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 July 2025

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

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)

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

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

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

References:
1. Coles, AJ, et al. Alemtuzumab for patients with relapsing MS after disease-modifying therapy: a RC phase 3 trial. Lancet. 2012;380:1829-1839.
2. Coles, AJ, et al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 Clinical Trial. Neurology. 2012;78:1069-78.
3. EDSS. http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/10-2-3-29-EDSS_Form.pdf . Accessed 2/5/15.
4. Cohen JA, Coles AJ, et al. Alemtuzumab versus interferon beta 1a as first-line treatment ofr patients with RRMS; A RCT phase 3. Lancet. 2012;380:1819-28.
5. Medscape on new risk with alemtuzumab. https://www.medscape.com/viewarticle/911741?nlid=129300_4822&src=WNL_mdplsfeat_190416_mscpedit_phar&uac=126299PK&spon=30&impID=1938647&faf=1

EDSS scale for MS:
0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
1.0 - No disability, minimal signs in one FS* (i.e., grade 1).
1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
4.0 - Fully ambulatory w/o aid, self-sufficient, up and about some 12 h/d despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk w/o aid or rest some 500 m.
4.5 - Fully ambulatory w/o aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk w/o aid or rest some 300 m.
5.0 - Ambulatory w/o aid or rest for about 200 m; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
5.5 - Ambulatory w/o aid for about 100 m; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).

6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+). ❑ 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).
7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).
8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).
8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).
9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).
9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).
10.0 - Death due to MS.
*Excludes cerebral function grade 1.
Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.
Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.
Sources:
Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.
Haber A, LaRocca NG. eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society; 1985.

Alglucosidase Alfa (Lumizyme 50mg IV)
EBRx PA Criteria

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

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

Note: If yes, approve for 1 year.

References:

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

Amivantamab (Rybrevant)
EBRx PA Criteria (Medical Benefit)

is FDA-approved for:

- In combination with **lazertinib** for the ***first-line*** treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test NOT COVERED
  - Lazertinib+amivantamab improved progression free survival and increased toxicity compared to osimertinib monotherapy. Overall survival data is not yet mature.
  - References:
    - Lazcluze PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219008s000lbledt.pdf. Accessed 8/29/2024.
    - Cho BC et al. Amivantamab plus Lazertinib in Previously Untreated *EGFR*-Mutated Advanced NSCLC. N Engl J Med. 2024 Jun 26. doi: 10.1056/NEJMoa2403614. Epub ahead of print. PMID: 38924756.
- In combination with **carboplatin and pemetrexed** for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor NOT COVERED
  - The benefit of amivantamab+chemotherapy over chemotherapy only is limited to progression free survival.
  - Reference: Passaro A et al. Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. Ann Oncol. 2024 Jan;35(1):77-90. doi: 10.1016/j.annonc.2023.10.117. Epub 2023 Oct 23. PMID: 37879444.
- In combination with **carboplatin and pemetrexed** for the ***first-line*** treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test NOT COVERED
  - The benefit of amivantamab+chemotherapy over chemotherapy only is limited to progression free survival.
  - Reference: Zhou C et al. Amivantamab plus Chemotherapy in NSCLC with *EGFR* Exon 20 Insertions. N Engl J Med. 2023 Nov 30;389(22):2039-2051. doi: 10.1056/NEJMoa2306441. Epub 2023 Oct 21. PMID: 37870976.
- As a **single agent** for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy SEE CRITERIA

Criteria for new users (EGFR exon 20 insertion mutations after platinum chemotherapy)
1. Diagnosis of non-small cell lung cancer (NSCLC)
2. NSCLC is locally advanced or metastatic
3. Disease is positive for EGFR exon 20 insertion mutation
4. Disease has progressed on or after platinum-based chemotherapy
5. Amivantamab will be used as single agent
If all criteria met, approve for 12 months.

Note:
Amivantamab monotherapy in this setting is associated with a median overall survival of 22.8 months. This compares favorably with the median survival of other agents that may be used in this setting (10-15 months)

References:

1. Amivantamab package insert. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/RYBREVANT-pi.pdf. Accessed 9/20/2024
2. Park K et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol. 2021 Oct 20;39(30):3391-3402. doi: 10.1200/JCO.21.00662. Epub 2021 Aug 2. PMID: 34339292; PMCID: PMC8791812.

Atezolizumab (Tecentriq)
840 mg/14 mL and 1200 mg/20 mL vials for IV use
Atezolizumab/Hyaluronidase (Tecentriq Hybreza)
1875-30000mg-units/15 ml vials for SQ use
EBRx PA Criteria

Note: As of 10/24/24, Tecentriq Hybreza and Tecentriq have identical indications and pricing. Both should be administered by a healthcare professional. Coverage criteria will be identical for these products.

is FDA-approved for:

- **Non-small cell lung cancer, metastatic (NSCLC)**
  - As adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test. COVERED FOR PD-L1 >50% ONLY
  - As monotherapy for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (**EITHER** PD-L1 stained ≥50% of tumor cells [TC ≥50%] **OR** PD-L1 stained tumor-infiltrating immune cells covering ≥10% of the tumor area [IC ≥10%]), with no EGFR or ALK genomic tumor aberrations
  - In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations
  - In combination with paclitaxel protein-bound (Abraxane) and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations
  - As monotherapy in patients with disease progression during or following platinum-containing chemotherapy. Patients should have disease progression on approved therapy for EGFR or ALK genomic tumor mutations (if present) prior to receiving atezolizumab
- **Small Cell Lung Cancer (SCLC)**
  - In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage SCLC.
- **Hepatocellular Carcinoma (HCC)**
  - in combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy
- **Melanoma**
  - in combination with cobimetinib and vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma NOT COVERED
    - Benefit of this combination is limited to progression free survival. Overall survival nor quality of life have been shown to be improved at this time.
    - References:
      - Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;395(10240):1835-1844. doi:10.1016/S0140-6736(20)30934-X PMID 32534646
      - Ascierto PA et al. Overall survival with first-line atezolizumab in combination with vemurafenib and cobimetinib in BRAFV600 mutation-positive advanced melanoma (IMspire150): second interim analysis of a multicentre, randomised, phase 3 study. Lancet Oncol. 2023 Jan;24(1):33-44. doi: 10.1016/S1470-2045(22)00687-8. Epub 2022 Nov 29. PMID: 36460017.
      - Ascierto PA et al. Overall survival with first-line atezolizumab in combination with vemurafenib and cobimetinib in BRAFV600 mutation-positive advanced melanoma (IMspire150): second interim analysis of a multicentre, randomised, phase 3 study. Lancet Oncol. 2023 Jan;24(1):33-44. doi: 10.1016/S1470-2045(22)00687-8. Epub 2022 Nov 29. PMID: 36460017.
- **Alveolar Soft Part Sarcoma (ASPS)** NOT COVERED
  - Treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic ASPS
    - Data limited to single arm trial with no QOL/OS/symptom improvement
    - Chen AP, Sharon E, O'Sullivan-Coyne G, Moore N, Foster JC, Hu JS, Van Tine BA, Conley AP, Read WL, Riedel RF, Burgess MA, Glod J, Davis EJ, Merriam P, Naqash AR, Fino KK, Miller BL, Wilsker DF, Begum A, Ferry-Galow KV, Deshpande HA, Schwartz GK, Ladle BH, Okuno SH, Beck JC, Chen JL, Takebe N, Fogli LK, Rosenberger CL, Parchment RE, Doroshow JH. Atezolizumab for Advanced Alveolar Soft Part Sarcoma. N Engl J Med. 2023 Sep 7;389(10):911-921. doi: 10.1056/NEJMoa2303383. PMID: 37672694; PMCID: PMC10729808.

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).

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

References:

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

Metastatic Non-Small Cell Lung Cancer (NSCLC)

PATIENTS WITH PREVIOUSLY-TREATED ADVANCED/METASTATIC DISEASE:

1. Patient must have diagnosis of metastatic NSCLC diagnosis (squamous or non-squamous)

2. Patient must have been treated previously with platinum-based chemotherapy.

3. If patient is ALK/EGFR mutation positive, patient also has previously been treated with targeted therapy (e.g. erlotinib, afatinib, dacomitinib, gefitinib, osimertinib, alectinib, crizotinib, brigatinib, ceritinib)

4. At initial request, patient must be ECOG performance status 0-1.

5. No prior PD-L1 or PD-1 inhibitor

If all criteria met, approve for 12 months

PATIENTS WITH NO PRIOR THERAPY FOR ADVANCED/METASTATIC DISEASE:

1. Patient must have diagnosis of metastatic NSCLC

2. Tumor does NOT harbor EGFR or ALK mutations.

3. At initial request, patient must be ECOG performance status 0-1.

4. If atezolizumab monotherapy will be used, tumor has high PD-L1 expression (TC ≥50% or IC ≥10%) [tumor histology can be squamous or non squamous]

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

If 1, 2, 3, and either 4 or 5 are met, approve for 12 months

Note:
-In patients previously treated with platinum-based chemotherapy (and targeted therapy if EGFR/ALK mutation +), atezolizumab improved OS compared to docetaxel with median OS 13.8 mo vs 9.6 mo (HR 0.73 95% CI 0.62-0.87). 1-2 prior chemo regimens with one being platinum based were required prior to enrollment.[1] Fewer severe adverse events were observed in atezolizumab arm (15% vs 43%)
-If newly-diagnosed, untreated, and non-squamous histology, atezolizumab/bevacizumab/carboplatin/paclitaxel improved OS vs bevacizumab/carboplatin/paclitaxel with median OS of 19.2 mo vs. 14.7 mo (HR 0.78; 95% CI, 0.64 to 0.96).[2] Atezolizumab/carboplatin/nab-paclitaxel also improved OS vs carboplatin/nab-paclitaxel with median OS of 18.6 mo vs. 13.9 mo.[3]
-If newly-diagnosed, untreated, any histology, and high PD-L1 expression (TC >50% or IC >10%), atezolizumab monotherapy improved overall survival compared with platinum-based doublet (median OS 20 mo vs 13 mo).[4] [data from trial Impower 110 study, NCT02409342—results published in PI only as of 6/2/2020]

References:

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

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

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

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

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

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

Note:
Atezolizumab+bevacizumab was compared to sorafenib. Median overall survival was improved in the atezo/bev group compared to sorafenib (median not reached in atezo/bev group versus 13.2 mo; HR 0.58; 95% CI 0.42-0.79; p=0.0006). Median overall survival in the atezo/bev group was later reported as 19.2 mo.

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

References:
Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382(20):1894-1905. doi:10.1056/NEJMoa1915745. PMID 32402160 NCT03434379
Cheng AL et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022 Apr;76(4):862-873. doi: 10.1016/j.jhep.2021.11.030. Epub 2021 Dec 11. PMID: 34902530.

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

FDA-approved for:

Merkel Cell Carcinoma (MCC)[1]

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

References (two reports of same study):

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

Urothelial Carcinoma (UC)

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

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

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

Reference:

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

Renal Cell Carcinoma (RCC)

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

Reference:

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

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

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

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

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

Reference:

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

Quantity Limits: n/a

Axatilimab (Niktimvo)
EBRx PA Criteria

is FDA-approved for:

- Treatment of chronic graft-versus-host disease (cGVHD) after failure of ≥2 prior lines of systemic therapy in adult and pediatric patients ≥40 kg

Criteria for new users
1. History of allogeneic hematopoietic stem cell transplantation (HSCT)
2. Diagnosis of chronic graft-versus-host disease (cGVHD)
3. Failure of at least 2 prior systemic therapies for cGVHD treatment (could include ruxolitinib, ibrutinib, and/or belumosudil)
4. Age ≥ 2 years
5. Weight ≥ 40 kg

Note:
Dose 0.3 mg/kg (max 35 mg) IV infusion every 2 weeks

In a heavily pre-treated population (median 4 prior lines of therapy for cGVHD), 74% of patients had a response in cGVHD symptoms with axatilimab, and 60% of patients had a decrease in symptom burden (as defined by a reduction of ≥5 points on the modified Lee Symptom Scale).

Reference:
Wolff D, et al. Axatillimab in recurrent or refractory chronic graft-versus-host disease. N Engl J Med. 2024;319:1002-1014.

Quantity Limits: maximum of 35 mg per dose

Belatacept (Nulojix) 250mg IV infusion
EBRx PA Criteria

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

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

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

References:
1. Nulojix website. http://packageinserts.bms.com/pi/pi_nulojix.pdf Accessed 8/3/11.
2. Vincenti F, Blancho G, Durrbach A, Friend P, et al. Five year safety and efficacy of belatacept in renal transplantation. J Am Soc Nephrol. 2010. 21:1587-96.
3. Neuberger, James M., et al. "Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and clinical checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group." *Transplantation* 101.4S (2017): S1-S56.

Belimumab (Benlysta)
EBRx PA Criteria

is FDA-approved for:

- Lupus nephritis, treatment of patients 5y+ with active LN who are receiving standard therapy
- Systemic lupus erythematosus, treatment of patients 5y+ with active SLE who are receiving standard therapy

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

ACR= American College of Rheumatology

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

Criteria for NEW users with SLE
1. Diagnosis of SLE
2. The patient must be 5y+.
3. Autoantibody positive (positive anti-double stranded DNA and low complement)
4. SELENA-SLEDAI score of 10 or above, despite standard treatment.
If the initial criteria are satisfied, the PA will be good for 26 weeks and inform the clinic and patient that followup evaluation must be met to continue.
Continuation criteria for SLE
1. For continuation beyond 24 weeks, the SELENA-SLEDAI score must have improved by ≥4 points while on belimumab treatment.
2. For continuation beyond 52 total weeks, SRI must be maintained to the SRI score at week 24 and beyond. Access would be denied if the SRI score worsens above the score they reached at week 24. (futility). The SRI score must be reported by the prescriber.
If the criteria above are satisfied, approve PA for 1 year.

Quantity Limits: 30ds limit

References:

1. Furie, Richard, et al. "Two-year, randomized, controlled trial of belimumab in lupus nephritis." *NEJM* 383.12 (2020): 1117-1128.
2. Singh_JA, Shah_NP, Mudano_AS. Belimumab for systemic lupus erythematosus. Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD010668. DOI: 10.1002/14651858.CD010668.pub2
3. Fanouriakis, Antonis, et al. "Update on the diagnosis and management of systemic lupus erythematosus." *Annals of the rheumatic diseases* 80.1 (2021): 14-25.

Blinatumomab (Blincyto) 35 mcg vial
EBRx PA Criteria

is FDA-approved for:

- Relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL). **See criteria for relapsed or Refractory disease**
- 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%. **See criteria for Post-Remission (Consolidation) Therapy**
- CD19-positive Philadelphia chromosome-negative B-cell precursor ALL in consolidation phase of multiphase chemotherapy **See criteria for Post-Remission (Consolidation) Therapy**

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

Note:
Adult dosing (see PI for pediatric dosing):

Note: Hospitalization is recommended for the first 9 days of cycle 1, and the first 2 days of cycle 2.
Cycle 1: IV: 9 mcg daily administered as a continuous infusion on days 1 to 7, followed by 28 mcg daily as a continuous infusion on days 8 to 28 of a 6-week treatment cycle.
Cycles 2 through 5: 28 mcg daily administered as a continuous infusion on days 1 to 28 of a 6-week treatment cycle.
Cycles 6 through 9: 28 mcg daily administered as a continuous infusion on days 1 to 28 of a 12-week treatment cycle.

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

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

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

Post-Remission (Consolidation) Therapy
1. Diagnosis of acute lymphocytic leukemia (ALL)
2. Disease is in a complete remission (CR) or complete remission with incomplete count recovery (CRi) after induction chemotherapy
3. Leukemia is CD19 positive
If criteria are met, approve x 12 months. Maximum duration of therapy is 4 cycles. Blinatumomab may be alternated with chemotherapy in this setting.

After a complete remission is achieved with multiagent chemotherapy, blinatumomab improves overall survival in patients with minimal residual disease (MRD)-negative and likely MRD-positive ALL.

References:
1. Litzgow MR et al. Blinatumomab for MRD-negative acute lymphoblastic leukemia in adults. N Engl J Med. 2024 July;391(4):320-333. DOI: 10.1056/NEJMoa2312948.
2. Gökbuget N et al. Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia. Leuk Lymphoma. 2020 Nov;61(11):2665-2673. doi: 10.1080/10428194.2020.1780583. Epub 2020 Jul 3. PMID: 32619115.

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

is FDA-approved for:

- Osteomalacia, tumor-induced: Treatment of fibroblask 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) OR • Be intolerant of oral phosphate w/ active vitamin D.
5. Must have an X-Ray confirming rickets @ the growth plates OR bowing of femur, tibia, or both femur and tibia.
6. Must be age 1-12 years.

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

References:
1. Carpenter, Thomas O., et al. "Burosumab therapy in children with X-linked hypophosphatemia." *N Eng J Med* 378.21 (2018): 1987-1998.
2. UpToDate (accessed 6/12/19), XLH.
3. Clinicaltrials.gov. NCT02915705 Efficacy and safety of burosumab (KRN23) versus oral phosphate and active vitamin D treatment in pediatric patients with X-linked hypophosphatemia (XLH).

Caplacizumab (Cablivi Kit 11mg)
EBRx PA Criteria
Medical PA if needed; SQ can be self-administered.

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

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

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

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

Quantity Limits: 58 days max.

References:

1. UpToDate. Thrombotic thrombocytopenia purpura. Accessed 5/6/19.
2. Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. Lancet Haematol 2017 Apr;4(4):e157.
3. Peyvandi, Flora, et al. "Caplacizumab for acquired thrombotic thrombocytopenic purpura." *New England Journal of Medicine* 374.6 (2016): 511-522. TITAN
4. Scully, Marie, et al. "Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura." *New England Journal of Medicine* 380.4 (2019): 335-346. HERCULES

Carfilzomib (Kyprolis) 10 mg, 30 mg, 60 mg single dose vial
EBRx PA Criteria

FDA-approved for:

- Relapsed or refractory multiple myeloma after one to three lines of therapy in combination with
  - lenalidomide and dexamethasone (SEE CRITERIA) **OR**
  - dexamethasone (SEE CRITERIA) **OR**
  - daratumumab and dexamethasone NOT COVERED
    - Daratumumab/carfilzomib/dexamethasone was compared to carfilzomib dexamethasone. Progression free survival benefit was demonstrated, but a statistically significant overall survival or quality of life benefit has not been demonstrated to date

      References:
      - Dimopoulos, Meletios, et al. "Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study." The Lancet 396.10245 (2020): 186-197.
      - David Siegel et al. (2021) Health-related quality of life outcomes from the CANDOR study in patients with relapsed or refractory multiple myeloma, Leukemia & Lymphoma, 62:12, 3002-3010, DOI: 10.1080/10428194.2021.1941927
      - Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes from a randomised, multicentre, open-label, phase 3 study. Lancet Oncol. 2022;23(1):65-76. doi:10.1016/S1470-2045(21)00579-9
      - Usmani SZ et al. Final analysis of carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone in the CANDOR study. Blood Adv. 2023 Jul 25;7(14):3739-3748. doi: 10.1182/bloodadvances.2023010026. PMID: 37163358; PMCID: PMC10368773.
  - Isatuximab and dexamethasone NOT COVERED
    - Benefit is limited to progression free survival only compared to carfilzomib plus dexamethasone
      - Reference: Moreau P et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet. 2021 Jun 4:S0140-6736(21)00592-4. doi: 10.1016/S0140-6736(21)00592-4. Epub ahead of print. PMID: 34097854.
      - Martin T et al. Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized Phase 3 study. Blood Cancer J. 2023 May 9;13(1):72. doi: 10.1038/s41408-023-00797-8. Erratum in: Blood Cancer J. 2023 Sep 27;13(1):152. PMID: 37156782; PMCID: PMC10166682.
- Relapsed/refractory multiple myeloma, as a single agent for the treatment of patients who have received one or more lines of therapy (NOT COVERED) Monotherapy with carfilzomib was no better than steroid alone in a heavily pretreated population.
  - Reference: Hájek R et al. A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). Leukemia. 2017 Jan;31(1):107-114. PMID 27416912 NCT01302392

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

Note:

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

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

References:

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

Collagenase (Xiaflex)
EBRx PA Criteria

is FDA-approved for:

- Peyronie Disease - Indicated for treatment of adult men with Peyronie disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.
- Dupuytren Contracture - Treatment of adults with Dupuytren contracture with a palpable cord (not covered at this time)

Peyronie's Disease
1. The patient must have diagnosis of Peyronie's disease**, NON active** disease (no pain or change in deformity)
2. No Peyronie's plaques that involve the penile urethra
3. Must be male with palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.
4. Limit to 4 treatment cycles (8 Injections total) Cycle = 2 injections (0.58mg then repeat in 1-3 days)
5. Must be prescribed by urologist.

