, as determined by an FDA-approved test. COVERED FOR PD-L1 >50% ONLY
  o As monotherapy for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (EITHER PD-L1 stained >50% of tumor cells [TC >50%] OR PD-L1 stained tumor-infiltrating immune cells covering >10% of the tumor area [IC >10%]), with no EGFR or ALK genomic tumor aberrations
  o 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
  o 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
  o 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)**
  o In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage SCLC.

- **Hepatocellular Carcinoma (HCC)**
  o In combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy

- **Melanoma**
  o 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:

- **Alveolar Soft Part Sarcoma (ASPS)** NOT COVERED
  o 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
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 7th 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 >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).

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

References:

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 ≥50% or IC ≥10%) [tumor histology can be squamous or non squamous]
5. If atezolizumab combination therapy will be used, both of the following criteria are met:
   - Tumor histology is non squamous (e.g. adenocarcinoma, large cell) AND
   - Atezolizumab will be used in combination with bevacizumab, carboplatin, and conventional paclitaxel OR in combination with carboplatin and nab-paclitaxel (Abraxane). [PD-L1 expression can be present or absent]

If 1, 2, 3, and either 4 or 5 are met, approve for 12 months
Atezolizumab improved OS compared to docetaxel with median OS 13.8 mo vs 9.6 mo (HR 0.73 95% CI 0.62-0.87). 1-2 prior chemo regimens with one being platinum based were required prior to enrollment. 1 Fewer severe adverse events were observed in atezolizumab arm (15% vs 43%).

If newly-diagnosed, untreated, and non-squamous histology, atezolizumab/bevacizumab/carboplatin/paclitaxel improved OS vs bevacizumab/carboplatin/paclitaxel with median OS of 19.2 mo vs 14.7 mo (HR 0.78; 95% CI, 0.64 to 0.96). 2 Atezolizumab/carboplatin/nab-paclitaxel also improved OS vs carboplatin/nab-paclitaxel with median OS of 18.6 mo vs 13.9 mo. 3

If newly-diagnosed, untreated, any histology, and high PD-L1 expression (TC >50% or IC >10%), atezolizumab monotherapy improved overall survival compared with platinum-based doublet (median OS 20 mo vs 13 mo). 4 [data from trial Impower 110 study, NCT02409342—results published in PI only as of 6/2/2020]

References:

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:

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:
Sacituzumab govitecan (Trodelvy) 180 mg vial
EBRx PA Criteria

is FDA-approved for:

- Adults with 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
- Adults with unresectable locally advanced or metastastic 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.
    - Ongoing RCT with primary completion date: 10/2024: NCT04527991

<table>
<thead>
<tr>
<th>Triple Negative Breast Cancer</th>
<th>HR+ Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagnosis of unresectable locally advanced or metastatic breast cancer</td>
<td>1. Diagnosis of metastatic breast cancer</td>
</tr>
<tr>
<td>2. Disease is HER2 negative (IHC 0, IHC 1+ or IHC 2+/ISH–)</td>
<td>2. Disease is HER2 negative (IHC 0, IHC 1+ or IHC 2+/ISH–)</td>
</tr>
<tr>
<td>3. Disease is refractory to or relapsed after two or more prior systemic therapies</td>
<td>3. Disease is estrogen and/or progesterone receptor positive (i.e. ER+, PR+, HR+).</td>
</tr>
<tr>
<td>4. Patient has been treated with at least one regimen for advanced/metastatic disease.</td>
<td>4. Patient has received at least two prior chemotherapy regimens for advanced/metastatic disease (one could have been used in the neoadjuvant or adjuvant setting if recurrence occurred within 12 months)</td>
</tr>
<tr>
<td>5. Sacituzumab will be used as single agent</td>
<td>5. Patient has received at least one prior endocrine therapy (e.g. tamoxifen, anastrozole, letrozole, exemestane fulvestrant)</td>
</tr>
<tr>
<td>If criteria met, approve for 12 months. Therapy continues until disease progression.</td>
<td>If criteria met, approve for 12 months. Therapy continues until disease progression.</td>
</tr>
</tbody>
</table>

Note:

In patients with triple negative breast cancer who had been treated with at least 2 prior therapies, sacituzumab govitecan improved overall survival compared to standard chemotherapy (median OS 12.1 mo vs 6.7 months).