References:

1. Gelbard, Martin, et al. "Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of peyronie disease in 2 large double-blind, randomized, placebo-controlled phase 3 studies." *The Journal of urology* 190.1 (2013): 199-207.
2. Up-to-Date Collagenase accessed 05/16/2024.
3. Micromedex Collagenase accessed 05/16/2024.

Daratumumab (Darzalex) 100mg/5mL and 400mg/20mL vials
Daratumumab and hyaluronidase (Darzalex Faspro)
1800 mg daratumumab and 30,000 units hyaluronidase per 15 ml vial
EBRx PA Criteria

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

Darzalex and Darzalex Faspro are FDA-approved for:

- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant (SEE NEWLY-DIAGNOSED CRITERIA) and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy (SEE RELAPSED/REFRACTORY CRITERIA)
- In combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (SEE NEWLY DIAGNOSED CRITERIA)
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed multiple myeloma patients who are eligible for autologous stem cell transplant (SEE NEWLY DIAGNOSED CRITERIA)
- In combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy (SEE RELAPSED/REFRACTORY CRITERIA)
- In combination with carfilzomib and dexamethasone in multiple myeloma patients who have received one to three prior lines of therapy NOT COVERED. Daratumumab/carfilzomib/dexamethasone was compared to carfilzomib/dexamethasone. Progression free survival benefit was demonstrated, but a statistically significant overall survival or quality of life benefit has not been demonstrated to date
    - References:
    - Dimopoulos, Meletios, et al. "Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study." The Lancet 396.10245 (2020): 186-197.
    - David Siegel et al. (2021) Health-related quality of life outcomes from the CANDOR study in patients with relapsed or refractory multiple myeloma, Leukemia & Lymphoma, 62:12, 3002-3010, DOI: 10.1080/10428194.2021.1941927
    - Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes from a randomised, multicentre, open-label, phase 3 study. Lancet Oncol. 2022;23(1):65-76. doi:10.1016/S1470-2045(21)00579-9
    - Usmani SZ et al. Final analysis of carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone in the CANDOR study. Blood Adv. 2023 Jul 25;7(14):3739-3748. doi: 10.1182/bloodadvances.2023010026. PMID: 37163358; PMCID: PMC10368773.
- As monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent (SEE RELAPSED/REFRACTORY CRITERIA)
- In combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy including lenalidomide and a proteasome inhibitor (NOT COVERED). Benefit is limited to progression free survival at this time.

References:

- Chari A et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood. 2017 Aug 24;130(8):974-981. PMID 28637662 NCT01998971 (EQUULEUS; MMY1001)
- Dimopoulos MA et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021 Jun;22(6):801-812. doi: 10.1016/S1470-2045(21)00128-5. PMID: 34087126. NCT03180736 (APOLLO)
- Bahlis NJ et al. Pomalidomide, dexamethasone, and daratumumab immediately after lenalidomide-based treatment in patients with multiple myeloma: updated efficacy, safety, and health-related quality of life results from the phase 2 MM-014 trial. Leuk Lymphoma. 2022 Jun;63(6):1407-1417. doi: 10.1080/10428194.2022.2030477. Epub 2022 Feb 8. PMID: 35133221.

Darzalex Faspro is also FDA-approved for:

- Multiple myeloma in combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in newly diagnosed patients who are eligible for autologous stem cell transplant (SEE NEWLY DIAGNOSED CRITERIA)
- light chain (AL) amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone in newly diagnosed patients. (accelerated approval). Limitation of use: DARZALEX FASPRO is not indicated and is not

recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials

- NOT COVERED due to lack of improvement in overall survival or quality of life. There is some evidence of benefit in delaying organ deterioration, but endpoints are largely based on surrogate markers.
- Reference:
  - Kastritis E et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. N Engl J Med. 2021 Jul 1;385(1):46-58. doi: 10.1056/NEJMoa2028631. PMID: 34192431. (NCT03201965)

Criteria for new users (NEWLY DIAGNOSED)

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

2. If the patient is eligible for high-dose therapy with autologous stem-cell transplantation, daratumumab will be used in combination with bortezomib, thalidomide, and dexamethasone (D-VTD), **OR** bortezomib, lenalidomide, and dexamethasone (D-VRD).

3. If the patient is ineligible for high-dose therapy with autologous stem-cell transplantation, daratumumab will be used in combination with bortezomib, melphalan, and prednisone (D-VMP) **OR** lenalidomide and dexamethasone (D-RD).

Approve x 8 months if criteria 1 and 2 are met. This timeframe should allow for completion of entire treatment course barring any major complications. Renewals are not allowed.
Approve x 12 months if criteria 1 and 3 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 or 1800mg SQ

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

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

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

Daratumumab schedule for D-RD regimen (transplant ineligible)	
Weeks	**Schedule**
Weeks 1 to 8	Weekly (total of 8 doses)
Weeks 9-24	Every 2 weeks (total of 8 doses)
Weeks 25 and beyond (Until progression of disease)	Every 4 weeks

Note:

1. 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]
2. 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).[4,5] 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.
3. 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).[6,7] 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.
4. In newly-diagnosed, transplant eligible patients, daratumumab/bortezomib/lenalidomide/dexamethasone **(D-VRD)** improved progression free survival and overall survival compared to VRD alone. Median overall survival was not reached with daratumumab vs. 128.9 months without (p = 0.034). 2-year overall survival rates were 94% vs. 91%, respectively. Overall survival data presented but not yet published as of 12/3/2024.

References:

D-VRD:

1. Sonneveld P et al. Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024 Jan 25; 390(4):301-313. Doi: 10.1056/NEJMoa2312054. Epub 2023 Dec 12. PMID: 38084760.
2. Joseph NS et al. Efficacy of Dara-RVD induction therapy in newly diagnosed myeloma (NDMM) patients ≥65 years of age. Presented at: 21st International Myeloma Society Annual Meeting & Exposition; September 25-29, 2024; Rio de Janeiro, Brazil. Abstract OA-51.

D-VTD:

3. Moreau P et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019 Jul 6;394(10192):29-38. PMID 31171419 NCT02541383.
4. Moreau P et al. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021 Oct;22(10):1378-1390. doi: 10.1016/S1470-2045(21)00428-9. Epub 2021 Sep 13. PMID: 34529931.
5. Roussel M et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab for transplantation-eligible patients with newly diagnosed multiple myeloma (CASSIOPEIA): health-related quality of life outcomes of a randomised, open-label, phase 3 trial. Lancet Haematol. 2020 Dec;7(12):e874-e883. doi: 10.1016/S2352-3026(20)30356-2. PMID: 33242444.

D-VMP:

6. Mateos MV et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet. 2020 Jan 11;395(10218):132-141. doi: 10.1016/S0140-6736(19)32956-3. Epub 2019 Dec 10. PMID 31836199
7. Mateos MV et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. NEJM. 2018;378(6):518-528. PMID 29231133 NCT02195479

D-RD:

8. Facon T et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019 May 30;380(22):2104-2115. NCT02252172 PMID 31141632
9. Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(11):1582-1596. doi:10.1016/S1470-2045(21)00466-6

Criteria for new users (RELAPSED/REFRACTORY)

1. Must have a diagnosis of multiple myeloma that is progressing

2. If daratumumab will be used in combination with other agents, patient must have received at least 1 prior line of therapy AND be planning to take daratumumab with dexamethasone + lenalidomide **OR** dexamethasone + bortezomib

3. If daratumumab monotherapy is to be used, patient must have been treated with at least 3 prior therapies including a proteasome inhibitor (bortezomib, carfilzomib, ixazomib) AND an immunomodulatory agent (lenalidomide, thalidomide, pomalidomide) OR be double-refractory to a proteasome inhibitor and an immunomodulatory agent.

If criterion 1 and either 2 or 3 is met, approve for 12 months. May renew approval if no progression of disease.

Note:

- Therapy continues until progression or unacceptable toxicity.
- Daratumumab/bortezomib/dexamethasone improved progression free survival compared with bortezomib/dexamethasone alone. Overall survival was not significantly better but trended towards an improvement and post-trial use of daratumumab may have confounded overall survival analysis.[1]
- Daratumumab/lenalidomide/dexamethasone improved progression free survival compared with lenalidomide/dexamethasone alone. Overall survival is trending towards improvement but still considered immature at last follow up.[2,3]
- Daratumumab monotherapy was found have improved overall survival compared to pomalidomide/dexamethasone in a matched adjusted indirect comparison analysis.[4]

References:

1. Spencer A et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018 Dec;103(12):2079-2087. PMID 30237264 NCT02136134
2. Dimopoulos MA et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Oct 6;375(14):1319-1331. PMID27705267 NCT02076009
3. Dimopoulos MA et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. Haematologica. 2018 Dec;103(12):2088-2096. PMID 30237262 NCT02076009
4. Van Sanden S et al. Comparative Efficacy of Daratumumab Monotherapy and Pomalidomide Plus Low-Dose Dexamethasone in the Treatment of Multiple Myeloma: A Matching Adjusted Indirect Comparison. Oncologist. 2018 Mar;23(3):279-287. PMID 29192016

Denosumab (Xgeva or Prolia)
Xgeva 120mg/1.7mL (1.7mL) for SC injection
Prolia 60mg/mL (1mL) for SC injection

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

- Bone metastases from solid tumors (Xgeva)
- Giant cell tumor of bone (Xgeva) that is unresectable or where surgical resection is likely to result in severe morbidity
- Hypercalcemia of malignancy (treatment), refractory to bisphosphonate therapy (Xgeva)
- Prevention of skeletal-related events in patients with multiple myeloma (Xgeva)
- Osteoporosis/bone loss (Prolia)

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. The patient must have adequate blood levels of albumin-adjusted serum calcium levels before approval. OR
3. Requested indication is prevention of skeletal-related events in patients with multiple myeloma AND patient has a CrCl < 35 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. The patient must have adequate blood levels of albumin-adjusted serum calcium levels before approval.
If one of the above is fulfilled, approve for 12 months. Avoid use in patients with hypocalcemia.

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

- Osteoporosis treatment in postmenopausal women at high risk for fracture
- Osteoporosis treatment in postmenopausal women with failure of or intolerance to other available osteoporosis treatments
- Osteoporosis treatment to increase bone mass in men at high risk for fracture
- Glucocorticoid-induced osteoporosis in patients at high risk of fracture who are initiating or continuing systemic glucocorticoids at a daily prednisone equivalent of 7.5mg+
- 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

Discontinuation/interruption of therapy: Discontinuation or interruption (eg, >1 month beyond next scheduled dose) of denosumab should not occur without subsequent antiresorptive therapy (eg, with a bisphosphonate) due to increased risk of vertebral fracture; drug holidays are not recommended.

CRITERIA for: Prolia 60mg/1mL (dose: 60 mg SQ every 6 months)
1. For any request, the patient must have a serum level of albumin-adjusted serum calcium in the normal range.
2. 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*.
3. Request is for treatment of bone loss in men receiving androgen-deprivation therapy for non-metastatic prostate cancer
4. Request is for treatment of bone loss in women receiving an aromatase inhibitor (anastrozole, letrozole, or exemestane) therapy for breast cancer
5. Request if for treatment of osteoporosis in men IF the reported estimated creatinine clearance is 35mL/min or worse (lower), making a bisphosphonate not a choice.
*failure: fracture or decrease in bone mineral density (BMD) while compliant on bisphosphonate therapy

*contraindications to IV bisphosphonates: CrCl <35 ml/min (zoledronic acid, alendronate)
*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 criteria 1 is satisfied and either 2,3,4, or 5, then approve for 1 year.

Dostarlimab (Jemperli)
EBRx PA Criteria

is FDA-approved for:

- Endometrial cancer:
  - as a single agent, for treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation NOT COVERED. Data limited to response rate only.
  - in combination with carboplatin and paclitaxel, followed by dostarlimab as a single agent for the treatment of adult patients with primary advanced or recurrent endometrial cancer SEE CRITERIA
- Mismatch Repair Deficient Recurrent or Advanced Solid Tumors
  - as a single agent for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options NOT COVERED Data limited to response rate only.

Criteria for new users
1. Diagnosis of advanced (stage III or IV) or recurrent endometrial cancer
2. No prior treatment for advanced/recurrent endometrial cancer
3. Dostarlimab will be used in combination with carboplatin and paclitaxel for 6 cycles followed by dostarlimab monotherapy.
If all criteria met, approve for 12 months. Dostarlimab continues until progression of disease, unacceptable toxicity, or for up to 3 years.

Note:
Dose: With chemo: 500 mg every 3 weeks. After chemotherapy completes, 1000 mg every 6 weeks.
Dostarlimab + chemo improved overall survival in this population. Median OS was 44.6 months in the dostarlimab group vs 28.2 months in the chemo group; HR 0.69; 95% CI, 0.54-0.89; P = 0.002
References:

1. Dostarlimab package insert. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Jemperli/pdf/JEMPERLI-PI-MG.PDF. Accessed 6/24/2024.
2. Powell MA et al. Overall Survival in Patients with Endometrial Cancer Treated with Dostarlimab plus Carboplatin-Paclitaxel in the Randomized ENGOT-EN6/GOG-3031/RUBY Trial. Ann Oncol. 2024 Jun 10:S0923-7534(24)00721-X. doi: 10.1016/j.annonc.2024.05.546. Epub ahead of print. PMID: 38866180.

Quantity Limits: n/a (medical benefit drug)

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

FDA-approved for:

- In combination with platinum-containing chemotherapy as neoadjuvant treatment, followed by single-agent adjuvant treatment after surgery, for adult patients with resectable (tumors ≥4 cm and/or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements
- 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
- treatment of adult patients with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy (cCRT)
- 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)
- in combination with tremelimumab-actl, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC)
- in combination with carboplatin and paclitaxel followed by durvalumab as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR) NOT COVERED (SEE DOSTARLIMAB OR PEMBROLIZUMAB)
    - Benefit is limited to progression free survival. Overall survival and patient reported outcomes are pending
    - Westin SN et al. Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial. J Clin Oncol. 2024 Jan 20;42(3):283-299. doi: 10.1200/JCO.23.02132. Epub 2023 Oct 21. PMID: 37864337; PMCID: PMC10824389.
- In combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by single agent durvalumab as adjuvant treatment following radical cystectomy, for the treatment of adult patients with muscle invasive bladder cancer (MIBC)

Non-Small Cell Lung Cancer (STAGE II - IIIB; PERIOPERATIVE)

1. Diagnosis of stage IIA – IIIB, resectable, non-small cell lung cancer (NSCLC)
2. No EGFR or ALK mutation
3. Planned for surgical treatment (i.e., lobectomy, sleeve resection, or bilobectomy)
4. Pre-operative (neoadjuvant) durvalumab to be given in combination with platinum-based chemotherapy

If all criteria are met, approve x 18 months. Maximum duration of therapy AFTER surgery is 12 cycles (~1 year).

Notes:
Dose: 1500 mg (if ≥30 kg) or 20 mg/kg (if <30 kg) every 3 weeks in combination with platinum-containing chemotherapy for 4 cycles, followed by surgery, followed by 1500 mg (if ≥30 kg) or 20 mg/kg (if <30 kg) every 4 weeks (single-agent) until disease progression, recurrence, unacceptable toxicity, or to a MAXIMUM of 12 cycles after surgery.
[1] AEGEAN Trial: Phase III, RCT, neoadjuvant platinum-based chemo + durvalumab or placebo, followed by adjuvant durvalumab or placebo for up to 12 cycles. 1` endpts were EFS and pathological CR. 2` endpts were major pathological response, DFS, and OS. N=802 (400 durvalumab, 402 placebo). Median f/u 11.7m. 12 m EFS 73.4% vs 64.5%, 24m EFS 63.3% vs 52.4%, stratified HR 0.68 (95% CI 0.53-0.88, p=0.004). Pathological CR 17.2% vs 4.3% (95% CI 2.5-6.9, p<0.001).

	Median EFS (months)	12 m EFS rate (95%CI)	24m EFS rate (95%CI)	Harms Grade 3/4 AEs	Harms: DC 2` AEs	Harms: SAEs
Durvalumab	NR (31.9 - NR)	73.4% (67.9-78.1)	63.3% (56.1-69.6)	32.4%	12%	37.7%
Placebo	25.9 (18.9 - NR)	64.5% (58.8-69.6)	52.4% (45.4-59.0)	32.9%	6%	31.4%
	HR for disease progression, recurrence, or death 0.68 (95% CI, 0.53-0.88), p=0.004					

References:
1. Heymach JV, et al. Perioperative durvalumab for resectable non-small-cell lung cancer. N Engl J Med 2023;389:1672-1684.

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

1. Diagnosis of stage III, unresectable non-small cell lung cancer (NSCLC)

2. Patient must have received at least two cycles of platinum-based chemotherapy given concurrently with radiation therapy (containing either cisplatin or carboplatin along with another chemotherapy agent).

3. Must NOT have had progression of disease after platinum-based, concurrent chemoradiotherapy (verified with imaging such as CT or MRI done after completion of radiation)

4. Last chemoradiation session must have been no more than 42 days ago, from first request of durvalumab.

If all criteria are met, approve x 1 year. **Maximum duration of therapy for this indication is 1 year**. No renewals allowed.

Notes:
Dose: 10mg/kg q2w for a maximum of 1 year
[1]PACIFIC Trial: Phase III, RCT, durvalumab IV 10mg/kg or placebo q2w for 12 m. 1` endpts were PFS and OS; 2` endpts time to death or distant mets, time to second progression, safety. N=713 (709 received the assigned interventions: 473 durvalumab, 236 placebo). Median f/u 34.2m. 24m OS was 66.3% (95%CI,61.7 to 70.4m) vs 55.6% (95%CI 48.9 to 61.8m, p=0.0005). HR for death 0.68; 99.73%CI 0.47 to 0.997; p=0.00025)

	Median OS (months)	12 m OS rate (95%CI)	24m OS rate (95%CI)	Harms Grade 3/4 AEs	Harms: DC 2` AEs	Harms: SAEs
Durvalumab	47.5 (38.4-52.6)	83.1% (79.4-86.2)	66.3 (61.7-70.4)	30.5%	15.4%	29.1%
Placebo	29.1 (22.1-35.1)	75.3 (69.2-80.4)	55.6 (48.9-61.8)	26.1%	9.8%	23.1%
	HR for death 0.68 (99.73%CI, 0.47-0.997; P=0.0025)					

References:
1. Antonia, Scott J., et al. "Overall survival with Durvalumab after Chemoradiotherapy in stage III NSCLC." *New England Journal of Medicine*(2018).
2. Faivre-Finn C, et al. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC – an updated from the PACIFIC trial. J Thorac Oncol 2021;16(5):860-867.
3. Spigel DR, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. J Clin Oncol. 2022;40(12):1301-1311.

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

1. Diagnosis of stage IV non-small cell lung cancer (NSCLC)

2. No ALK or EGFR mutation

3. No prior therapy for stage IV NSCLC

4. Durvalumab will be given in combination with tremelimumab and carboplatin/cisplatin-based chemotherapy.

If all criteria are met, approve x 1 year. Durvalumab continues until disease progression or unacceptable toxicity.

Notes:
Dose: 1500 mg every 3 weeks x 4 cycles then every 4 weeks until disease progression.
Reference:
1. Johnson ML et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. J Clin Oncol. 2023 Feb 20;41(6):1213-1227. doi: 10.1200/JCO.22.00975. Epub 2022 Nov 3. PMID: 36327426; PMCID: PMC9937097.
2. Peters S et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy in First-Line Metastatic NSCLC: Five-Year Overall Survival Outcomes From the Phase 3 POSEIDON Trial. J Thorac Oncol. 2025 Jan;29)1):76-93. Doi: 10.1016/j.jtho.2024.09.1381. PMID: 39243945

Small Cell Lung Cancer (LIMITED STAGE; ADJUVANT CONSOLIDATION)

1. Diagnosis of limited-stage small cell lung cancer (SCLC)

2. Patient has received prior concurrent platinum-based chemoradiotherapy.

3. Must NOT have had progression of disease after platinum-based, concurrent chemoradiotherapy (verified with imaging such as CT or MRI done after completion of radiation)

4. Last chemoradiation session must have been no more than 42 days ago, from first request of durvalumab.

If criteria met, approve for 1 year. Durvalumab continues for up to 24 months.

Notes:
Dose: 1500 mg every 4 weeks until disease progression or intolerable toxicity, or for a maximum of 24 months.
Outcomes (durvalumab vs placebo):
Median overall survival: 55.9 months versus 33.4 months (HR 0.73, 95% CI 0.54-0.98; p=0.01)
Median PFS: 16.6 months vs 9.2 months (HR 0.76, 95% CI 0.59-0.98; p=0.02)
Grade 3-4 AEs similar (24.4% vs 24.2%)

Reference:
Cheng Y, et al. Durvalumab after chemoradiotherapy in limited-stage small-cell lung cancer. N Engl J Med 2024;391:1313-1327. [ADRIATIC trial]

Small Cell Lung Cancer (EXTENSIVE STAGE)

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. Durvalumab continues until disease progression or unacceptable toxicity.

Notes:
Dose: 1500 mg every 3 weeks (in combination with platinum + etoposide) for 4 cycles, followed by 1500 mg every 4 weeks until disease progression or unacceptable toxicity.
Outcomes (durvalumab+chemo vs chemo):
Median overall survival: 13 months versus 10.3 months (HR 0.73, 95% CI 0.59-0.91; p=0.0047)
-12-month overall survival: 54% versus 40%
-18-month overall survival: 34% versus 25%
-36-month overall survival: 17.6% versus 5.8%
Reference:
Paz-Ares L et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019 Nov 23;394(10212):1929-1939. doi: 10.1016/S0140-6736(19)32222-6. Epub 2019 Oct 4. PMID 31590988 NCT03043872
Paz-Ares L et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO Open. 2022 Apr;7(2):100408. Doi: 10.1016/j.esmoop.2022.100408. PMID: 35279527.

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%
-36-month overall survival: 14.6% versus 6.9%
-ESMO magnitude of clinical benefit score is 4 due to >10% improvement in OS at 2 years.
Grade 3/4 toxicities were similar between groups.
References:

1. Oh D et al. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. DOI: 10.1200/JCO.2022.40.4_suppl.378 Journal of Clinical Oncology 40, no. 4_suppl (February 01, 2022) 378-378. NCT03875235
2. Oh D et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evid 2022; 1 (8) DOI:https://doi.org/10.1056/EVIDoa2200015. NCT03875235
3. NCCN Guidelines for Hepatobiliary Cancers. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf
4. Oh D-Y et al. Durvalumab plus chemotherapy in advanced biliary tract cancer: 3-year overall survival update from the phase III TOPAZ-1 study. J. Hepatol. 2025 May 15:S0168-8278(25)02201-9. Doi: 10.1016/j.jhep.2025.05.003. PMID: 40381735.

Hepatocellular Carcinoma

1. Diagnosis of hepatocellular carcinoma

2. No prior systemic therapy for hepatocellular carcinoma

4. Durvalumab will be used in combination with tremelimumab

If all criteria are met, approve x 1 year. Durvalumab continues until disease progression or unacceptable toxicity.

Notes:
Dose: 1500 mg every 4 weeks until disease progression.
Reference:

1. Abou-Alfa, G et al. (2022, June 6). Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma. New England Journal of Medicine Evid. Retrieved May 1, 2023, from https://evidence.nejm.org/doi/full/10.1056/EVIDoa2100070
2. Rimassa L et al. Five-year overall survival update from the HIMALAYA study of tremelimumab plus durvalumab in unresectable HCC. J. Hepatol. 2025 Apr 11:S0168-8278(25)00226-0. Doi: 10.1016/j.jhep.2025.03.033. PMID: 40222621.

Bladder Cancer
1. Diagnosis of muscle-invasive bladder cancer
2. No prior systemic therapy for muscle-invasive bladder cancer
3. Durvalumab will be used in combination with gemcitabine and cisplatin in the neoadjuvant setting, and as a single agent in the adjuvant setting. Patient must also be planning to undergo radical cystectomy.
4. Patient must be planning to undergo radical cystectomy after neoadjuvant cycles
If all criteria are met, approve x 1 year. May extend approval if patient unable to complete full treatment course within 1 year.
Notes: Dose: 1500mg (≥30kg) or 20 mg/kg (<30kg) every 3 weeks for 4 cycles prior to radical cystectomy. After surgery, continue every 4 weeks for a maximum of 8 doses. [1]24-month OS was 82.2% in the durvalumab+gemcitabine+cisplatin group and 75.2% in the gemcitabine+cisplatin group (p=0.01; HR 0.75 (95% CI, 0.59-0.93) Reference: 1. Powles T, et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. N Engl J Med. 2024 Nov 14;391(19):1773-1786. doi: 10.1056/NEJMoa2408154. PMID: 39282910.

Eculizumab (Soliris) injection [MEDICAL BENEFIT ONLY] 300mg/30mL for intravenous use
EBRx PA Criteria

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

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

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

References:
1. Greenbaum, Larry A., et al. "Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome." Kidney international 89.3 (2016): 701-711.
2. Lee, Jong Wook, et al. "Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study." *Blood* 133.6 (2019): 530-539.
3. Kulasekararaj, Austin G., et al. "Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor–experienced adult patients with PNH: the 302 study." *Blood* 133.6 (2019): 540-549.

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

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

References:
1. Hillmen P, et al. the complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006;355:1233-43.
2. Eculizumab in Lexicomp. Accessed 5/15/17.
3. Azoulay, Elie, et al. "Expert statements on the standard of care in critically ill adult patients with atypical haemolytic uraemic syndrome." Chest (2017).

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

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

References:
1. Howard Jr, James F., et al. "Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study." *The Lancet Neurology* 16.12 (2017): 976-986.
2. Andersen, Henning, et al. "Eculizumab improves fatigue in refractory generalized myasthenia gravis." *Quality of Life Research* (2019): 1-8.
3. UpToDate. Chronic immunosuppressive therapy for myasthenia gravis. Accessed 8/10/2020.

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

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

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

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

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

Quantity Limits: Edaravone is supplied in 2-30mg IV infusion bags.
The QL is 2 bags QD; 28 bags/28 days initially.
The QL is 20 bags/28 days after the initial 28 days.

References:
1. Abe K, Itoyama Y, Sobue G, et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2014;15:610-617.
2. The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled trial. Lancet Neurol 2017;16:505-12.

Efgartigimod alfa-fcab (Vyvgart) IV infusion—MEDICAL BENEFIT DRUG
Efgartigimod alfa-fcab/hyaluronidase-qvfc (Vyvgart Hytrulo) SC
[NOT substitutable w/ IV]-May be a MEDICAL BENEFIT DRUG
EBRx PA Criteria

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

Criteria for new users
1. The patient must have the diagnosis of generalized myasthenia gravis (gMG) with anti-acetylcholine receptor antibody positivity.
2. The patient must have the gMG Foundation of America clinical classification class II-IV.
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.
4. The patient must be on stable therapy of at least 1 treatment for gMG (corticosteroids, acetylcholinesterase inhibitors (pyridostigmine), nonsteroidal immunosuppressive therapies (NSIST)).
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).
If approved, the initial PA is good for 6 months.
Criteria for continuation
1. The patient must be a responder to efgartigimod as defined. 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). 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.
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:

1. Vyvgart (efgartigimod alfa) [prescribing information]. Boston, MA: Argenx US, Inc; December 2021.
2. Overview of the treatment of myasthenia gravis - UpToDate. Accessed January 8, 2022. https://www-uptodate-com.libproxy.uams.edu/contents/overview-of-the-treatment-of-myasthenia-gravis?search=myasthenia%20gravis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H1
3. Howard JF, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2021;20(7):526-536. doi:10.1016/S1474-4422(21)00159-9
4. Lexicomp. Accessed January 8, 2022. https://online-lexi-com.libproxy.uams.edu/lco/action/doc/retrieve/docid/patch_f/7185347?cesid=0vBh0Hs72Xf&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dvyvgart%26t%3Dname%26va%3Dvyvgart#fda-date
5. Howard Jr, James F., et al. "Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial." *The Lancet Neurology* 20.7 (2021): 526-536. NCT03669588
6. Barnett, Carolina, et al. "Measuring clinical treatment response in myasthenia gravis." *Neurologic clinics* 36.2 (2018): 339-353.

Myasthenia Gravis Activities of Daily Living (MG-ADL)

Physicians use this tool to score a patient's MG symptoms based on the patient's recall of the symptoms during the prior week. A person's score can range from 0 (normal) to 24 (most severe).

	Score = 0	Score = 1	Score = 2	Score =3	Your Score
1.Talking	Normal	Intermittent slurring or nasal speech	Constant slurring, but can be understood	Difficult to understand speech	
2.Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3.Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
4.Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5.Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
6.Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
7.Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8.Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				MG-ADL Score Total = Add lines 1-8	

Elapegademase-lvlr (Revcovi) IM for self-injection
EBRx PA Criteria

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

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

Note: HSCT is curative.
Dose: *normal maintenance=20units/kg/wk ¥based on initial dosing since maintenance is based on levels (unsure what an estimate would be)
Elapegademase dose is 0.2mg/kg (ideal body weight) twice weekly for a minimum of 12-24 weeks; may increase dose by 0.033mg/kg once weekly based on ADA trough levels.

References:

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

Elranatamab-bcmm (Elrexfio) 76 mg/1.9 ml and 44 mg/1.1 ml single-dose vials
EBRx PA Criteria

is FDA-approved for:

Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody

Criteria for new users
1. Diagnosis of multiple myeloma (MM)
2. Patient has been treated with at least 4 prior lines of therapy (i.e. 4 different regimens). Note: Stem cell transplant does not qualify as a line of therapy
3. Patient has been previously treated with a proteosome inhibitor Note: Available proteosome inhibitors include bortezomib (Velcade), carfilzomib (Kyprolis), and ixazomib (Ninlaro)
4. Patient has been previously treated with an immunomodulatory agent Note: Immunomodulatory agents include lenalidomide (Revlimid), thalidomide (Thalomid), polmalidomide (Pomalyst)
5. Patient has been previously treated with an anti-CD38 monoclonal antibody Notes: Anti-38 monoclonal antibodies include daratumumab, isatuximab
6. MM has not progressed on a prior anti-BCMA bispecific T cell engager (i.e. teclistamab [Tecvayli])
If criteria met, approve for 1 year.

Note:

Elranatamab Dosing Schedule

Dosing Schedule	Day	Elranatamab Dose	
Step-up Dosing Schedule	Day 1	Step-up dose 1	12 mg
	Day 4	Step-up dose 2	32 mg
	Day 8	First treatment dose	76 mg
Weekly Dosing Schedule	One week after first treatment dose and weekly thereafter through week 24	Subsequent treatment doses	76 mg
Biweekly (Every 2 Weeks) Dosing Schedule*	Week 25 and every 2 weeks thereafter	Subsequent treatment doses	76 mg

*Responders only week 25 onward

Elranatamab was studied in a single arm trial (MagnetisMM-3) which, in the FDA approved population, reported a response rate of 58% and 15-month overall survival of 57% which compares favorably with other therapies used in this setting.

References:

1. Elranatamab (Elrexfio) PI. https://labeling.pfizer.com/ShowLabeling.aspx?id=19669#section-12. Accessed 8/25/2023.
2. Lesokhin AM et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med. 2023 Aug 15. doi: 10.1038/s41591-023-02528-9. Epub ahead of print. PMID: 37582952.

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
- adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy NOT COVERED Lack of overall survival or quality of life data.
    - Linton KM et al. Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study. Lancet Haematol. 2024 Jun 13:S2352-3026(24)00166-2. doi: 10.1016/S2352-3026(24)00166-2. Epub ahead of print. PMID: 38889737.

Criteria for new users

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

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:

Cycle of treatment[a]	Day of treatment	Dose of EPKINLY	
Cycle 1	1	Step-up dose 1	0.16 mg
	8	Step-up dose 2	0.8 mg
	15	First full dose	48 mg
	22	48 mg	
Cycles 2 and 3	1, 8, 15 and 22	48 mg	
Cycles 4 to 9	1 and 15	48 mg	
Cycle 10 and beyond	1	48 mg	

[a] 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:

1. Epkinly PI. https://www.genmab-pi.com/prescribing-information/epkinly-pi.pdf.
2. Thieblemont C et al. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. J Clin Oncol. 2023 Apr 20;41(12):2238-2247. doi: 10.1200/JCO.22.01725. Epub 2022 Dec 22. PMID: 36548927; PMCID: PMC10115554.
3. Phillips T et al. Improvements in Lymphoma Symptoms and Health-Related Quality of Life in Patients with Relapsed or Refractory Large B-Cell Lymphoma Treated with Subcutaneous Epcoritamab (EPCORE NHL-1). Blood (2022) 140 (Supplement 1): 8022–8023. https://doi.org/10.1182/blood-2022-159544.
4. NCCN Guidelines B Cell Lymphomas (Version 4.2023). www.nccn.org.

Quantity Limits: n/a

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

is FDA-approved for:

- Metastatic breast cancer after 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. (SEE CRITERIA)
- Unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen (SEE CRITERIA)

Metastatic Breast Cancer
1. Diagnosis of metastatic or unresectable breast cancer
2. Previously treated with at least 2 chemotherapeutic regimens for treatment of metastatic or unresectable breast cancer
If above criteria are fulfilled, approve x 1 year

Note:
Eribulin was compared to physician's choice chemotherapy in patients who had received at least two prior chemotherapy regimens that included anthracycline- and taxane-containing regimens. 70% of subjects had also received prior capecitabine. Median overall survival was improved in the eribulin group (13.1 mo vs 11.8 mo; HR 0.81, 95% CI 0.66-0.99).[1]
Eribulin was also compared directly to capecitabine in patients who had received 0-3 prior chemotherapy regimens that included anthracycline- and taxane-based regimens. Median overall survival was not statistically improved in the eribulin arm (15.9 mo vs 14.5 mo; HR 0.88, 95% CI 0.77-1.00; p=0.056). Quality of life scores were similar between groups.[2,3]
Pooled analysis of the above two studies found an improvement in median overall survival in the eribulin group (15.2 mo vs 12.8 mo; HR 0.85, 95% CI 0.76-0.94).[4] A separate analysis including only patients who had received at least 1 prior therapy found an improvement in median overall survival in the eribulin group (15.2 mo vs 12.8 mo; HR 0.85, 95% CI 0.77-0.95).[5]
Dose: 1.4 mg/m^2 IV over 2-5 minutes on days 1 and 8 of a 21-day treatment cycle
Approximate cost per cycle of therapy (will vary based on BSA): $6,430 (average sales price, 9/3/24)
REFERENCES:

1. 1. Cortes J et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (**EMBRACE**): a phase 3 open-label randomised study. Lancet. 2011 Mar 12;377(9769):914-23. doi: 10.1016/S0140-6736(11)60070-6. Epub 2011 Mar 2. PMID 21376385 NCT00388726
2. Kaufman PA et al. Phase III open-label randomized study of eribulin mesylate versus **capecitabine** in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015 Feb 20;33(6):594-601. doi: 10.1200/JCO.2013.52.4892. Epub 2015 Jan 20. PMID 25605862 NCT00337103
3. Cortes J et al. Health-related **quality of life** in patients with locally advanced or metastatic breast cancer treated with eribulin mesylate or capecitabine in an open-label randomized phase 3 trial. Breast Cancer Res Treat. 2015 Dec;154(3):509-20. doi: 10.1007/s10549-015-3633-7. Epub 2015 Nov 14. PMID 26567010
4. Twelves C et al. Efficacy of eribulin in women with metastatic breast cancer: a **pooled analysis** of two phase 3 studies. Breast Cancer Res Treat. 2014 Dec;148(3):553-61. doi: 10.1007/s10549-014-3144-y. Epub 2014 Nov 8. PMID 25381136
5. Pivot X et al. **Pooled analyses** of eribulin in metastatic breast cancer patients with at least one prior chemotherapy. Ann Oncol. 2016 Aug;27(8):1525-31. doi: 10.1093/annonc/mdw203. Epub 2016 May 13. PMID 27177860

Liposarcoma
1. Diagnosis of metastatic or unresectable liposarcoma
2. Prior treatment of metastatic or unresectable disease with an anthracycline-containing regimen (such as epirubicin or doxorubicin)
If above criteria are fulfilled, approve x 1 year

Evidence:
Eribulin was compared to dacarbazine in patients with advanced liposarcoma or leiomyosarcoma. In the liposarcoma subgroup, median overall survival was improved in the eribulin group (15.6 mo vs 8.4 mo, HR 0.51, 95% CI 0.35-0.75). No overall survival difference was observed in leiomyosarcoma subgroup.
Reference:

1. Schöffski P et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet. 2016 Apr 16;387(10028):1629-37. doi: 10.1016/S0140-6736(15)01283-0. Epub 2016 Feb 10. PMID 26874885 NCT01327885

Esketamine (Spravato)
EBRx PA Criteria

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

Criteria for new users
1. Patient must be between ages 18 and 75 years old.
2. Patient must have the diagnosis of treatment-resistant depression.
3. Patient must show treatment-resistance in the following ways: a. have on their profile, in the past 2 years, at least 3 different antidepressant strategies (2 previous and 1 concomitant) nonconcurrent antidepressant therapies. i. either 3 from different classes (SSRIs, or SNRIs, or bupropion monotherapies). ii. 2 monotherapies plus one augmentation strategy iii. 1 monotherapy, 1 augmentation strategy, ECT/Repetitive transcranial magnetic stimulation (rTMS) i.v. other combination of the above
4. The profile must show *a fill history of at least 6* weeks EACH* for the nonconcurrent monotherapies, at the maximum or maximally tolerated dose, before esketamine.
5. Patient must have *current fill* of at least 2 30-day fills of SSRI, SNRI, or bupropion at the maximum or maximally tolerated dose.
6. The prescriber must be a psychiatrist.
7. The prescriber must have checked the AR PMP to rule out substance abuse.
8. The prescriber must, in good conscience, attest to the patient NOT being a current, active substance abuser.
The initial PA is good for 4 weeks. QL is 84mg TWICE weekly.