Reference:

In patients with hormone receptor positive, HER2 negative unresectable locally advanced or metastatic breast cancer, sacituzumab govitecan improved overall survival compared to standard chemotherapy (median OS 14.4 vs 11.2 months).

Reference:

Quantity Limits: n/a (medical benefit drug)
is FDA-approved for:

- relapsing multiple sclerosis,
- Crohn's disease

### 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 immunosuppressive drugs
4. 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

References:

2. UpToDate. DMT for RRMS. Accessed 9/18/19.
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.

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must have the diagnosis of PAH, WHO group I, and NYHA functional class III or IV symptoms.</td>
</tr>
<tr>
<td>2. The patient must taking a PDE5 inhibitor daily (i.e. tadalafil, sildenafil) or must be unable to take one.</td>
</tr>
<tr>
<td>3. The patient must have tried and failed combination ambrisentan or bosentan, plus PDE5i.</td>
</tr>
<tr>
<td>4. The patient must not have concurrent iloprost with IV epoprostenol, IV treprostinil, or SC treprostinil.</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>1. The patient must have the diagnosis of PAH Group 5 after treating underlying causes.</td>
</tr>
</tbody>
</table>

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:

Addendum:

<table>
<thead>
<tr>
<th>Diagnostic Criteria and WHO categorization of PH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Elevated PAP</td>
</tr>
<tr>
<td>Up to 10-20% of the general population</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PA pressure, mmHg</td>
</tr>
<tr>
<td>PCWP or LVEDP, mmHg</td>
</tr>
<tr>
<td>PVR, dynes/s/cm</td>
</tr>
</tbody>
</table>
Pozelimab-bbfg injection 400mg/2mL (Veopoz 200mg/mL SDV) for IV or SC use—by a HCP
EBRx PA Criteria

**is FDA-approved for:** granted a rare pediatric disease priority review voucher for treatment of Chaple disease pt >1y old with CD55-deficient protein-losing enteropathy (PLE). Post marketing submissions are expected by the FDA.

### Criteria for new users

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>The patient must have the diagnosis of Chaple disease with CD55-deficient protein-losing enteropathy. (hypoalbuminemia); the diagnosis must be confirmed by a genotype biallelic CD55 loss-of-function mutation.</td>
</tr>
<tr>
<td>2.</td>
<td>The patient must be at least 1y of age.</td>
</tr>
<tr>
<td>3.</td>
<td>The patient must not be receiving concurrent complement inhibitors (eculizumab or other).</td>
</tr>
<tr>
<td>4.</td>
<td>The patient must be symptomatic (edema, pleural or pericardial effusions)</td>
</tr>
<tr>
<td>5.</td>
<td>It is suggested that meningococcal vaccines be completed or updated at least 2 w prior to beginning pozelimab.</td>
</tr>
</tbody>
</table>

If approved, the PA is good for 3 months.

### Criteria for continuation

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>The patient must have experienced clinical improvement of symptoms. (fewer albumin infusions or other sign of improvement)</td>
</tr>
</tbody>
</table>

If approved, the PA is good for 12 months.

**Note:** **Dose by HCP:** 30mg/kg IV infusion X1, then 8 days later 10mg/kg SC QW. May increase to 12mg/kg. Max is 800mg QW

**References:**

1. UpToDate. Chaple syndrome. 9/19/23.
Efgartigimod alfa-fcab (Vyvgart) IV infusion
Efgartigimod alfa-fcab/hyaluronidase-vqfc (Vyvgart Hytrulo) SC [NOT substitutable w/ IV]

EBRx PA Criteria

is FDA-approved for: treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) Ab+.