Criteria for continuation
1. The patient must be currently adherent with receiving esketamine nasal.
2. The patient must be receiving a concurrent antidepressant therapy (SSRI, SNRI, bupropion or other drug or procedure) as evident by the fill history of paid claims or medical claims.
3. The psychiatrist must submit a plan outlining the treatment plan for esketamine treatment.
###The continuation PA will be good for 1 month. QL will be 84mg ONCE weekly.###

Note: Dosing is:
- Induction: 56mg twice wkly up to 84mg twice wkly for 4 weeks total
- Maintenance: After 5 wks from the induction phase, the dosing moves to QW, then after 9wks can decrease to q2wks.
- After 4wks evaluate for evidence of therapeutic benefit to determine need for continued treatment

Quantity Limits: Twice weekly if in the initial 4 weeks of therapy. Once weekly after the first 4 weeks.

References:

1. Canuso, Carla M., et al. "Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study." *American journal of psychiatry* 175.7 (2018): 620-630.
2. Duru, Gérard, and Bruno Fantino. "The clinical relevance of changes in the Montgomery–Asberg Depression Rating Scale using the minimum clinically important difference approach." *Current medical research and opinion* 24.5 (2008): 1329-1335.
3. Aripiprazole (Abilify): Depression, Major Depressive Disorder (MDD) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Nov. Table 18, Validity and Minimal Clinically Important Difference of Outcome Measures.
4. UpToDate: Treatment resistant depression
5. LexiComp: esketamine. Accessed 3/26/19.
6. Daly, Ella J., et al. "Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial." *JAMA psychiatry* 75.2 (2018): 139-148.
7. ICER Draft Evidence Report. Esketamine for the Treatment of TreatmentResistant Depression: Effectiveness and Value. 3/21/2019.

Gemtuzumab ozogamicin (Mylotarg) 4.5 mg vials
EBRx PA Criteria MEDICAL PRIOR AUTHORIZATION

is FDA-approved for:

- Treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML)
  - In combination with daunorubicin and cytarabine (**CURRENTLY ONLY COVERED INDICATION**)
    OR
  - As monotherapy NOT COVERED (see venetoclax, glasdegib) in older adults not suited for intensive chemotherapy, overall survival benefit over best supportive care (transfusion, hydroxyurea) was minimal (median 4.9 mo vs 3.6 mo). Complete response (CR) rate with gemtuzumab was also low at 8.1%. Other therapies have longer overall survival and higher CR rates (e.g. decitabine or azacitidine with or without venetoclax, glasdegib).
    Reference: Amadori S et al. Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial. J Clin Oncol. 2016 Mar 20;34(9):972-9. PMID 26811524
- Treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older NOT COVERED. Data limited to a single arm, phase II trial (Taksin AL et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the alfa group. Leukemia. 2007 Jan;21(1):66-71. PMID 17051246)

Criteria for new users
1. The patient **must have** a diagnosis of acute myeloid leukemia (AML) and fulfill all of the following criteria: • AML is previously untreated. • Pt does not have diagnosis of acute promyelocytic leukemia (aka APL or M3 AML) • AML is not therapy related or myelodysplastic syndrome (MDS)-related • Cytogenetic risk is favorable or intermediate (not poor risk; see below for definitions) • AML blasts express CD33 (CD33-positive AML) • ECOG 0-2 • The patient does NOT have CNS involvement of AML • The patient does NOT have liver or renal abnormalities defined as AST or ALT ≥ 2.5 x upper limit of normal (ULN), serum bilirubin ≥ 2 x ULN, OR serum creatinine ≥ 2.5 x ULN.
If patient meets criteria above, approve medical PA for 4 months. Medication is excluded from pharmacy benefit. **For patients who do not achieve an adequate response during first induction cycle, no further gemtuzumab is indicated. Medication is approved ONLY in combination with cytarabine and daunorubicin.**

Dosing: IV:

- **Induction Cycle**: gemtuzumab 3 mg/m^2 (**up to one 4.5 mg vial**) on Days 1, 4, and 7 in combination with daunorubicin (60 mg/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/m^2 (**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[1,2]

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

Ref:

1. Castaigne, Sylvie, et al. "Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study." The Lancet 379.9825 (2012): 1508-1516. PMID 22482940
2. Lexicomp and gemtuzumab package insert accessed 7/23/19.

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: 1. NICE guidelines: Adalimumab, etanercept and infliximab for ankylosing spondylitis. May 2008. http://publications.nice.org.uk/adalimumab-etanercept-and-infliximab-for-ankylosing-spondylitis-ta143/evidence-and-interpretation 2. €DERP. Report on Targeted Immune Modulators Update 3/8/12.

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
Beukelman T, Patkar NM, Saag KG, Toleson-Rinehart S, et al. 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features. *Arthritis Care & Research*. 2011(April);63(4):465–482.

Psoriatic Arthritis (must be used in combo with DMARD)

Med Impact: Preferred

1. The patient must have a diagnosis of psoriatic arthritis
2. The patient must have failed 3 months of a DMARD therapy (examples: methotrexate, sulfasalazine, penicillamine, azathioprine, leflunomide).
3. Trial of adalimumab for 12 weeks

References:
1. DERP. Report on Targeted Immune Modulators Update 3/8/12.
2. Treatment of Psoriatic Arthritis. UpToDate. http://www.uptodate.com/contents/treatment-of-psoriatic-arthritis?source=search_result&search=psoriatic+arthritis&selectedTitle=2%7E105#H18 . Accessed 7/3/12.
3.Treatment of Psoriatic Arthritis: UpToDate. https://www-uptodate-com.libproxy.uams.edu/contents/treatment-of-psoriatic-arthritis?search=treatment%20of%20psoriatic%20arthritis&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1. Accessed 08/12/24

Rheumatoid Arthritis

Med impact: Preferred

6. 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.

7. 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.
8. 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:
1. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of RA with synthetic and biological DMARDs: 2013 update. Ann Rheum Dis. 2014;73:492-509.
2. Moreland LW, O'Dell JR, et al. A randomized comparative effectiveness study of triple therapy versus etanercept plus methotrexate in early aggressive RA. TEAR Trial. Arthritis & Rheumatism. 2012;64(9):2824-2835.
3. O'Dell JR, Mikuls TR, et al. Therapies for active RA after methotrexate failure. N Engl J Med. 2013;369:307-18.
4. Van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early RA (Swefot trial): 1-y results of a randomized trial. Lancet. 2009;374:459-66.
5. Van Vollenhoven RF, Geborek P, Forslind K, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early RA: 2 y follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012;379:1712-20.
6. Bathon JM, McMahon DJ. Making rational treatment decisions in RA when methotrexate fails. N Engl J Med. 369;4:384-85.
7. Singh, Jasvinder A., et al. "2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis." *Arthritis & rheumatology* 68.1 (2016): 1-26.

Ulcerative Colitis

Med Impact: Preferred

1. The patient must have the diagnosis of moderate to severe ulcerative colitis
2. The patient must have failed ≥3 months of mesalamine or sulfasalazine or glucocorticoids.
3. The patient must have tried and failed adalimumab (8 weeks)
4. Must be prescribed by gastroenterologist.

General References:

1. Drug Effectiveness Review Project. Targeted Immune Modulators Update 3/8/12.
2. Kornbluth A, Sachar DB, The Practice Parameters Committee of the American College of Gastroenterology. Ulcerative Colitis practice guidelines in adults: ACG, Practice Parameters Committee. *Am J Gastroenterol* 2010; 105:501–523.

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

is FDA-approved for:
in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens

Criteria for new users
1. Patient must have a cancer diagnosis
2. Patient must be receiving moderately emetogenic chemotherapy or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens
3. Patient must have previous failure of an oral 5HT3 antagonist given daily on a scheduled basis OR palonosetron given 30-60 minutes prior to chemotherapy
4. Creatinine clearance must be >30 ml/min
If above criteria met, approve for 6 months maximum. Use of Sustol with successive chemotherapy cycles for more than 6 months is not recommended per product labeling.

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

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

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

References:

1. Raftopoulos H et al. Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, noninferiority phase 3 trial. Support Care Cancer. 2015 Mar;23(3):723-32. PMID 25179689
2. Schnadig ID et al. APF530 (granisetron injection extended-release) in a three-drug regimen for delayed CINV in highly emetogenic chemotherapy. Future Oncol. 2016;12(12):1469-1481. PMID 26997579
3. Sustol monograph. LexiComp. Accessed 5/23/19

Histrelin (Supprelin LA)
EBRx PA Criteria

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

Criteria for new users
1. Diagnosis of central precocious puberty
2. Child must be between the ages of 4 and 12 years of age.

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

Quantity Limits: 1 implant per year.

References:

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

imetelstat (Rytelo)
EBRx PA Criteria

is FDA-approved for:
Treatment of adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA) COVERED FOR RING SIDEROBLAST NEGATIVE DISEASE ONLY (See luspatercept for ring sideroblast positive disease)

Criteria for new users
1. Diagnosis of myelodysplastic syndrome (MDS)
2. MDS is classified as low or intermediate-1 risk by IPSS-R (see below)
3. MDS is ring sideroblast (RS) negative
4. Age ≥18 years or older
5. Patient currently requires at least 4 units of red blood cells transfusion over 8 weeks
6. Anemia is refractory to erythropoiesis-stimulating agents (ESAs)* **OR** serum erythropoietin level is >500 mU/ml [note: higher epo level predicts poor response to ESAs]
If criteria met, approve for 6 months.

Criteria for continuation
After 6 months of therapy (6 doses), renew approval for 12 months if the patient experienced a decrease in red blood cell transfusion burden.

***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.

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

	Score Value						
Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetic[e]	**Very good**	**—**	**Good**	**—**		**Poor**	**Very**
Marrow blasts (%)	**≤2**	**—**	**>2-<5**	**—**	**5-10**	**>10**	**—**
Hemoglobin	**≥10**	**—**	**8-<10**	**<8**	**—**	**—**	**—**
Platelets	**≥100**	**50-<100**	**<50**	**—**	**—**	**—**	**—**
ANC	**≥0.8**	**<0.8**	**—**	**—**	**—**	**—**	**—**

Note:
Dose: 7.1 mg/kg IV over 2 hours every 4 weeks

Imetelstat increased the rate of transfusion independence compared to placebo from 15% to 40% in patients with lower risk MDS with and without ring sideroblasts.

References

1. Imetelstat Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216686s000lbl.pdf
2. NCCN guidelines for Myelodysplastic Syndrome Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf
3. Platzbecker U et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024 Jan 20;403(10423):249-260. doi: 10.1016/S0140-6736(23)01724-5. Epub 2023 Dec 1. Erratum in: Lancet. 2024 Jan 20;403(10423):248. doi: 10.1016/S0140-6736(24)00057-6. PMID: 38048786.

Quantity Limits: n/a (medical benefit drug)

Imiglucerase (Cerezyme)
EBRx PA Criteria

Imiglucerase is FDA-approved for: Long term enzyme replacement therapy for patients with type 1 Gaucher disease that results in at least one of the following; anemia, bone disease, hepatomegaly or splenomegaly, and thrombocytopenia

Criteria for new users
1. Patient must have the diagnosis of type 1 Gaucher disease diagnosed by mutation analysis. (**The patient must lack central nervous system involvement**. This is what distinguishes type 1 from types 2 & 3.)
2. The patient must be symptomatic (anemia, bone disease, hepatomegaly, splenomegaly, or thrombocytopenia)
3. The patient is not receiving concurrent substrate-reduciton therapy (eliglustat or miglustat).
If all the criteria are satisfied, the PA is valid for 12 months.

Note: Dose is 30-60 IU/kg q2weeks. Long term outcomes with ERT with imiglucerase at two centers using low-dose (median dose 15-30 U/gh q4w) and high-dose (median dose 80 u/kg q4w) were compared retrospectively. Improvement in hemoglobin, platelet count, and hepatosplenomegaly was not significantly different between cohorts.

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

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

Quantity Limits: Dose of 60IU/kg q2w.

References:

1. Charrow J, Andersson HC, Kaplan P, et al, "Enzyme Replacement Therapy and Monitoring for Children With Type 1 Gaucher Disease: Consensus Recommendations," *J Pediatr*, 2004, 144(1):112-20.
2. Barton NW, Brady RO, Dambrosia JM, et al, "Replacement Therapy for Inherited Enzyme Deficiency - Macrophage-Targeted Glucocerebrosidase for Gaucher's Disease," *N Engl J Med*, 1991, 324(21):1464-70.
3. Whittington R and Goa KL, "Alglucerase: A Review of Its Therapeutic Use in Gaucher's Disease," *Drugs*, 1992, 44(1):72-93.
4. UpToDate. Gaucher disease: Treatment. Accessed 8/11/2020.

IncobotulinumtoxinA (Xeomin)—covered by EBD plans (only non-cosmetic uses)
EBRx PA Criteria (EBD commercial)

FDA approved for:

- **Blepharospasm:** indicated for the treatment of adults with blepharospasm
- **Cervical dystonia:** indicated for the treatment of adults with cervical dystonia
- **Chronic Migraine, prophylaxis:** indicated for the prophylaxis of headaches in adult patients with chronic migraine (at least 15 days per month with headache lasting 4 hours a day or longer) (**NOT FDA APPROVED, BUT COVERED USE BY EBD Commercial plans)**
- **Excessive Salivation, Chronic:** indicated for the treatment of chronic sialorrhea in adults and pediatric patients 2 years or older
- **Upper limb Spasticity:** indicated for the treatment of upper limb spasticity in adults and in pediatric patients 2 to 17 years, excluding spasticity caused by cerebral palsy
- **Lower Limb Spasticity:** Treatment of post-stroke lower limb spasticity involving the ankle and foot in adults
- **Wrinkled Face (Moderate to Severe):** indicated for the temporary improvement in the appearance of upper facial lines, including moderate to severe glabellar lines (GL) associated with corrugator and/or procerus muscle activity, moderate to severe horizontal forehead lines (HFL) associated with frontalis muscle activity, and moderate to severe lateral canthal lines (LCL) associated with orbicularis oculi muscle activity, in adult patients – **COSMETIC NOT COVERED**

Blepharospasm:
1. The patient must have the diagnosis of blepharospasm
If the criteria are fulfilled, approve PA for 1 year

Cervical dystonia:
1. The patient must have the diagnosis of cervical dystonia
If the criteria are fulfilled, approve PA for 1 year

Chronic Migraine: (not FDA approved but covered use by EBD – AML; ASP; ASU; EBD commerical 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.
If the criteria are fulfilled, approve PA for 1 year

Sialorrhea indication:
1. The patient must have the diagnosis of sialorrhea.
If the criteria are fulfilled, approve PA for 1 year

Spasticity indication:
1. The patient must have the diagnosis of spasticity.
If the criteria are fulfilled, approve PA for 1 year.

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

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

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

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

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.

Migraine prophylaxis:

There seems to be little difference between OnA and InA in terms of the efficacy or longevity of effects. InA appears to be effective for the management of CM but may not be as well suited as OnA due to excessive pain on injection. If the pain on injection was negated, perhaps with a buffering solution, InA would likely be a good alternative to OnA for CM treatment. In cases where OnA fails because of the development of antibodies, it might be reasonable to switch to InA treatment.

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

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

- Bruloy, Eva (01/2019). "Botulinum Toxin versus Placebo: A Meta-Analysis of Prophylactic Treatment for Migraine.". *Plastic and reconstructive surgery (1963)* (0032-1052), 143 (1), p. 239.
- Herd, Clare P., et al. "Botulinum toxins for the prevention of migraine in adults." *Cochrane Database of Systematic Reviews* 6 (2018).
- Lucchese, Scott, Bob Daripa, and Shruthi Pulimamidi. "Onabotulinum toxin A vs. incobotulinum toxin A for the treatment of chronic migraine: a retrospective review." *Research Square* (2023): rs-3.

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

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

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

Spasticity:

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

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

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[a] NOT COVERED: data is limited to a single arm trial
- **Hepatocellular Carcinoma (HCC)**
  - Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib, in combination with nivolumab.[a] NOT COVERED:
  - NCT01658878 compared different regimens of nivolumab/ipilimumab in patients with HCC who had been treated previously with sorafenib. Overall survival was promising with one regimen (which is now FDA approved), but no comparative trials have shown it to be superior to other therapies or placebo.
    Reference: Yau T, Kang YK, Kim TY, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial [published correction appears in JAMA Oncol. 2021 Jan 1;7(1):140]. JAMA Oncol. 2020;6(11):e204564. doi:10.1001/jamaoncol.2020.4564
- **Non-Small Cell Lung Cancer (NSCLC)**
  - Treatment of adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with nivolumab.
  - Treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy.
- **Malignant Pleural Mesothelioma**
  - Adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab

a=This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Melanoma, metastatic
1. Diagnosis of unresectable or metastatic melanoma.
2. If the patient has received no prior therapy, ipilimumab will be used in combination with nivolumab
3. If the patient has received prior therapy for advanced/metastatic, tumor is progressing.
4. The patient must be ECOG performance status 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity) at initiation
5. Patient does not have diagnosis of ocular/uveal melanoma.
If criteria fulfilled, approve ipilimumab for 4 months (maximum of 4 doses total).
Criteria for continuation
Continuation not allowed if 4 doses already given. If doses were delayed due to toxicity or other reason and reapproval is needed, approve as indicated if no disease progression and no unacceptable toxicity.
Notes: -Not covered for first line use as monotherapy, due to other checkpoint inhibitors having superior efficacy (see nivolumab or pembrolizumab) -Ipilimumab/Nivolumab comes extremely close to statistically improving overall survival compared to nivolumab alone in the 5-year update of the CHECKMATE 067 trial. Due to consistency of results compared to initial release of data and strong trend to improving overall survival, EBRx recommends coverage. However, note that toxicity is also increased in the ipi/nivo arm compared to nivolumab alone (grade 3-5 toxicity incidence: 59% vs 23%).[1,2]

-Ipilimumab does have activity after nivolumab or pembrolizumab though this is based on a retrospective review[3]
-Ipilimumab showed improved survival vs. placebo/vaccine in patients previously treated with chemotherapy. Median OS was 10 mo for ipilimumab vs. 6.4 mo in placebo/vaccine group. Vaccine had no effect on efficacy and should be considered as placebo for the purpose of interpreting study results.[4]
Dosing: 3 mg/kg IV every 3 weeks x 4 doses MAX

REFERENCES:
1. Hodi F, VAnna C, Rene G et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (Checkmate 067): 4-year outcomes of a multicenter, randomized, phase 3 trial. Lancet Oncol 2018; 19:1480-92.
2. Larkin J et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019 Oct 17;381(16):1535-1546.
3. PMID 31562797 NCT01844505
4. Zimmer L et al. Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. Eur J Cancer. 2017 Apr;75:47-55.
5. Hodi FS et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010 Aug 19;363(8):711-23. NCT00094653

Renal Cell Carcinoma (RCC)

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

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

Non-Small Cell Lung Cancer (NSCLC)

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

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

Malignant Pleural Mesothelioma

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

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

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

Isatuximab (Sarclisa) 100mg/5ml and 500mg/25 ml vial
EBRx PA Criteria

is FDA-approved for:

- treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (use in combination with pomalidomide and dexamethasone) SEE CRITERIA
- in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy
    - NOT COVERED: benefit is limited to progression free survival only compared to carfilzomib plus dexamethasone
        - Reference: Moreau P et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet. 2021 Jun 4:S0140-6736(21)00592-4. doi: 10.1016/S0140-6736(21)00592-4. Epub ahead of print. PMID: 34097854.
        - Martin T et al. Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized Phase 3 study. Blood Cancer J. 2023 May 9;13(1):72. doi: 10.1038/s41408-023-00797-8. PMID: 37156782; PMCID: PMC10166682.
        - Yong K et al. Isatuximab plus carfilzomib-dexamethasone versus carfilzomib-dexamethasone in patients with relapsed multiple myeloma (IKEMA): overall survival analysis of a phase 3, randomized, controlled trial. Lancet Haematol. 2024 Jul 24:S2352-3026(24)00148-0. doi: 10.1016/S2352-3026(24)00148-0. Online ahead of print. PMID: 39067465.
- In combination with bortezomib, lenalidomide and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant (ASCT) NOT COVERED
    - Benefit is limited progression free survival at this time.
    - Reference: Facon T et al. Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024 Jun 3. doi: 10.1056/NEJMoa2400712. Epub ahead of print. PMID: 38832972.

Criteria for new users
1. Diagnosis of multiple myeloma
2. Age is 75 years or older
3. Patient has been treated with at least two prior therapies, which included lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, ixazomib).
4. If patient received prior anti-CD38 monoclonal antibody therapy (e.g. daratumumab), disease was not refractory to this therapy (e.g. disease did not progress ON or within 60 days of this therapy*)
5. Patient has not experienced disease progression on pomalidomide
6. Isatuximab will be given in combination with pomalidomide and dexamethasone
If all criteria met, approve for 12 months.

*Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009 Jan;23(1):3-9. doi: 10.1038/leu.2008.291. Epub 2008 Oct 30. Erratum in: Leukemia. 2014 Apr;28(4):980. PMID: 18971951; PMCID: PMC2627786.

Note:
Isatuximab/pomalidomide/dexamethasone was compared to pomalidomide/dexamethasone in patients who were previously treated with at least two prior therapies including lenalidomide and a proteasome inhibitor. The triplet therapy improved progression free survival (median 11.53 mo vs 6.47 mo). In the overall population, a statistically significant overall survival benefit has not been demonstrated at this time. However, in the subset of patients who were age ≥75 y, a statistically significant improvement in overall survival was demonstrated (median not reached in triplet group versus 10.25 mo in the control group (HR 0.522 95% CI 0.296- 0.921).[1,2]
Dose:
Cycle 1: 10 mg/kg IV on days 1, 8, 15, and 22 of a 28-day cycle (in combination with pomalidomide and dexamethasone.
Cycle 2 and beyond: 10 mg/kg IV on days 1 and 15 of a 28-day cycle (in combination with pomalidomide and dexamethasone), continue until disease progression or unacceptable toxicity.
References:

1. Attal M et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019 Dec 7;394(10214):2096-2107. doi: 10.1016/S0140-6736(19)32556-5. Epub 2019 Nov 14. PMID 31735560 NCT02990338
2. Schjesvold FH et al. Efficacy of Isatuximab with Pomalidomide and Dexamethasone in Elderly Patients with Relapsed/Refractory Multiple Myeloma: Icaria-MM Subgroup Analysis. Blood (2019) 134 (Supplement_1): 1893. https://ashpublications.org/blood/article/134/Supplement_1/1893/427649/Efficacy-of-Isatuximab-with-Pomalidomide-and
3. Richardson P et al. Isatuximab-pomalidomide-dexamethasone *versus* pomalidomide-dexamethasone in patients with relapsed and refractory multiple myeloma: final overall survival analysis. Haematologica. 2024 Jul 1;109(7):2239-2249. doi: 10.3324/haematol.2023.284325. PMID 38299578

SOMATULINE DEPOT (lanreotide)
120 mg/0.5 mL, 60 mg/0.2 mL, 90 mg/0.3 mL prefilled syringes for SQ injection
EBRx PA Criteria

FDA approved for:

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

Acromegaly
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: 1. Caplin ME et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014 Jul 17;371(3):224-33. PMID 25014687 NCT00353496 2. Caplin ME et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. Endocr Relat Cancer. 2016 Mar;23(3):191-9. PMID 26743120

Carcinoid Syndrome
1. Diagnosis of carcinoid syndrome with presence of symptoms (e.g. flushing, diarrhea)
2. Diagnosis of neuroendocrine or carcinoid tumor
3. Somatostatin-receptor scintigraphy is grade 2 or higher (e.g. positive OctreoScan)
If all criteria fulfilled, approve for 12 months.
Dose is 120 mcg SQ every 4 weeks given until disease progression or unacceptable toxicity. Lanreotide improves symptoms in patients with carcinoid syndrome to a greater extent than placebo. Reference: 1. Fisher GA Jr et al. Patient-Reported Symptom Control of Diarrhea and Flushing in Patients with Neuroendocrine Tumors Treated with Lanreotide Depot/Autogel: Results from a Randomized, Placebo-Controlled, Double-Blind and 32-Week Open-Label Study. Oncologist. 2018 Jan;23(1):16-24. doi: 10.1634/theoncologist.2017-0284. Epub 2017 Oct 16. PMID 29038234

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:
    -Reblozyl PI. https://media.celgene.com/content/uploads/reblozyl-pi.pdf. Accessed 12/10/19.
    -Cappellini MD, Viprakasit V, Taher AT, et al. A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia. N Engl J Med. 2020;382(13):1219–1231. doi:10.1056/NEJMoa1910182

- Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)

- 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, EBRx prefers ESA due to cost advantage. See criteria if patient has failed ESA or if erythropoietin level is >500 mU/mL.
    - Reference: Platzbecker U et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet. 2023 Jul 29;402(10399):373-385. doi: 10.1016/S0140-6736(23)00874-7. Epub 2023 Jun 10. PMID: 37311468.

Limitations of Use: luspatercept is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia

Criteria for new users (anemia due to myelodysplastic syndrome)
1. Diagnosis of myelodysplastic syndrome (MDS) with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RL-T)* *Must have <5% bone marrow blasts and either ≥15% of erythroid precursors with ring sideroblasts OR ≥5% ring sideroblasts if an SF3B1 mutation was present.
2. MDS is classified as very low, low, or intermediate risk by IPSS-R (see below)
3. Age ≥18 years or older
4. Patient currently requires at least 2 red cell transfusions every 8 weeks
5. Anemia is refractory to erythropoiesis-stimulating agents (ESAs)* **OR** serum erythropoietin level is >500 mU/ml which predicts poor response to ESAs. (note: study used cutoff of 200 mU/mL but NCCN guidelines and UpToDate algorithm recommend a cutoff of 500 mU/mL)
If all criteria met, approve for 4 months.
Continuation criteria
After 4 months of treatment, may renew PA approval for 1 year if there is documentation of a reduction in RBC transfusion burden by at least 2 units over an 8 week period compared to baseline (see dosing recommendations below).

***Per NCCN,** the usual dosing for Procrit/Epogen/Retacrit and Aranesp in MDS is 40,000-60,000 Units 1-2 x/wk and 150-300 mcg every other wk, respectively. Consider patients ESA refractory if they do not achieve a hemoglobin level that avoids transfusion after approximately 8 weeks of the upper limits of these dosing recommendations.

Evidence:
Luspatercept was compared to placebo in this patient population. More patients in the luspatercept group achieved transfusion independence for 8 weeks or longer compared to placebo (38% vs 13%).
Note:
Dose:
1 mcg/kg SQ every 3 weeks. Dose may be titrated to a maximum of 1.25 mg/kg based on response. Therapy is stopped if no reduction in transfusion burden after 3 maximized doses. Package insert and study did not define "reduction in transfusion burden." The above criteria for continuation (≥2 unit reduction over 8 weeks) was taken from the endpoints used in beta thalassemia trial. Clinical judgment may be used.
References:

1. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. N Engl J Med. 2020;382(2):140–151. doi:10.1056/NEJMoa1908892 PMID 31914241
2. NCCN Guidelines for Myelodysplastic Syndrome Version 2.2020. Accessed 4/28/2020.
3. Treatment of lower-risk myelodysplastic syndromes (MDS). https://www.uptodate.com/contents/treatment-of-lower-risk-myelodysplastic-syndromes-mds?search=luspatercept&source=search_result&selectedTitle=3~10&usage_type=default&display_rank=2#H48. Accessed 4/28/2020.

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

	Score Value						
Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetic[e]	**Very good**	**—**	**Good**	**—**		**Poor**	**Very**
Marrow blasts (%)	**≤2**	**—**	**>2-<5**	**—**	**5-10**	**>10**	**—**
Hemoglobin	**≥10**	**—**	**8-<10**	**<8**	**—**	**—**	**—**
Platelets	**≥100**	**50-<100**	**<50**	**—**	**—**	**—**	**—**
ANC	**≥0.8**	**<0.8**	**—**	**—**	**—**	**—**	**—**

Mepolizumab (Nucala®)
EBRx PA Criteria

Asthma, eosinophilic type
1. The prescriber must be a pulmonologist or allergist.
2. The patient must be age ≥ 6 and have demonstrated an eosinophil count of >150 cells/microliter in the past 6 weeks or >300 cells/microliter in the past year.
3. The patient must have an inadequate response to standard controller despite proper adherence.
4. There must be no concurrent asthma biologic agent use. (No overlapping days supply)
5. Does the patient have FEV1 <80% at the time he/she is requesting the first prior authorization[3]?
Patients must be 12 or older (no published data in younger) with the diagnosis of asthma not controlled by continued inhaled corticosteroids. They (arbitrarily) should have 75% ICS adherence rate.
Note: Nucala® (mepolizumab) is FDA approved as add-on therapy to optimal asthma therapy. Currently there is not peer-reviewed published literature to support its use as monotherapy in asthma and therefore will not be covered in this manner.
DOSE is 100mg SC in a physician office q4w.
If approved for coverage, PA is good for 3 months. Re-authorization for a PA will require the patient to be compliant with optimal asthma drug therapy as per the current NHLBI Asthma guidelines. Subsequent requests for PA require that the past 3 of 4 months have a paid claim for a LABA/ICS either separately or as a combination product. If this is not the case, the PA should be denied.
Eosinophilic granulomatosis with polyangiitis (EGPA)
1. The patient must be at least 18 years of age or older

2. The patient must have a diagnosis eosinophilic granulomatosis with polyangiitis for at least 6 months. Defined as:
• History or presence of asthma AND
• Blood eosinophil level of 10% or an absolute eosinophil count of more than 1000 cells/mm^3 AND
• Presence of 2+ criteria below typical of EGPA:
  • A biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation;
  • Neuropathy, mono or poly (motor deficit or nerve conduction abnormality);
  • Pulmonary infiltrates, non-fixed;
  • Sino-nasal abnormality;
  • Cardiomyopathy (established by echocardiography or mri);
  • Glomerulonephritis (hematuria, red cell casts, proteinuria);
  • Alveolar hemorrhage (by bronchoalveolar lavage);
  • Palpable purpura;
  • Antineutrophil cytoplasmic antibody (anca) positive (mpo or pr3)

3. History of **relapsing OR refractory disease**
4. The patient must have tried azathioprine, methotrexate, leflunomide, OR mycophenolate 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:

1. Ortega, HG, et al. “Mepolizumab treatment in patients with severe eosinophilic asthma” New England Journal of Medicine 2014 September 25:371(13):1198-207. MENSA
2. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189-97. SIRIUS.
3. Wechsler, Michael E., et al. "Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis." *New England Journal of Medicine* 376.20 (2017): 1921-1932.

Natalizumab (Tysabri) MEDICAL PA
EBRx PA Criteria

is FDA-approved for:

- relapsing multiple sclerosis,
- Crohns 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:

1. Lexicomp. Natalizumab. Accessed 9/18/19.
2. UpToDate. DMT for RRMS. Accessed 9/18/19.
3. AAN. Practice Guideline: Disease-modifying Therapies for Adults with multiple sclerosis. American Academy of Neurology 4/24/2018. https://www.aan.com/Guidelines/Home/GetGuidelineContent/900
4. Sandborn, William J., et al. "Natalizumab induction and maintenance therapy for Crohn's disease." *New England Journal of Medicine* 353.18 (2005): 1912-1925.

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
  - Adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma
- **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.
  - Adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
  - Metastatic NSCLC and progression on or after platinum based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.
- **Malignant Pleural Mesothelioma**
  - Adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab
- **Renal Cell Carcinoma (RCC)**
  - 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)**
  - CHL that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin[a]
  - CHL that has relapsed or progressed after 3 or more lines of systemic therapy that includes autologous HSCT[a]
- **Head and Neck Cancer**
  - 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
  - Adult patients with unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine (NOT COVERED)
    - Nivolumab/chemo was compared to chemotherapy alone. Median overall survival was improved by 2.8 mo in nivolumab/chemo arm (HR 0.78; 21.7 mo vs 18.9 mo). However, EBRx prefers pembrolizumab/enfortumab in this setting which appears to be more effective (improved median OS by 15.4 mo compared to chemo alone). NCCN guidelines also prefer pembrolizumab/enfortumab in this setting. Another alternative is gemcitabine/platinum followed by avelumab maintenance therapy.
      - Reference: van der Heijden MS et al. Nivolumab plus Gemcitabine-Cisplatin in Advanced Urothelial Carcinoma. N Engl J Med. 2023 Nov 9;389(19):1778-1789. doi: 10.1056/NEJMoa2309863. Epub 2023 Oct 22. PMID: 37870949.
  - Locally advanced or metastatic disease with progression during or following platinum-containing chemotherapy[a] NOT COVERED: lack of comparative data (SEE PEMBROLIZUMAB)
  - Locally advanced or metastatic disease with progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy[b] NOT COVERED: lack of comparative data (SEE PEMBROLIZUMAB)
- **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[a] 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[a] 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
  - Treatment of patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy.
  - Treatment of patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with ipilimumab.
  - Treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy.
- **Gastric, gastroesophageal junction, and esophageal cancer**
  - 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.

Melanoma, metastatic (new users)
1. Diagnosis of unresectable or metastatic melanoma.
2. Patient does not have a diagnosis of ocular/uveal melanoma.
3. No prior treatment for unresectable/metastatic melanoma.
4. Nivolumab will be used as single agent **OR** in combination with ipilimumab
If above criteria fulfilled, approve for 12 months
Notes: -Two trials support use of nivolumab in the first line setting in BRAF mutated and non-mutated melanoma. One showed improvement in overall survival vs chemo in untreated BRAF unmutated patients (37.5m vs 11.2 m[a]) and another showed improvement in overall survival vs. ipilimumab in untreated patients with or without BRAF mutation (36.9m vs. 19.9 mo[b]). Nivolumab also studied in second line setting after ipilimumab and showed better response rates vs chemo. Survival not improved in overall population per clinical trials.gov (NCT01721746), so EBRx will not cover in the second line setting. -Ocular/uveal melanoma behaves differently and is treated differently from cutaneous melanoma. -Nivolumab+ipilimumab has been shown to improve overall survival vs ipilimumab alone. Ipilimumab/nivolumab also comes extremely close to statistically improving overall survival compared to nivolumab alone in the 5-year update of the CHECKMATE 067 trial. Due to consistency of results compared to initial release of data and strong trend to improving overall survival, EBRx recommends coverage. However, note that toxicity is also increased in the ipi/nivo arm compared to nivolumab alone (grade 3-5 toxicity incidence: 59% vs 23%).[b,c] NCCN guidelines for cutaneous melanoma (version 2.2019) recommend nivolumab monotherapy as a preferred regimen for this indication. Nivolumab+ipilimumab has a category 1 recommendation but is non-preferred and should be considered for a very fit patient population. -Nivolumab dosing is 240 mg every 2 weeks or 480 mg every 4 weeks IV infusion until disease progression or unacceptable toxicity REFERENCES: a. Ascierto PA et al. Survival Outcomes in Patients With Previously Untreated BRAF Wild-Type Advanced Melanoma Treated With Nivolumab Therapy: Three-Year Follow-up of a Randomized Phase 3 Trial. JAMA Oncol. 2018 Oct 25. b. Hodi F, VAnna C, Rene G et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (Checkmate 067): 4-year outcomes of a multicenter, randomized, phase 3 trial. Lancet Oncol 2018; 19:1480-92. PMID 30361170 c. Larkin J et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019 Oct 17;381(16):1535-1546. PMID 31562797 NCT01844505 d. NCCN guidelines for cutaneous melanoma (version 2.2019). https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed 8/8/19.

Melanoma, adjuvant (new users)
1. Diagnosis of stage IIB, IIC, III, or IV melanoma that has been completely surgically resected

2. Patient does not have a diagnosis of ocular/uveal melanoma.

If all criteria fulfilled, approve for 12 months. NOTE: maximum treatment duration is 1 year. Do not approve more than 1 year TOTAL.

Note:
The endpoint to the trial showed a hazard ratio for disease ***recurrence or death*** of 0.65 (97.56%CI 0.51 to 0.83, P<0.001. In this trial, the grade 3 or 4 AE rates were 14.4% Nivolumab vs 45.9% Ipilimumab.
REFERENCE:
Weber J et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. NEJM 2017 1826-1835 [CHECKMATE-238] NCT02388906 PMID 28891423

EARLY STAGE Non-Small Cell Lung Cancer (NSCLC)

1. Diagnosis of non-small cell lung cancer (adenocarcinoma or squamous cell carcinoma)
2. Disease is resectable
3. Tumor is either lymph node positive or size is 4 cm or greater
4. Tumor does not harbor EGFR or ALK mutations
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.

CHECKMATE-816 NCT02998528 Randomized, Open Lable, Multicenter Platinum-based chemotherapy x 3 cycles with or without nivolumab N=358 Primary endpoint: Event free survival Time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression of disease in the absence of surgery, or death from any cause.	Inclusion: Resectable NSCLC; resectable, histologically confirmed Stage IB (≥4 cm), II, or IIIA Excluded: known EGFR mutations or ALK translocations (testing not required)	**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:
1. Opdivo PI. https://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed 4/25/2022.
2. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer [published online ahead of print, 2022 Apr 11]. N Engl J Med. 2022;10.1056/NEJMoa2202170. doi:10.1056/NEJMoa2202170

METASTATIC Non-Small Cell Lung Cancer (NSCLC)

1. **If previously treated, all of the following criteria must be met:**
   - Diagnosis of metastatic NSCLC (squamous or non-squamous)
   - Progression of disease after 1 prior platinum-containing doublet regimen (cisplatin or carboplatin plus another agent).
   - The tumor must be EGFR negative. (Few EGFR+ patients were in the trials comparing PD-1 immunotherapies with docetaxel; however, two such trials did report on this subgroup. ICER's meta-analysis suggests there is a difference in OS for PD-1 immunotherapy. Compared with docetaxel, PD-1 OS was different in EGFR- and EGFR+ patients. Their analysis suggests there is little if any benefit with PD-1 immunotherapy compared to docetaxel in EGFR+ patients treated after progression on TKI therapy and prior to treatment with a platinum doublet. As such, there are reasons to be concerned that PD-1 immunotherapy could be inferior to a platinum doublet, which is more efficacious than docetaxel monotherapy).[1]

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

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

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

Notes:

SECOND-LINE SETTING:

-CHECKMATE 017/CHECKMATE 057 showed pooled median OS was 11.1m nivolumab vs 8m docetaxel (a difference of 3.1m); HR 0.72, 95% CI 0.62, 0.84 at 2-year f/u.[2]

FIRST-LINE SETTING (nivolumab+ipilimumab):

-In patients with any level of PD-L1, nivolumab + ipilimumab was compared with platinum-doublet chemotherapy.

-In patients with PD-L1 ≥1%, nivolumab + ipilimumab improved overall survival compared with platinum-doublet chemotherapy (median 17.1 mo vs 14.9 mo; HR 0.79; rate of survival at 3-yr was 33% vs 22%).