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must have the diagnosis of generalized myasthenia gravis (gMG) with anti-acetylcholine receptor antibody positivity.</td>
</tr>
<tr>
<td>2. The patient must have the gMG Foundation of America clinical classification class II-IV.</td>
</tr>
<tr>
<td>3. The patient must have a Myasthenia Gravis Activities of Daily Living score of at least 5 at initiation. The score will need to be recorded now.</td>
</tr>
<tr>
<td>4. The patient must be on stable therapy of at least 1 treatment for gMG (corticosteroids, acetylcholinesterase inhibitors (pyridostigmine), nonsteroidal immunosuppressive therapies (NSIST)).</td>
</tr>
<tr>
<td>5. The patient has been educated to avoid medications that may exacerbate MG. (neuromuscular blocking agents, aminoglycosides, fluoroquinolones, macrolides, beta blockers, procainamide, quinidine, botulinum toxin, chloroquine, deferoxamine, statins, hydroxychloroquine, immune checkpoint inhibitors, iodinated contrast, magnesium, penicillamine, quinine).</td>
</tr>
</tbody>
</table>

If approved, the initial PA is good for 6 months.

<table>
<thead>
<tr>
<th>Criteria for continuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must be a responder to efgartigimod as defined.</td>
</tr>
<tr>
<td>a. (MG-ADL responder was defined as a patient who had at least a 2-point improvement (reduction) in MG-ADL score, sustained for at least 4 consecutive weeks, with the first improvement occurring by week 4 of the cycle (1 week after the fourth infusion).</td>
</tr>
<tr>
<td>b. The score will need to be reassessed now to compare it to the score at the start of efgartigimod to determine whether or not the patient is a responder.</td>
</tr>
</tbody>
</table>

If approved, the PA can continue for 1 year with reapproval at 1 year intervals.

Note: Administered as 4 infusions per cycle (one infusion per week). Subsequent cycles can commence no sooner than 8 weeks from initiation of the previous cycle. A max of 3 cycles may occur in 26 weeks.

References:
**IncobotulinumtoxinA (Xeomin)—covered by EBD plans (only non-cosmetic uses)**

**EBRx PA Criteria**

**Cervical dystonia indication:**
1. The patient must have the diagnosis of cervical dystonia. OR

**Chronic Migraine: (not FDA approved but covered use by EBD plans)**
1. The patient must have the diagnosis for chronic migraine defined as >15 headache days/month for the previous 3 months, lasting > 4 hours per day; AND still have inadequate response to triptan therapy. OR

**Spasticity indication:**
1. The patient must have the diagnosis of spasticity. OR

**Blepharospasm indication:**
1. The patient must have the diagnosis of blepharospasm. OR

**Sialorrhea indication:**
The patient must have the diagnosis of sialorrhea.

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

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

<table>
<thead>
<tr>
<th>FDA-approved uses:</th>
<th>Axillary hyperhidrosis</th>
<th>Cervical dystonia</th>
<th>Chronic migraine</th>
<th>Glabellar lines</th>
<th>Forehead lines</th>
<th>Lateral canthal lines</th>
<th>Upper limb spasticity</th>
<th>Lower limb spasticity</th>
<th>Spasticity in adults</th>
<th>Overactive bladder</th>
<th>Strabismus and blepharospasm associated w/ dystonia</th>
<th>Urinary incontinence due to detrusor overactivity</th>
<th>Blepharospasm</th>
<th>Sialorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botox (onabotulinumtoxin A)</td>
<td></td>
<td>Cosmetic</td>
<td>Cosmetic</td>
<td>Cosmetic</td>
<td></td>
<td></td>
<td>2-17y</td>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dysport (Abobotulinumtoxin A)</td>
<td></td>
<td>Cosmetic</td>
<td></td>
<td>Age ≥2y</td>
<td>Age ≥2y</td>
<td></td>
<td></td>
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<tr>
<td>Xeomin (Incobotulinumtoxin A)</td>
<td></td>
<td>Cosmetic</td>
<td>2-17y</td>
<td></td>
<td></td>
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<tr>
<td>Jeuveau (Prabotulinumtoxin A)</td>
<td></td>
<td>Cosmetic</td>
<td></td>
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<tr>
<td>Myobloc (Rimabotulinumtoxin A)</td>
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</table>
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.


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.


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.


Sialorrhea (excessive salivation associated w/ neurological disorders or local anatomical abnormalities):
This mixed treatment NMA of 15 trials determined that compared to placebo, benztrpine and BTX A & B are associated with drooling. Benztrpine showed to be substantially and statistically superior to BTX A &/or B. In children with cerebral palsy or adults with Parkinson’s disease, benztrpine and BTXB and glycopyrrolate were superior to placebo, while BTXA was not.