-In patients with PD-L1 <1%, this regimen did not statistically improve overall survival (median 15.2 mo vs 12.2 mo; HR 0.78, 95% CI 0.6-1.02). To achieve statistical significance for this *interim* analysis, p value must have been <0.023. Actual P value was 0.035).[4,5] FDA approved this regimen for PD-L1 ≥1% only.

FIRST-LINE SETTING (nivolumab+ipilimumab+2 cycles of chemo):

-In patients with PD-L1 of any level, nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy improved overall survival compared to platinum-doublet chemotherapy (median 15.6 mo vs 10.9 mo; HR 0.66; rate of survival at 1-yr 63% vs 47%.[6,7]

REFERENCES:

3. ICER review re: use for EGFR negative tumors: https://icer-review.org/wp-content/uploads/2016/08/MWCEPAC_NSCLC_Evidence_Report_Plus_Supplement_101716.pdf
4. Horn L et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). J Clin Oncol. 2017 Dec 10;35(35):3924-3933. [CHECKMATE-017 and 057; NCT01642004 and NCT01673867]
5. Carbone DP et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med. 2017 Jun 22;376(25):2415-2426. CHECKMATE 026, NCT02041533
6. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2019;381(21):2020-2031. doi:10.1056/NEJMoa1910231. PMID 31562796. NCT02477826
7. Ramalingam SS et al. Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: Three-year update from CheckMate 227 Part 1. J Clin Oncol 38: 2020 (suppl; abstr 9500). https://meetinglibrary.asco.org/record/184651/abstract. Accessed 7/9/2020. NCT02477826
8. Opdivo PI. https://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed 7/9/2020.
9. Reck M et al. Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA. https://meetinglibrary.asco.org/record/184688/abstract. NCT03215706

Malignant Pleural Mesothelioma

1. Diagnosis of unresectable malignant pleural mesothelioma
2. No prior therapy for unresectable malignant pleural mesothelioma
3. Nivolumab will be used in combination with ipilimumab
4. No active autoimmune disease, interstitial lung disease, or systemic immunosuppression
5. No active, untreated brain metastasis
6. ECOG performance status of 0 or 1

If all criteria are met, approve for 12 months. May renew approval if no progression of disease.

Note:

- Ipilimumab + Nivolumab was compared to standard, platinum-based chemotherapy in the above patient population. Ipilimumab/Nivolumab improved overall survival compared to chemotherapy (median 18.1 mo vs 14.1 mo; HR 0.74 95% CI 0.61-0.89). 2-year overall survival rates were 41% in the nivolumab plus ipilimumab group and 27% in the chemotherapy group. 3-year OS rates were 23% versus 15%, respectively.

References:

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

Renal Cell Carcinoma (RCC)

FIRST LINE TREATMENT CRITERIA for use with IPILIMUMAB

2. Diagnosis of advanced RCC
3. 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]
4. Tumor must have clear cell component
5. Nivolumab will be used in combination with ipilimumab
6. 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
7. 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 sunitnib; HR 0.63 99.8% CI 0.44-0.89). Improvement in OS was accompanied by clinically meaningful improvement in QOL.[1,2]

-Nivo/ipi does not appear superior to sunitinib in FAVORABLE risk patients and is not FDA approved and should not be used at this time.[1]

-Dose: Nivolumab 3 mg/kg every 3 weeks PLUS ipilimumab 1 mg/kg every 3 weeks x 4 doses; THEN nivolumab monotherapy continues at 240 mg every 2 weeks or 480 mg every 4 weeks IV infusion until disease progression or unacceptable toxicity

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

Classical Hodgkin Lymphoma (relapsed/refractory)

1. Diagnosis of Classical Hodgkin Lymphoma
2. Classical Hodgkin Lymphoma has relapsed or progressed after autologous hematopoietic stem cell transplant
3. No prior PD-L1 or PD-1 inhibitor
4. Nivolumab will be used as single agent

If above criteria fulfilled, approve x 12 months

Note:
-Classical Hodgkin Lymphoma includes the following subtypes: nodular sclerosis, mixed cellularity, lymphocyte-predominant, and lymphocyte-rich, which are all treated similarly.
- Nodular lymphocyte-predominant Hodgkin lymphoma is NOT a type of classical Hodgkin lymphoma and is not covered under this criteria

Notes:
Therapy continues until disease progression or unacceptable toxicity. An indirect comparison found that nivolumab was superior for overall survival compared to brentuximab and best supportive care (median overall survival 100 mo vs 48 mo vs 25 mo, respectively) in patients who had undergone previous autologous hematopoietic stem cell transplant.

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

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 carcinoma

If all criteria fulfilled, approve for 12 months

Note:
-OS benefit vs single agent systemic therapy (methotrexate, docetaxel, cetuximab) was 7.5 mo for nivolumab vs 5.1 months with standard therapy. At 1 year, 36% of patients were alive in nivolumab group vs 17% in control group. Severe adverse events occurred in fewer nivolumab patients vs chemotherapy (13% vs 35%).
-Nivolumab has not been well studied for treatment of nasopharyngeal tumors. These tumors behave differently from other head and neck cancers and were excluded from reference trial.
-Dose: 240 mg every 2 weeks or 480 mg every 4 weeks IV infusion. Continue until disease progression or unacceptable toxicity

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

Urothelial Carcinoma

All of the following 3 criteria are required:

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

In addition to 1-3, either #4 or #5 must be met:

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

-Staging of surgical specimen (i.e. pathological stage) is pT2, pT3, pT4a, or is node positive

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

Note:
Dose: 240 mg every 2 weeks OR 480 mg every 4 weeks for 1 year.
In this patient population, nivolumab improved disease free survival (DFS) was improved with nivolumab treatment compared to placebo. The median DFS in the intention-to-treat population was 20.8 months with nivolumab and 10.8 months with placebo (HR 0.70; 98.22% CI, 0.55 to 0.90; P<0.001). Overall survival results are pending.
REFERENCE:

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

Completely Resected Esophageal Cancer

1. Diagnosis of esophageal or gastroesophageal junction cancer
2. The patient has undergone complete resection of tumor with negative margins
3. The patient was treated with concurrent chemotherapy and radiation prior to surgery (neoadjuvant chemoradiotherapy/chemoradiation)
4. The patient has residual disease on surgical pathology specimen (i.e. after resection, tumor cells still remained in the resected tissue)
5. The patient does not have metastatic disease
6. Nivolumab will be used as single agent

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

Notes:
Treatment was continued until disease recurrence, unacceptable toxicity, or for up to 1 year in total duration.
In the CHECKMATE-577 (NCT02743494) trial, patients meeting the above key criteria were randomized to either 1 year of nivolumab or placebo. Nivolumab statistically improved disease free survival (DFS) regardless of PD-L1 expression and histology. The following results were taken from the package insert:

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

[a] Based on a stratified proportional hazards model.
[b] Based on a stratified log-rank test.

REFERENCES:

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

Advanced/Metastatic/Unresectable Esophageal Cancer (FIRST LINE)

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

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

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

Esophageal Squamous Cell Carcinoma (ESCC)

1. Diagnosis of advanced/metastatic esophageal squamous cell carcinoma (not adenocarcinoma)
2. Previously treated with fluoropyrimidine- and platinum-based chemotherapy (treatment must have contained a fluoropyrimidine (fluorouracil or capecitabine) AND a platinum agent (oxaliplatin, cisplatin, or carboplatin)
3. No prior PD-L1 or PD-1 inhibitor
4. Nivolumab will be used as single agent

If above criteria fulfilled, approve x 12 months

Notes:
In the above population, nivolumab was compared to investigator's choice of either paclitaxel or docetaxel. Overall survival was improved in the nivolumab group (median 10.9 mo vs 8.4 mo; HR 0.77) with fewer grade 3/4 adverse events in the nivolumab group (18% vs 63%). Serious grade 3/4 adverse events were also reduced in the nivolumab group (10% vs 20%). Quality of life parameters were also significantly improved in the nivolumab group.

REFERENCES:
Kato K et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial Lancet Oncol. 2019;20(11):1506-1517. doi:10.1016/S1470-2045(19)30626-6. PMID 31582355, NCT02569242

Gastric cancer, gastroesophageal cancer, esophageal adenocarcinoma

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

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

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

Table 58: Efficacy Results - CHECKMATE-649

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

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

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

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

Criteria for new users
2. The patient must be 12 years or younger at initial request.[4]
• The patient **must have** a diagnosis of Spinal Muscular Atrophy with all of the following criteria:[1,4] including genetic documentation of homozygous deletion or mutation in **SMN1 gene.** • Onset of clinical signs/symptoms consist with SMA at ≤ 48 months of age.[1,4] • Disease duration of ≤ 7 years.[4]
3. For infantile SMA, then they must also have 2 copies of the SMN2 gene[1], and no more than 3 copies of SMN. (Patients with 4 or more copies of SMN2 are likely to not develop the most severe forms of SMA and it may be reasonable to wait and monitor for signs of disease progression.)
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:
1. Finkel, Richard S., et al. "Nusinersen versus sham control in infantile-onset spinal muscular atrophy." *New England Journal of Medicine* 377.18 (2017): 1723-1732. ENDEAR
2. ICER SMA Draft Evidence Report. Accessed 1/17/19.
3. Swoboda, Kathryn J., et al. "SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy." *PLos one* 5.8 (2010): e12140.[estimated meaningful endpoint of HMFSE to be 3 points]
4. Mercuri, Eugenio, et al. "Nusinersen versus sham control in later-onset spinal muscular atrophy." *New England Journal of Medicine* 378.7 (2018): 625-635. CHERISH
5. ICER Report. Spinraza and Zolgensma for SMA. https://icer-review.org/wp-content/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf

Obinutuzumab (Gazyva) 1000 mg/40 ml vial
EBRx PA Criteria

FDA Approved Indications:

- Treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) in combination with chlorambucil.
- in combination with bendamustine followed by obinutuzumab monotherapy for treatment of follicular lymphoma in patients who relapsed after, or are refractory to, a rituximab-containing regimen
- In combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adults with previously untreated stage II bulky, III or IV follicular lymphoma
    - NOT COVERED: Obinutuzumab + chemotherapy was compared to rituximab + chemotherapy. A slight benefit in progression free survival was demonstrated but no benefit has been demonstration for overall survival or quality of life yet.
    - Reference: Hiddemann W et al. Immunochemotherapy With Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety. J Clin Oncol. 2018 Aug 10;36(23):2395-2404. NCT01332968 PMID 29856692

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

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) in combination with CHLORAMBUCIL (first line)
1. The patient must have previously untreated CD20-positive CLL.
2. The patient must be planning to use concomitant chlorambucil.
3. The patient must have Binet stage C or symptomatic disease
If the above criteria are met, approve coverage for 6 months. At this time, continuation of treatment beyond 6 cycles has not been studied and will not be approved. However, if the start of a cycle was delayed, and the schedule adjusted accordingly, a PA may be extended to account for that and allow the entire 6 cycles to be administered.
Dosing: Dosing is limited to 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: Goede V et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014 Mar 20;370(12):1101-10. PMID 24401022 NCT01010061

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) in combination with VENETOCLAX or ACALABRUTINIB (first line)
1. The patient must have previously **untreated** CLL.
2. The patient must be planning to use concomitant venetoclax or acalabrutinib.
If the above criteria are met, approve coverage for 6 months. At this time, continuation of treatment beyond 6 cycles has not been studied and will not be approved. However, if the start of a cycle was delayed, and the schedule adjusted accordingly, a PA may be extended to account for that and allow the entire 6 cycles to be administered.
Dosing: Dosing is limited to **SIX** 28-day cycles. Cycle 1: 100mg on day 1, followed by 900mg on day 2, followed by 1,000mg weekly for 2 doses (days 8 and 15). Cycles 2 through 6: 1,000mg on day 1 every 28 days for 5 doses.

Evidence:
The approval for first line use of venetoclax in combination with obinutuzumab was based on a study that enrolled older patients or patients with comorbidities. Progression free survival (PFS) was improved with obinutuzumab+venetoclax compared with obinutuzumab + chlorambucil (5-yr rate of PFS 63% vs 27%). At a median follow up of 65 mo, the 5-yr overall survival difference did not reach significance (HR, 0.72; 95% CI, 0.48-1.09; P = 12). At 5 years, 72% of patients in the ventoclax arm had not started new treatment compared with 43% in the control arm.
The approval for first-line use of acalabrutinib in combination with obinutuzumab was based on the ELEVATE-TN study which compared acalabrutinib +/- obinutuzumab to chlorambucil + obinutuzumab. Acala+Obi improved overall survival compared to the Chlor+Obi group (HR 0.55). No difference in overall survival has been demonstrated to date between the acalabrutinib and the Chlor+Obi group.

Venetoclax + obinutuzumab references:

- Fischer K et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med. 2019 Jun 6;380(23):2225-2236. doi: 10.1056/NEJMoa1815281. Epub 2019 Jun 4. PMID 31166681 NCT02242942
- Al-Sawaf O et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2020 Sep;21(9):1188-1200. doi: 10.1016/S1470-2045(20)30443-5. PMID: 32888452.
- Al-Sawaf O et al. Rapid Improvement of Patient-Reported Outcomes with Venetoclax Plus Obinutuzumab in Patients with Previously Untreated CLL and Coexisting Conditions: A Prospective Analysis from the CLL14 Trial. https://ash.confex.com/ash/2019/webprogram/Paper126542.html. Accessed 1/21/2020.
- 4-year follow up data (press release only; data presented at European Hematology Association 2021 Virtual Congress): https://www.cancernetwork.com/view/three-year-follow-up-continues-to-support-fixed-dose-venetoclax-obinutuzumab-in-treatment-na-ve-cll. Accessed 9/28/2021.
- European Hematology Association Abstract: https://library.ehaweb.org/eha/2022/eha2022-congress/357012/othman.al-sawaf.venetoclaxobinutuzumab. for.previously.untreated.chronic.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Ds148. Accessed 9/23/2022

Acalabrutinib + obinutuzumab references:

- Sharman JP et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020 Apr 18;395(10232):1278-1291. doi: 10.1016/S0140-6736(20)30262-2. Erratum in: Lancet. 2020 May 30;395(10238):1694. PMID: 32305093; PMCID: PMC8151619.
- Sharman JP et al. Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Five-year follow-up of ELEVATE-TN.DOI: 10.1200/JCO.2022.40.16_suppl.7539 Journal of Clinical Oncology 40, no. 16_suppl (June 01, 2022) 7539-7539. https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.7539

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:

1. Sehn LH et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016 Aug;17(8):1081-1093. PMID 27345636 NCT01059630
2. Cheson BD et al. Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. J Clin Oncol. 2018 Aug 1;36(22):2259-2266. PMID 29584548 NCT01059630
3. Cheson BD et al. Health-related quality of life and symptoms in patients with rituximab-refractory indolent non-Hodgkin lymphoma treated in the phase III GADOLIN study with obinutuzumab plus bendamustine versus bendamustine alone. Ann Hematol. 2017 Feb;96(2):253-259. PMID 27900446. NCT01059630

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.**
• **Ruxience is covered biosimilar of rituximab with NO PA required**

References:

1) Hawker, Kathleen, et al. "Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial." *Annals of neurology* 66.4 (2009): 460-471.
2) Montalban, Xavier, et al. "Ocrelizumab versus placebo in primary progressive multiple sclerosis." *N Eng J Med* 376.3 (2017): 209-220.
3) Ocrelizumab FDA package insert.
4) Kurtzke, John F. "Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS)." *Neurology* 33.11 (1983): 1444-1444. **http://www.neurology.org/content/33/11/1444.full.pdf+html**
5) 1. He, Dian, et al. "Rituximab for relapsing-remitting multiple sclerosis." ***Cochrane Database Syst Rev*****12 (2011).**
6) Hauser, Stephen L., et al. "B-cell depletion with rituximab in RRMS." ***NEngJMed.*** **358.7 (2008): 676-688. HERMES Trial Group; phase 2 trial. [NCT00097188]**
7) **3. ICER. Disease-modifying therapies for RRMS and PPMS: Effectiveness and Value. 3/6/17, prepared by California Technology Assessment Forum.** https://icer-review.org/announcements/final-ms-report/
8) NCT02746744. **Rituximab Versus Fumarate in Newly Diagnosed Multiple Sclerosis. (RIFUND-MS). Rituximab, dimethyl fumarate or placebo. Population:** N = 200, ages 18-40, both sexes. Diagnosis of RRMS or one demyelinating episode with ≥2 asymptomatic high-intensity lesions compatible with MS diagnosis No previous MS tx other than with interferon or glatiramer acetate, <5 years disease duration, ≥1 relapse, ≥ 2 T2 lesions or >Gd+ lesions in previous year, EDSS score 0-5.5. Primary outcomes: RR of relapse during study period. Est. Completion Date 8/2021.

Kurtzke Functional Systems Scores (FSS)

❏ Pyramidal Functions:

0 – Normal
1 - Abnormal signs without disability
2 - Minimal disability
3 - Mild to moderate paraparesis or hemiparesis (detectable weakness but most function sustained for short periods, fatigue a problem); severe monoparesis (almost no function)
4 - Marked paraparesis or hemiparesis (function is difficult), moderate quadriparesis (function is decreased but can be sustained for short periods); or monoplegia
5 - Paraplegia, hemiplegia, or marked quadriparesis
6 - Quadriplegia
9 - (Unknown)

Omalizumab (Xolair)
EBRx PA Criteria

is FDA-approved for:

- **Idiopathic urticaria, chronic, H1 antihistamine-refractory -** indicated for the treatment of chronic idiopathic urticaria in adults and adolescents (12 years or older) who remain symptomatic despite H1 antihistamine therapy
- **IgE-mediated allergic asthma, Not controlled by inhaled corticosteroid -** indicated in patients 6 years or older with symptoms of moderate to severe persistent asthma not controlled by inhaled corticosteroids (ICS) and who have a positive skin test or in vitro reactivity to a perennial aeroallergen
- **Allergy to food, IgE-mediated allergic reaction (Type 1) -** indicated for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods in adult and pediatric patients aged 1 year and older with IgE-mediated food allergy; to be used in conjunction with food allergen avoidance **EXCLUDED INDICATION**
- **Chronic rhinosinusitis with nasal polyps, Inadequate response to nasal corticosteroids; Adjunct -** indicated for add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids (TBD-presenting at upcoming PT meeting in November 2024)

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 >6 consecutive weeks despite current use of H1 antihistamine treatment during this time period. 3. The patient must have tried: cetirizine 10mg daily, levocetirizine 5mg daily, fexofenadine 180mg daily, loratadine 10mg daily, or desloratadine 5mg daily for 2 weeks. 4. The patient must also avoid non-steroidal anti-inflammatory drugs and any other relevant triggers. 5. Dose elevation of desloratadine or levocetirizine should be advanced to 4X the labeled dose. 6. A second, different antihistamine should be added if dose escalation does not help. 7. Montelukast 10mg daily must be tried for at least 4 weeks. 8. If still not controlled, first generation antihistamines hydroxyzine 100mg-200mg, or doxepin 100-150mg, must be tried at bedtime.
Usual dose is 150-300mg q4 weeks regardless of IgE or body weight. Don't exceed 300mg q4w.
If approved, the PA may be approved for 12m.
Continuation Criteria for Chronic Idiopathic Urticaria
1. The patient must not have missed more than 33% of scheduled omalizumab doses. (must receive at least 4 of the last 6 scheduled doses) on time.