Blepharospasm (focal dystonia involving the orbicularis oculi muscles and other periorcular 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 periorcular 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].
**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.”


**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.

Omalizumab (Xolair®)
EBRx PA Criteria

ASTHMA
2. The patient must be age 6y or older.
2. The patient must have a diagnosis of moderate or severe persistent asthma with either a positive skin test or with in vitro reactivity to a perennial aeroallergen.
3. The patient must have a total serum IgE level ≥30 IU/mL.
3. The patient must be adherent to prescribed asthma controller medications and must have filled inhaled corticosteroids/LABA combination for a minimum of the past 3 of 4 months prior to this request.
4. The patient must NOT be dependent on systemic steroids to prevent serious asthma exacerbations.
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.

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.

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, levo cetirizine 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 levo cetirizine 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.

Notes:
1Per 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.
2Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.
3In 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.

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.
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 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. 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.

- **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.

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

If criteria fulfilled, approve ipilimumab for 4 months (maximum of 4 doses total). | Criteria for continuation |
Renal Cell Carcinoma (RCC)

1. 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.

   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%).
   - Ipilimumab does have activity after nivolumab or pembrolizumab though this is based on a retrospective review
   - 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.

Dosing: 3 mg/kg IV every 3 weeks x 4 doses MAX

REFERENCES:
3. PMID 31562797 NCT01844505

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

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

<table>
<thead>
<tr>
<th>Criteria for new users</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must be 2 (two) years or younger.</td>
</tr>
<tr>
<td>2. The patient must have the confirmed diagnosis of SMA-1 by genetic testing for both symptomatic and presymptomatic patients.</td>
</tr>
<tr>
<td>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.)</td>
</tr>
<tr>
<td>4. The patient must have bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>6. Prescriber must be a neuromuscular specialist.</td>
</tr>
<tr>
<td>7. At request, the patient must have NO HISTORY of the ability to walk independently (defined as the ability to walk &gt;15 feet unaided).</td>
</tr>
</tbody>
</table>

Medication is excluded from pharmacy.

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

Ref:
**Retifanlimab (Zynyz) 500 mg/20 ml single dose vial**

**EBRx PA Criteria**

**is FDA-approved for:**
treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma

<table>
<thead>
<tr>
<th>Criteria for new users</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagnosis of either metastatic OR recurrent locally advanced Merkel cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>2. Disease has not progressed on another immune checkpoint inhibitor, such as pembrolizumab (Keytruda) or nivolumab (Opdivo)</td>
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</tr>
</tbody>
</table>

If above criteria are met, approve for 12 months

**Note:**
Dose: 500 mg IV over 30 minutes every 4 weeks
Retifanlimab appears to have similar efficacy as pembrolizumab (Keytruda) which has been shown to improve overall survival compared to historical controls.

**References:**

**Quantity Limits:** n/a
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

<table>
<thead>
<tr>
<th>Rheumatoid Arthritis—PA updated 4/22/21JJ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>csDMARD</strong> (conventional synthetic)</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>Leflunomide</td>
</tr>
<tr>
<td><strong>tsDMARD</strong> (targeted synthetic)</td>
</tr>
<tr>
<td>Tofacitinib</td>
</tr>
<tr>
<td>Baricitinib (targets JAK)</td>
</tr>
<tr>
<td><strong>boDMARD</strong> (biologic originator)</td>
</tr>
<tr>
<td>Adalimumab</td>
</tr>
<tr>
<td>Certolizumab</td>
</tr>
<tr>
<td>Etanercept</td>
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<tr>
<td>Golimumab</td>
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<tr>
<td>Upadacitinib</td>
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<tr>
<td>Sarilumab</td>
</tr>
<tr>
<td>Infliximab</td>
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<tr>
<td>Abatacept</td>
</tr>
<tr>
<td>Rituximab*</td>
</tr>
<tr>
<td>Tocilizumab</td>
</tr>
<tr>
<td>Anakinra</td>
</tr>
</tbody>
</table>

1. The patient must have the diagnosis of rheumatoid arthritis.

**Early RA (diagnosis less than 6 months ago and still symptomatic):**

1a. If the patient has had the diagnosis of rheumatoid arthritis for 6 months or less, and who are symptomatic with RA symptoms, the patient must reach the optimal dose of methotrexate 25-30 mg weekly and maintain this dose for at least 8 weeks TOGETHER WITH another DMARD (MTX-hydroxychloroquine-sulfasalazine 2-4g/d). (Or else, the patient must have a contraindication to MTX.