Asthma
2. The patient must be age 6y or older.
2. The patient must have a diagnosis of moderate or severe persistent asthma with either a positive skin test or with in vitro reactivity to a perennial aeroallergen.
3. The patient must have a total serum IgE level ≥30 IU/mL.
3. The patient must be adherent to prescribed asthma controller medications and must have filled inhaled corticosteroids/LABA combination for a minimum of the past 3 of 4 months prior to this request.
4. The patient must NOT be dependent on systemic steroids to prevent serious asthma exacerbations[2].
5. The patient's FEV1 must NOT be better than 80% of the predicted value at the time he/she is requesting the first prior authorization[3].
Xolair failed to show a benefit in patients with FEV1 >80% at initiation. Xolair also failed to reduce exacerbations requiring maintenance systemic steroids.
Note: Xolair® (omalizumab) is FDA approved as add-on therapy to optimal asthma therapy. Currently there is not peer-reviewed published literature to support its use as monotherapy in asthma and therefore will not be covered in this manner.
DOSE is 150-375mg SC q2 or 4w as determined by serum total IgE level measured before the start of therapy. (See chart in the package insert.)
If approved for coverage, PA is good for 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[4].

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.

Notes:
[1]Per the PI: Considering the risk of anaphylaxis and malignancy seen in Xolair-treated patients ≥12 years old and the modest efficacy of Xolair in the pivotal pediatric study, the risk-benefit assessment does not support the use of Xolair in patients 6-<12 years of age.
[2]Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.
[3]In all three of the studies, a reduction of asthma exacerbations was not observed in the Xolair-treated patients who had FEV1 > 80% at the time of randomization.
[4]NHLBI Asthma Guidelines 2007.
Omalizumab
The Expert Panel recommends that omalizumab may be considered as adjunctive therapy in step 5 or 6 care for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and LABA (Evidence B).
(See Evidence Table 13, Immunomodulators: Anti-IgE.)
Omalizumab, a recombinant DNA-derived humanized monoclonal antibody to the Fc portion of the IgE antibody, binds to that portion preventing the binding of IgE to its high-affinity receptor (FcεRI) on mast cells and basophils. The decreased binding of IgE on the surface of mast cells leads to a decrease in the release of mediators in response to allergen exposure. Omalizumab also decreases FcεRI expression on basophils and airway submucosal cells (Djukanovic et al. 2004; Lin et al. 2004). That study also showed significant decreases in sputum and bronchial eosinophils as well as in CD3+, CD4+, and CD8+ T cells in bronchial biopsy (Djukanovic et al. 2004). The vast majority of patients in clinical trials of omalizumab had moderate or severe persistent asthma incompletely controlled with ICS (Walker et al. 2004); all had atopy and IgE ≥30 IU/mL. Adding omalizumab to ICS therapy generally produced a significant reduction in asthma exacerbations (Busse et al. 2001a; Soler et al. 2001; Vignola et al. 2004) but not always (Holgate et al. 2004; Milgrom et al. 2001). (See Evidence Table 13, Immunomodulators: Anti- IgE.) Omalizumab, added to ICS, was associated with a small but significant improvement in lung function (Busse et al. 2001a; Soler et al. 2001). In two trials, one open-label, in patients who had severe persistent asthma inadequately controlled on ICS plus LABAs, omalizumab reduced asthma exacerbations and ED visits (Ayres et al. 2004; Humbert et al. 2005). Omalizumab appears to have a modest steroid-sparing effect, allowing a median reduction of 25 percent over that of placebo in the trials (Busse et al. 2001a; Holgate et al. 2004; Milgrom et al. 2001; Soler et al. 2001). Omalizumab has not been compared in clinical trials to the other adjunctive therapies for moderate persistent asthma (LABAs, leukotriene modifiers, and theophylline), all of which improve outcomes and allow reduction of ICS dose. Omalizumab is the only adjunctive therapy, however, to demonstrate added efficacy to high-dose ICS plus LABA in patients who have severe persistent allergic asthma (Humbert et al. 2005). In studies Section 3, Component 4: Medications 226 August 28, 2007 of patients who have severe persistent asthma, omalizumab resulted in clinically relevant improvements in quality-of-life scores in significantly more patients (approximately 60 percent) than did placebo (approximately 43 percent) (Holgate et al. 2004; Humbert et al. 2005). Omalizumab is approved for patients 12 years and older who have proven sensitivity to aeroallergens: studies have been done in patients who have sensitivity to dust mite, cockroach, cat, or dog. One study of omalizumab in children 6–12 years of age demonstrated nonsignificant reductions in exacerbations and no improvement in lung function but did show small but significant reduction in ICS dose compared to placebo (Milgrom et al. 2001). Urticaria and anaphylactic reactions have been reported in 0.1 percent of cases (Berger et al. 2003; FDA 2003; Holgate et al. 2004; Lanier et al. 2003). Postmarketing surveys have identified anaphylaxis in an estimated 0.2 percent of treated patients, which resulted in an FDA alert (FDA 2007). Most of these reactions occurred within 2 hours of the omalizumab injection, and after the first, second, or third injections. However, reactions have occurred after many injections and after many hours. Therefore, clinicians who administer omalizumab are advised to be prepared and equipped for the identification and treatment of anaphylaxis that may occur, to observe patients for an appropriate period of time following each injection (the optimal length of
the observation is not established), and to educate patients about the risks of anaphylaxis and how to recognize and treat it if it occurs (e.g., using prescription auto injectors for emergency self-treatment, and seeking immediate medical care) (FDA 2007). Adverse effects reported from omalizumab in the trials have also included injection-site pain and
bruising in up to 20 percent of patients (Holgate et al. 2004). In the trials reported to the FDA, twice as many patients receiving omalizumab had malignancies (20 of 48,127, or 0.5 percent) as did those receiving placebo (5 of 2,236, or 0.2 percent), but there were no trends for a specific tumor type.

References:
1. Xolair PI.
2. NHLBI Asthma Guidelines.
3. Humbert M, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy: INNOVATE. Allergy 2005: 60: 309–316.
4. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria. NEJM 2013; 368:924-935.
5. THIS GUIDELINE WAS PRODUCED BY HIGHLY CONFLICTED EDITORS: Bernstein JA, Lang DM, Khan DA. The diagnosis and management of acute and chronic urticarial: 2014 update. J Allergy Clin Immunol. 2014;133(5):1270-1277.
6. Nowak-Wegrzyn, Anna. (2024.) Management of IgE-mediated food allergy: An overview. In E. TePas (Ed.) *UpToDate*. Retrieved October 24, 2024 from https://www-uptodate-com.libproxy.uams.edu/contents/management-of-ige-mediated-food-allergy-an-overview?search=ige%20food%20allergy&source=search_result&selectedTitle=3%7E150&usage_type=default&display_rank=3#H270825159.

OnabotulinumtoxinA (Botox)
EBRx PA Criteria (Urinary Incontinence ONLY EBD commercial)
EBD Medicare plans all uses

FDA approved for:

- **Blepharospasm, associated with dystonia:** indicated for blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years or older.
- **Cervical dystonia:** indicated for the treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain associated with cervical dystonia
- **Chronic Migraine, prophylaxis:** indicated for the prophylaxis of headaches in adult patients with chronic migraine (at least 15 days per month with headache lasting 4 hours a day or longer)
- **Hyperhidrosis of axilla:** indicated for use in severe primary axillary hyperhidrosis that is inadequately managed with topical agents in adults
- **Incontinence due to detrusor instability, Associated with a neurologic condition:** indicated for the treatment of urinary incontinence due to detrusor overactivity related to a neurologic condition (eg, spinal cord injury, multiple sclerosis) in adults who have had an inadequate response to or are intolerant of at least one anticholinergic medication – **COVERED BY EBD Commercial**
- **Neurogenic detrusor overactivity, Associated with neurologic condition; following inadequate response or intolerance to anticholinergic medication:** indicated for the treatment of neurogenic detrusor overactivity (NDO) associated with a neurologic condition in pediatric patients 5 years or older who have an inadequate response to or are intolerant of anticholinergic medication
- **Overactive urinary bladder, Refractory to or intolerant of anticholinergic medication:** indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in patients with an inadequate response to or intolerance of anticholinergic medications
- **Spasticity:** indicated for the treatment of spasticity in patients 2 years of age or older
- **Strabismus:** indicated for the treatment of strabismus in patients 12 years or older – EBRx WILL NOT APPROVE FOR STRABISMUS
- **Wrinkled Face (Moderate to Severe):** indicated for temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator or procerus muscle activity, moderate to severe lateral canthal lines associated with orbicularis oculi activity, moderate to severe forehead lines associated with frontalis muscle activity, and moderate to severe platysma bands associated with platysma muscle activity – **COSMETIC NOT COVERED**

Blepharospasm:
2. The patient must have the diagnosis of blepharospasm
If the criteria are fulfilled, approve PA for 1 year

Cervical dystonia:
2. The patient must have the diagnosis of cervical dystonia
If the criteria are fulfilled, approve PA for 1 year

Chronic Migraine:
2. 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.
If the criteria are fulfilled, approve PA for 1 year

Hyperhidrosis of axilla:
2. The patient must have the diagnosis of Hyperhidrosis of axilla
If the criteria are fulfilled, approve PA for 1 year

Incontinence due to detrusor instability: Covered use by EBD – AML; ASP; ASU; EBD commercial plans)
1. The patient must have the diagnosis of incontinence due to detrusor instability, associated with a neurologic condition
2. The patient must have tried 12 weeks of the following: Antimuscarinic, Beta-3 adrenergic, OR pelvic floor PT
If the criteria are fulfilled, approve PA for 1 year

Neurogenic detrusor overactivity; following inadequate response or intolerance to anticholinergic medication:

1. The patient must have the diagnosis of Neurogenic detrusor overactivity
2. The patient must have tried and failed 12 weeks of antimuscarinic therapy or documented intolerance
If the criteria are fulfilled, approve PA for 1 year

Overactive urinary bladder, Refractory to or intolerant of anticholinergic medication:
1. The patient must have the diagnosis of Overactive urinary bladder
2. The patient must have tried and failed 12 weeks of antimuscarinic therapy or documented intolerance
If the criteria are fulfilled, approve PA for 1 year

Spasticity indication:
2. The patient must have the diagnosis of spasticity.
If the criteria are fulfilled, approve PA for 1 year.

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

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

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

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

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.

Migraine prophylaxis:

There seems to be little difference between OnA and InA in terms of the efficacy or longevity of effects. InA appears to be effective for the management of CM but may not be as well suited as OnA due to excessive pain on injection. If the pain on injection was negated, perhaps with a buffering solution, InA would likely be a good alternative to OnA for CM treatment. In cases where OnA fails because of the development of antibodies, it might be reasonable to switch to InA treatment.

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

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

- Bruloy, Eva (01/2019). "Botulinum Toxin versus Placebo: A Meta-Analysis of Prophylactic Treatment for Migraine.". *Plastic and reconstructive surgery (1963)* (0032-1052), 143 (1), p. 239.
- Herd, Clare P., et al. "Botulinum toxins for the prevention of migraine in adults." *Cochrane Database of Systematic Reviews* 6 (2018).
- Lucchese, Scott, Bob Daripa, and Shruthi Pulimamidi. "Onabotulinum toxin A vs. incobotulinum toxin A for the treatment of chronic migraine: a retrospective review." *Research Square* (2023): rs-3.

Hyperhidrosis:

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

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

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

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

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

Spasticity:

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

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

Strabismus:

Cochrane Systematic Reviews-insufficient evidence. "Further high quality trials using robust methodologies are required to compare the clinical and cost effectiveness of various forms of botulinum toxin (e.g. Dysport, Xeomin, etc), to compare botulinum toxin with and without adjuvant solutions and to compare botulinum toxin to alternative surgical interventions in **strabismus** cases with and without potential for binocular vision."
Rowe, Fiona J., and Carmel P. Noonan. "Botulinum toxin for the treatment of strabismus." *Cochrane Database of Systematic Reviews* 3 (2017)

Onasemnogene Abeparvovec (Zolgensma Kit) for 1-time IV infusion
EBRx PA Criteria—MEDICAL PA

is FDA-approved for: treatment of pediatric patients <2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.

Criteria for new users
1. The patient must be 2 (two) years or younger.
2. The patient must have the confirmed diagnosis of SMA-1 by genetic testing for both symptomatic and presymptomatic patients.
3. The patient must have not more than 3 copies of SMN. (Patients with 4 or more copies of SMN2 are likely to NOT develop the most severe forms of SMA and it may be reasonable to wait and monitor for signs of disease progression.)
4. The patient must have bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.
5. No prior use of Zolgensma. Previous use of Spinraza does not preclude the one time Zolgensma gene therapy; however, after Zolgensma, no further Spinraza will be covered.
6. Prescriber must be a neuromuscular specialist.
7. At request, the patient must have NO HISTORY of the ability to walk independently (defined as the ability to walk ≥15 feet unaided.
Medication is excluded from pharmacy.

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

Ref:
1. ICER Report. Spinraza and Zolgensma for SMA. https://icer-review.org/wp-content/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf
2. Giess, Doris, Judit Erdos, and Claudia Wild. "An updated systematic review on spinal muscular atrophy patients treated with nusinersen, onasemnogene abeparvovec (at least 24 months), risdiplam (at least 12 months) or combination therapies."*European Journal of Paediatric Neurology* (2024).

Pegunigalsidase Alfa-IWXJ (Elfabrio) IV infusion—MEDICAL BENEFIT DRUG
EBRx PA Criteria

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

Criteria for new users
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. a. A positive diagnosis in males is virtually undetectable (<3%) alpha-Gal A leukocyte activity; then, confirmation by genetic testing. b. In males with 3-35% alpha-Gal A leukocyte activity, a diagnosis should be considered and genetic testing should take place. c. In males with alpha-Gal A leukocyte activity >35% of mean normal, the diagnosis cannot be established. 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.
2. The patient must be 18y+.
3. The patient is not receiving concurrent pegunigalsidase with agalsidase alfa or agalsidase beta.
If approved, the PA is good for 1 year.

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

Note: Patients may receive concurrent migalastat.

References:

1. UpToDate. Fabry Disease Diagnosis. Also Treatment and Prognosis. 3/11/24.

Pertuzumab (Perjeta) 420 mg/14 ml vial
EBRx PA Criteria

FDA-approvals:

- Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
- Use in combination with trastuzumab and chemotherapy as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.
- Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence Covered for node-positive disease only

Metastatic Breast Cancer
1. Diagnosis of unresectable or metastatic breast cancer
2. Breast cancer is HER2 positive
3. No prior chemotherapy or anti-HER2 therapy for unresectable or metastatic breast cancer
4. Pertuzumab will be used in combination with trastuzumab and docetaxel
If above criteria are fulfilled, approve x 1 year [therapy continues until disease progression or unacceptable toxicity]

Notes:
Pertuzumab should not be given to patients whose tumors have previously progressed on pertuzumab.
For metastatic breast cancer, pertuzumab is ALWAYS given in combination with trastuzumab and docetaxel.
In the Cleopatra study, the population described in the above criteria was given pertuzumab, trastuzumab, and docetaxel OR placebo, trastuzumab, and docetaxel. The pertuzumab group had improved median overall survival (56.5 mo vs 40.8 mo, HR 0.68, 95% CI 0.56-0.84).

Dose:
840 mg IV x 1 followed 3 weeks later by 420 mg IV every 3 weeks. Therapy continues until disease progression or unacceptable toxicity

REFERENCES:

1. Swain SM et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2013 May;14(6):461-71. PMID 23602601 NCT00567190
2. Swain SM et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015 Feb 19;372(8):724-34. PMID 25693012 NCT00567190

Neoadjuvant Treatment of Breast Cancer (therapy begins BEFORE surgery)
1. Diagnosis of breast cancer
2. Breast cancer is HER2 positive
3. Breast cancer falls into one of the following categories: a. Inflammatory breast cancer b. Primary tumor is >2 cm in diameter c. Lymph node involvement is present
4. Pertuzumab will be used in combination with trastuzumab and taxane-based chemotherapy
If above criteria are fulfilled, approve x 12 months [maximum duration of therapy is 1 year or 18 doses of pertuzumab]

Notes:
Total duration of perioperative pertuzumab therapy is 1 year. Pertuzumab/trastuzumab+chemo is given x 3-6 cycles before surgery. After surgery, pertuzumab and trastuzumab are resumed to complete one year of therapy.

In studies, the population described in the above criteria was given pertuzumab, trastuzumab, and mostly taxane-based chemotherapy. Compared to conventional rates of pathological complete response (pCR) of ~40%[1], the pCR rates with these pertuzumab-containing regimens were ~60%[2,3,4]. Attainment of pCR has been strongly associated with overall survival in multiple analyses.[1,5,6]

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

REFERENCES:

1. Gianni L et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Jan;13(1):25-32. NCT00545688 PMID 22153890
2. Schneeweiss A et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013 Sep;24(9):2278-84. PMID 23704196

3. Swain SM et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol. 2018 Mar 1;29(3):646-653. PMID 29253081 NCT02132949
4. Cortazar P et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Jul 12;384(9938):164-72. PMID 24529560
5. Mieog JS, van der Hage JA, van de Velde CJ. Preoperative chemotherapy for women with operable breast cancer. Cochrane Database Syst Rev 2007;2:CD005002-CD005002. PMID 17443564
6. Kong X et al. Meta-analysis confirms achieving pathological complete response after neoadjuvant chemotherapy predicts favourable prognosis for breast cancer patients. Eur J Cancer. 2011 Sep;47(14):2084-90. PMID 21737257

Adjuvant Treatment of Breast Cancer (therapy begins AFTER surgery)

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

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

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

In the APHNITY study[1] (n=4804), the population described in the above criteria was given pertuzumab, trastuzumab, and chemotherapy OR placebo, trastuzumab, and chemotherapy. The primary endpoint was invasive disease free survival (IDFS). At 3 years, the rates of IDFS were as follows:
-all patients (pertuzumab 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:
1. von Minckwitz G et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017 Jul 13;377(2):122-131. PMID 28581356 NCT01358877
2. Garrison LP Jr et al. Cost-Effectiveness Analysis of Pertuzumab With Trastuzumab and Chemotherapy Compared to Trastuzumab and Chemotherapy in the Adjuvant Treatment of HER2-Positive Breast Cancer in the United States. Value Health. 2019 Apr;22(4):408-415. PMID 30975391

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

is FDA-approved for:

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

Criteria for new users
1. Diagnosis of diffuse large B-cell lymphoma (DLBCL) that is progressing
2. Lymphoma is refractory to or progressed on or after at least two prior regimens
3. Patient is not eligible for stem cell transplant
4. Polatuzumab will be used in combination with bendamustine and rituximab
If all of the above criteria are met, approve for 6 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:

4. San Miguel JF et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. Haematologica. 2015 Oct;100(10):1334-9. PMID 26160879 NCT01311687
5. Miguel JS et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1055-1066. PMID 24007748 NCT01311687

Quantity Limits: n/a

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
1. 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.
2. The patient must be at least 1y of age.
3. The patient must not be receiving concurrent complement inhibitors (eculizumab or other).
4. The patient must be symptomatic (edema, pleural or pericardial effusions)
5. It is suggested that meningococcal vaccines be completed or updated at least 2 w prior to beginning pozelimab.
If approved, the PA is good for 3 months.

Criteria for continuation
1. The patient must have experienced clinical improvement of symptoms. (fewer albumin infusions or other sign of improvement)
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.
2. Kurolap, A., Hagin, D., Freund, T., Fishman, S., Zunz Henig, N., Brazowski, E., ... & Baris Feldman, H. (2023). CD55-deficiency in Jews of Bukharan descent is caused by the Cromer blood type Dr (a−) variant. *Human Genetics*, *142*(5), 683-690.
3. Veopoz PI. Accessed 9/19/23.