**Established RA:**

1b. The patient with established RA and with moderate or high disease activity must use combination MTX 25-30mg weekly and another DMARD (MTX-hydroxychloroquine-sulfasalazine 2-4g/d) and maintain the combination for at least 8 weeks, unless MTX is contraindicated. If MTX is contraindicated, other combination DMARD therapy should be used.

2. For either early RA or established, two different TNF inhibitors must be tried consecutively (not concurrently) for at least 8 weeks each before tofacitinib is a covered drug.

3. Patients with a previously treated lymphoproliferative disorder, rituximab should be used over TNF inhibitor.

Notes:

a. Biologic DMARDs should all be used in combination with DMARD unless contraindicated.

b. Combination TNFi is not covered.

c. Combination TNFi and other biologic is not a covered combination.

**FOR RITUXIMAB**

NOTE: Rituximab is reserved for patients who have responded poorly to TNF blockers and not for csDMARDs.

4. Does the patient have contraindications to other agents (recent history of lymphoma, latent tuberculosis with contraindications to the use of chemoprophylaxis, living in a TB-endemic region, or a previous history of demyelinating disease? (If so, rituximab may be used as 2nd line therapy after csDMARDs.)

**TNF inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, biosimilars (as approved according to a thorough approval process, such as by EMA and/or FDA).**

†The ‘certain circumstances’, which include history of lymphoma or a demyelinating disease, are detailed in the accompanying text.†

‡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,
References:

Juvenile Idiopathic Arthritis (previously known as JRA)

<table>
<thead>
<tr>
<th>Etanercept (Enbrel®)-TNFa</th>
<th>Adalimumab (Humira®)-TNFa</th>
<th>*Infliximab (Remicade®)-TNFa – must be used w/ methotrexate, anakinra (Kinereit), infliximab-abda (Renflexis)</th>
</tr>
</thead>
</table>

Does the patient have the diagnosis of juvenile idiopathic arthritis? [Yes] [No]

Has the patient received glucocorticoid joint injections and at least 3 months of methotrexate or leflunomide at the maximum tolerated typical dose? [Yes] [No]

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? [Yes] [No]

OR

Has the patient received an adequate trial of NSAIDS and have sacroiliac arthritis? [Yes] [No]

Abatacept (Orencia®) Criteria (should apply the above criteria as well as the following:)

Has the JIA patient received more than one TNFaI sequentially and is now seeking to switch therapy due to high disease activity? [Yes] [No]

Rituximab (Rituxan®) Criteria (should have fulfilled the above criteria 1-3 and the following:)

Has the JIA patient received more than one TNFaI sequentially, then abatacept, and still have high disease activity, AND test positive for RF? [Yes] [No]

*Infliximab must be used with methotrexate due to the recognized potential for MTX to reduce the incidence of neutralizing antibodies to infliximab and consistent with the labeling of infliximab.


Ankylosing Spondylitis

<table>
<thead>
<tr>
<th>Adalimumab (Humira®)</th>
<th>Etanercept (Enbrel®)</th>
<th>Golimumab (Simponi®)</th>
<th>Certolizumab (Cimzia®)</th>
<th>Secukinumab (Cosentyx®)</th>
<th>Ixekizumab (Taltz®)</th>
<th>Infliximab (Remicade®) – no new starts; only allow if currently receiving.</th>
</tr>
</thead>
</table>

Does the patient have the diagnosis of active ankylosing spondylitis? [Yes] [No]

Has the patient failed a trial of 2 NSAIDS? Sequential NSAID trials should be 1 month in length and be optimally dosed. [Yes] [No]

Note: Initial PA should be good for 3 months. After physician confirms the patient’s positive response, defined as a reduction of the BASDAI‡ to 50% of the pre-treatment value, or a reduction of >2 units, together with a reduction of the spinal pain VAS by 2 cm or more, the patient would be eligible for re-approval.
‡BASDAI is Bath Ankylosing Spondylitis Disease Activity Index, a scale of measuring discomfort, pain, and fatigue (1 being no problem and 10 being the worst problem) in response to 6 questions asked of the patient pertaining to the major symptoms of AS, Fatigue, Spinal pain, Arthralgia, Enthesitis, or inflammation of tendons and ligaments, Morning stiffness duration, Morning stiffness severity. To give each symptom equal weighting, the average of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of >4 suggest suboptimal control of disease, and those patients are usually good candidates for a change in medical therapy, may benefit by treatment with biologic therapies.