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

is FDA-approved for:
Relapsed or refractory peripheral T-cell lymphomas

Criteria for new users
1. The patient must be >18 years of age and be diagnosed with peripheral T-cell lymphoma that has progressed after at least 1 prior treatment.
2. The patient must be ECOG 0-2.
If above criteria are met, approve x 1 year

Notes:
The dose is 30mg/m^2/week for 6 weeks followed by 1 week of rest. Then the cycle is repeated until progressive disease or unacceptable toxicity. B_{12} 1mg IM injection every 8-10w + daily folic acid 1-1.25mg was also administered.

An indirect comparison of patients who received pralatrexate and historical controls who did not receive pralatrexate found an improvement in overall survival in the pralatrexate arm (15.2 mo vs 4.07 mo). Although this is not a randomized controlled trial, EBRx will cover pralatrexate based on this data.

Quantity limits: n/a (medically administered drug)

References:
1. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral t-cell lymphoma: results from the pivotal PROPEL study. J Clin Onc. 2011;29(9):1182-1189.

2. O'Connor OA et al. Strategy for Assessing New Drug Value in Orphan Diseases: An International Case Match Control Analysis of the PROPEL Study. JNCI Cancer Spectr. 2018 Dec 1;2(4):pky038. doi: 10.1093/jncics/pky038. eCollection 2018 Oct. PMID 31360868

Ravulizumab (Ultomiris)—MEDICALLY ADMINISTERED DRUG
EBRx PA Criteria

is FDA-approved for:

- treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (**PNH**)
- treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (**aHUS**) to inhibit complement-mediated thrombotic microangiopathy (TMA)
- treatment of adult patients with generalized **myasthenia gravis** (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.
- treatment of adult patients with **neuromyelitis optica spectrum disorder (NMOSD)** who are anti-aquaporin-4 (AQP4) antibody-positive

Paroxysmal Nocturnal Hemoglobinuria (PNH)--Criteria for new users
1. Diagnosis of paroxysmal nocturnal hemoglobinuria (PNH)
2. Age is 1 month or older
3. PNH is **not** associated with Shiga toxin E. coli
4. Patient has undergone vaccination per ACIP guidelines against meningococcal serogroups A, C, W, Y, and B **OR** has initiated prophylactic treatment with antibiotics, such as penicillin
If criteria met, approve for 6 months
Paroxysmal Nocturnal Hemoglobinuria (PNH)--Criteria for continuation
1. Since initiation of ravulizumab, patient has experienced a decrease in PNH symptoms (e.g. fatigue), markers of hemolysis (e.g. LDH), or transfusion needs
If criteria met, renew PA for 12 months.

aHUS -- Criteria for new users
1. Diagnosis of atypical hemolytic uremic syndrome
2. Age is 1 month or older
3. Platelet count is less than or equal to 150×10^9 /L
4. Serum LDH (lactate dehydrogenase) is above the upper limits of normal
5. Serum creatinine is above the upper limits of normal or the patient requires dialysis
6. There is no evidence of thrombotic microangiopathy (TMA) due to any of the following: • ADAMTS13 deficiency • Shiga toxin Escherichia coli related HUS (STEC-HUS)
7. Patient has undergone vaccination per ACIP guidelines against meningococcal serogroups A, C, W, Y, and B **OR** has initiated prophylactic treatment with antibiotics, such as penicillin
aHUS -- Criteria for continuation
1. Since initiation of ravulizumab, patient has experienced improvement in platelet count, LDH, or creatinine.
If criteria met, renew PA for 12 months.

Myasthenia gravis, AChR+ -- Criteria for new users
1. Age ≥18 years
2. Diagnosis of generalized myasthenia gravis (gMG)
3. Class II to IV disease according to the Myasthenia Gravis Foundation of America (MGFA) clinical classification
4. Disease is positive for anti-AChR antibodies (AChR: anti-acetylcholine receptor)
5. MG-ADL total score is 6 or greater (MG-ADL: Myasthenia Gravis-Activities of Daily Living)
6. Patient has undergone vaccination per ACIP guidelines against meningococcal serogroups A, C, W, Y, and B **OR** has initiated prophylactic treatment with antibiotics, such as penicillin
If criteria met, approve for 6 months
Myasthenia gravis, AChR+ --Criteria for continuation
1. Since initiation of ravulizumab, patient has experienced improvement in gMG symptoms (e.g. reductions in exacerbations or improvements in speech, swallowing, mobility, and respiratory function)
If criteria met, renew PA for 12 months.

Neuromyelitis optica spectrum disorder (NMOSD)----Criteria for new users

1. Age ≥18 years
2. Diagnosis of NMOSD
3. Disease is positive for anti-AQP4 antibody (AQP4: aquaporin-4)
4. Patient experienced at least 1 relapse in the 12 months prior to request
5. Expanded Disability Status Scale (EDSS) score is 7 or less
6. Patient has undergone vaccination per ACIP guidelines against meningococcal serogroups A, C, W, Y, and B **OR** has initiated prophylactic treatment with antibiotics, such as penicillin
If criteria met, approve for 6 months
Neuromyelitis optica spectrum disorder (NMOSD)--Criteria for continuation
1. Since initiation of ravulizumab, patient has experienced clinical benefit for NMOSD (e.g. reduction in relapses and/or symptoms, slowed progression of symptoms)
If criteria met, renew PA for 12 months.

Retifanlimab (Zynyz) 500 mg/20 ml single dose vial
EBRx PA Criteria (medical benefit)

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

Criteria for new users
1. Diagnosis of either metastatic OR recurrent locally advanced Merkel cell carcinoma
2. Disease has not progressed on another immune checkpoint inhibitor, such as pembrolizumab (Keytruda) or nivolumab (Opdivo)
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:

1. Zynyz Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761334s000lbl.pdf. Accessed 5/15/2023.
2. Grignani G, Rutkowski P, Lebbe C, et al545 A phase 2 study of retifanlimab in patients with advanced or metastatic merkel cell carcinoma (MCC) (POD1UM-201)Journal for ImmunoTherapy of Cancer 2021;9:doi: 10.1136/jitc-2021-SITC2021.545
3. NCCN Guidelines. Merkel Cell Carcinoma Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf.

Quantity Limits: n/a

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 ≥12y old.
- Deficiency of interleukin-1 receptor antagonist: maintenance of remission of deficiency of IL-1 receptor antagonist in adults and peds patients weighting ≥10kg.
- Recurrent pericarditis, to reduce risk of recurrence in adults and peds patients ≥12y 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 Syndroem (FCAS) and Muckle Wells Syndrome (MWS)
2. The patient must be the appropriate age according to the FDA label. (age 12y+)
3. The patient must not be on concomitant TNF-alpha antagonists.
4. The patient has been educated to avoid getting live vaccines while on rilonacept.
If approved, the PA will be for 12 months.
Notes: Adults: LD=320mg delivered as 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 12y+ when all the following are met: Has additional pericarditis episodes following a symptom-free period of 4-6 weeks or longer, AND Has failed therapy with colchicine and non-steroidal anti-inflammatory drugs (NSAIDs).
If approved, the PA will be for 12 months.

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

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
- Moderately to severely active Ulcerative Colitis in adults

Plaque Psoriasis
1. Age is ≥18 years
2. The patient must have the diagnosis of plaque psoriasis that is moderate to severe defined as meeting all of the following requirements: • Body surface area (BSA) involvement of ≥5% • 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 • Psoriasis Area and Severity Index (PASI) score ≥12
3. If the patient ALSO HAS the diagnosis of psoriatic arthritis, approve Skyrizi without requiring prior therapy.
4. The patient must have failed 3 consecutive months of systemic or topical, non-biologic therapy including these options: • systemic therapy: methotrexate or cyclosporine or acitretin systemic therapy • phototherapy (broadband ultraviolet B (UVB), narrowband UVB, and psoralen with ultraviolet A (PUVA) • topical treatments (calcineurin inhibitors (tacrolimus or pimecrolimus), topical corticosteroids, vitamin D analogs (calcipotriene), topical retinoids (tazarotene))
If criteria met, approve for 12 months.

Psoriatic Arthritis (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 3 months of a DMARD therapy (examples: methotrexate, sulfasalazine, penicillamine, azathioprine, leflunomide).
6. Trial of adalimumab for 12 weeks
References: 1. DERP. Report on Targeted Immune Modulators Update 3/8/12. 2. Treatment of Psoriatic Arthritis. UpToDate. http://www.uptodate.com/contents/treatment-of-psoriatic-arthritis?source=search_result&search=psoriatic+arthritis&selectedTitle=2%7E105#H18 . Accessed 7/3/12. 3.Treatment of Psoriatic Arthritis: UpToDate. https://www-uptodate-com.libproxy.uams.edu/contents/treatment-of-psoriatic-arthritis?search=treatment%20of%20psoriatic%20arthritis&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1. Accessed 08/12/24

Crohn's Disease
1. Age is ≥18 years
2. The patient must have the diagnosis of active Crohn's disease
3. Crohn's Disease Activity Index (CDAI) is 220 to 450 and Simple Endoscopic Score for Crohn's disease (SES-CD) is ≥6 (or ≥4 for isolated ileal disease)
4. Inadequate response, loss of response, or intolerance to oral aminosalicylates (e.g. mesalamine, sulfasalazine), corticosteroids, or immunosuppressants (e.g. azathioprine, mercaptopurine, methotrexate)
If criteria met, approve for 12 months.

Quantity Limits: 30 day supply

Ulcerative Colitis
1. Age is ≥ 18 years
2. The patient must have the diagnosis of active moderate or active severe Ulcerative Colitis (Mayo Score of 6-12)
3. Inadequate response or intolerance to adalimumab (defined as no improvement after 8 weeks of therapy) • Adalimumab may be used with or without an immunomodulator
If criteria is met approve for 16 weeks
• Dosing: o Induction: IV: 1,200MG at weeks 0, 4, and 8 o Maintenance SubQ: 180-360mg at week 12 and every 8 weeks thereafter (use lowest effective dosage to maintain therapeutic response.
If improvement/remission seen after 16 weeks approve SubQ dose for one year.

References:

1. Risankizumab: Drug information; UpToDate; https://www-uptodate-com.libproxy.uams.edu/contents/risankizumab-drug-information?source=auto_suggest&selectedTitle=1~1---1~4---skyri&search=skyrizi; accessed 07/19/24
2. Cohen,R, Stein, A, et al; Management of moderate to severe ulcerative colitis in adults; UptoDate; https://www-uptodate-com.libproxy.uams.edu/contents/risankizumab-drug-information?source=auto_suggest&selectedTitle=1~1---1~4---skyri&search=skyrizi; accessed 07/19/2024

Rozanolixizumab-NOLI (Rystiggo) 280mg/2mL for SC injection, SDV—FOR MEDICAL EBRx PA Criteria

is FDA-approved for: treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody +.

Criteria for new users
1. The patient must have the diagnosis of generalized myasthenia gravis (gMG) with anti-acetylcholine receptor or anti-muscle-specific tyrosine kinast (MuSK) antibody+.
2. The patient must be on stable myasthenia gravis therapy including acetylcholinesterase inhibitors, steroids, nonsteroidal immunosuppressive therapies, either in combo or alone.
3. The patient must have serum IgG levels ≥5.5g/L.
If the patient is approved, the PA is good for 2 months

Criteria for continuation
1. The patient must have some improvement in QOL after 2 months. Specifically, the MG-ADL score or the QMG grading system showing improved muscle weakness must be improved. Physician attestation is accessible.
If approved, PA is good for 12 months.

Note: Dosing, once weekly for 6 weeks:

Body Weight	Dose	Volume to be infused
<50kg	420mg	3mL
50 to <100kg	560mg	4mL
100kg +	840mg	6mL

If the dose is missed, it may be administered up to 4 days after the scheduled time point.

References:
1. Package Insert, Rystiggo. Accessed 8/25/23.
2. Barnett, Carolina, et al. "Measuring clinical treatment response in myasthenia gravis." *Neurologic clinics* 36.2 (2018): 339-353.

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 metastatic hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting SEE CRITERIA
- Locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PDL1) inhibitor. (Accelerated approval) NOT COVERED
    - Data limited to single arm trial with response rates reported only.
        - Reference: Tagawa ST et al. TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. J Clin Oncol. 2021 Apr 30:JCO2003489. doi: 10.1200/JCO.20.03489. Epub ahead of print. PMID: 33929895.
        - Ongoing RCT with primary completion date: 10/2024: NCT04527991

Triple Negative Breast Cancer
1. Diagnosis of unresectable locally advanced or metastatic breast cancer
2. Disease is HER2 negative (IHC 0, IHC 1+ or IHC 2+/ISH–)
3. Disease is refractory to or relapsed after two or more prior systemic therapies
4. Patient has been treated with at least one regimen for advanced/metastatic disease.
5. Sacituzumab will be used as single agent
If criteria met, approve for 12 months. Therapy continues until disease progression.

HR+ Breast Cancer
1. Diagnosis of metastatic breast cancer
2. Disease is HER2 negative (IHC 0, IHC 1+ or IHC 2+/ISH–)
3. Disease is estrogen and/or progesterone receptor positive (i.e. ER+, PR+, HR+).
3. 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)
4. Patient has received at least one prior endocrine therapy (e.g. tamoxifen, anastrozole, letrozole, exemestane fulvestrant)
5. Sacituzumab will be used as single agent
If criteria met, approve for 12 months. Therapy continues until disease progression.

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:
Bardia A, Tolaney SM, Loirat D, et al: ASCENT: A randomized phase III study of sacituzumab govitecan vs treatment of physician's choice in patients with previously treated metastatic triple-negative breast cancer. ESMO Virtual Congress 2020. Abstract LBA17. Presented September 19, 2020. https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/ascent-a-randomized-phase-iii-study-of-sacituzumab-govitecan-sg-vs-treatment-of-physician-s-choice-tpc-in-patients-pts-with-previously-treat

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:
Rugo HS et al. Sacituzumab Govitecan in Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer. J Clin Oncol. 2022 Oct 10;40(29):3365-3376. doi: 10.1200/JCO.22.01002. Epub 2022 Aug 26. PMID: 36027558.

Quantity Limits: n/a (medical benefit drug)

Sarilumab (Kevzara) 150mg/1.14ml; 200mg/1.14ml injection (SQ)
EBRx PA Criteria

is FDA-approved for:

- **Polymyalgia Rheumatica**: treatment of adult patients with polymyalgia rheumatica who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper
- **Rheumatoid arthritis**: treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to 1 or more disease modifying antirheumatic drugs

Rheumatoid Arthritis
Med impact: Trial of 2 preferred agents (Enbrel, Humira, Xeljanz, Amjevita, Cyltezo, Cimzia, Hyrimox, Simponi)
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 15-25 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 15-25mg 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:
1. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of RA with synthetic and biological DMARDs: 2013 update. Ann Rheum Dis. 2014;73:492-509.
2. Moreland LW, O'Dell JR, et al. A randomized comparative effectiveness study of triple therapy versus etanercept plus methotrexate in early aggressive RA. TEAR Trial. Arthritis & Rheumatism. 2012;64(9):2824-2835.
3. O'Dell JR, Mikuls TR, et al. Therapies for active RA after methotrexate failure. N Engl J Med. 2013;369:307-18.
4. Van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early RA (Swefot trial): 1-y results of a randomized trial. Lancet. 2009;374:459-66.
5. Van Vollenhoven RF, Geborek P, Forslind K, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early RA: 2 y follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012;379:1712-20.
6. Bathon JM, McMahon DJ. Making rational treatment decisions in RA when methotrexate fails. N Engl J Med. 369;4:384-85.
7. Singh, Jasvinder A., et al. "2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis." *Arthritis & rheumatology* 68.1 (2016): 1-26.
8. Singh, Jasvinder A. "Treatment guidelines in rheumatoid arthritis." *Rheumatic Disease Clinics of North America* 48.3 (2022): 679-689.

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]

Baseline PSA (ng/ml)	Median OS (sipuleucel T vs placebo; months)	HR (95% CI)
≤22.1	**41 vs. 28**	**0.51 (0.31-0.85)**
>22.1 – 50.1	27 vs 20	0.74 (0.47-1.17)
>50.1-134.1	20 vs 15	0.81 (0.52-1.24)
>134	18 vs 16	0.84 (0.55-1.29)

Dosing:
Sipuleucel T is administered as 3 IV infusions, given 2 weeks apart. The sipuleucel T product is manufacturered by taking a sample of the patient's antigen presenting cells (via apheresis) and sensitizing them to prostatic acid phosphatase (PAP), which is expressed on prostate tumors. The cells are reinfused into the patient, and they elicit a T cell response against cells expressing PAP. The most common side effects are fever, fatigue, and headache.

References:
1. Kantoff PW et al. Sipuleucel T Immunotherapy for castration-resistant prostate cancer. NEJM 2010; 363:411-422. PMID 20818862
2. Schellhammer PF et al. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the immunotherapy for prostate adenocarcinoma treatment (IMPACT) trial. Urology 2013 Jun;81(6):1297-302. PMID 23582482
3. NCCN Prostate Cancer Guidelines. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 3/17/2020.

ECOG Performance Status
0 – Fully active, able to carry on all pre-disease performance without restriction
1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (light house work, office work)
2 – Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than about 50% of waking hours
3 – Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4 – Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5 - Dead

Quantity Limits: n/a

Talquetamab-tgvs (Talvey) 3 mg/1.5 ml and 40 mg/ml single-dose vials
EBRx PA Criteria

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

Criteria for new users
1. Diagnosis of multiple myeloma (MM)
2. Patient has been treated with at least 4 prior lines of therapy (i.e. 4 different regimens). Note: Stem cell transplant does not qualify as a line of therapy
3. Patient has been previously treated with a proteosome inhibitor Note: Available proteosome inhibitors include bortezomib (Velcade), carfilzomib (Kyprolis), and ixazomib (Ninlaro)
4. Patient has been previously treated with an immunomodulatory agent Note: Immunomodulatory agents include lenalidomide (Revlimid), thalidomide (Thalomid), polmalidomide (Pomalyst)
5. Patient has been previously treated with an anti-CD38 monoclonal antibody Notes: Anti-38 monoclonal antibodies include daratumumab, isatuximab
If criteria met, approve for 1 year

Note: Talquetamab may be dosed on a weekly or biweekly basis

TALVEY Weekly Dosing Schedule (2.2)

Dosing schedule	Day	Dose[a]	
Step-up dosing schedule	Day 1	Step-up dose 1	0.01 mg/kg
	Day 4[b]	Step-up dose 2	0.06 mg/kg
	Day 7[b]	First treatment dose	0.4 mg/kg
Weekly dosing schedule	One week after first treatment dose and weekly thereafter[c]	Subsequent treatment doses	0.4 mg/kg once weekly

TALVEY Biweekly (Every 2 Weeks) Dosing Schedule (2.2)

Dosing schedule	Day	Dose[a]	
Step-up dosing schedule	Day 1	Step-up dose 1	0.01 mg/kg
	Day 4[b]	Step-up dose 2	0.06 mg/kg
	Day 7[b]	Step-up dose 3	0.4 mg/kg
	Day 10[c]	First treatment dose	0.8 mg/kg
Biweekly (every 2 weeks) dosing schedule	Two weeks after first treatment dose and every 2 weeks thereafter[d]	Subsequent treatment doses	0.8 mg/kg every 2 weeks

Talquettamab was studied in a single arm trial (MonumentTAL-1) which, in the FDA approved population, reported a response rate of 73% and 12-month overall survival of ~76% which compares favorably with other therapies used in this setting.

References:

1. Talquetamab (Tavey) PI. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TALVEY-pi.pdf. Accessed 8/25/2023.
2. Chari