References:

Psoriatic Arthritis

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

***Ustekinumab (Stelara)—Please go to the EBD PA criteria “Ustekinumab” for criteria
Upadacitinib (Rinvoq)—FDA-approved 12/15/21 as 2nd 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:

Plaque Psoriasis

TNF inhibitors:
Adalimumab (Humira®) Etanercept (Enbrel®) Infliximab (Remicade®) infliximab-abda (Renflexis)

IL-17 inhibitors:
Secukinumab (Cosentyx®)
Ixeikizumab (Taltz®)
Brodalumab (Siliq®)

IL-12/23 inhibitors:
***Ustekinumab (Stelara)—Please go to EBD PA criteria “Ustekinumab” for criteria

IL-23 inhibitor:
Guselkumab (Tremfya®)
Risankizumab (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 >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.]

Crohn’s Disease
Adalimumab (Humira®) upadacitinib (Rinvoq®)—after TNF failure or intolerance
Certolizumab pegol (Cimzia®)
Infliximab (Remicade®)
infliximab-abda (Renflexis®)
infliximab-abda (Inflectra®)

1. The patient must have a diagnosis of Crohn’s disease.
2. 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 >2.4g/d) or budesonide (at a dose of >6 mg/day).
3. If items 1-2 are “yes” and the patient has severe, active Crohns disease (as opposed to fistulizing), then approval of infliximab 5mg/kg IV infusion may be approved. Readministration of 5mg/kg may be approved if disease recurs (not before 2 weeks after the original dose). In patients not responding within 2 weeks to the initial infusion, NO FURTHER INFLIXIMAB SHOULD BE USED AS THE RESPONSE IS UNLIKELY. Alternatively, adalimumab 80-160mg SC followed by 40mg SC at week 2 may be approved.
4. If items 1-2 are “yes” and the patient has fistulizing, active Crohn’s disease, then additional doses of 5mg/kg should be approved for weeks 2 and 6 after the original infusion. If the patient does not respond after these 3 doses, no additional treatment with infliximab should be given.

Natalizumab (Tysabri) (Patient should satisfy the above criteria as well as the one below.)
5. 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.

References:

Note: CDI 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 the diagnosis of ulcerative colitis
2. The patient must have failed >3 months of mesalamine or sulfasalazine or glucocorticoids?
3. The patient have moderate to severe disease (characterized by steroid dependence).

General References:

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 >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.

*Hurley Staging:
- Stage I: abscess formation, single or multiple, without sinus tracts and cicatization (scarring).
- Stage II: One or more widely separated recurrent abscesses with tract formation and cicatization (scars).
- Stage III: Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement.

Continuation Criteria
1. After 3 months of therapy the patient must have at least a 50% reduction from baseline in the total abscess and inflammation-nodule count, and with no increase in the abscess or draining-fistula count.

If approved, PA is good for 12 months.


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### Noninfectious uveitis

<table>
<thead>
<tr>
<th>Adalimumab (Humira®), etanercept (Enbrel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient must have the diagnosis of noninfectious uveitis.</td>
</tr>
<tr>
<td>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).</td>
</tr>
<tr>
<td>3. The patient must have had an inadequate response to systemic glucocorticoid therapy.</td>
</tr>
<tr>
<td>4. The patient must have had an inadequate response to cyclosporine and methotrexate, combined.</td>
</tr>
</tbody>
</table>

If approved, PA is good for 12 months.

Continuation Criteria
1. After 3 months of therapy the patient must have at least a 50% reduction from baseline in the total abscess and inflammation-nodule count, and with no increase in the abscess or draining-fistula count.

If approved, PA is good for 12 months.

Ref for uveitis:

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General References: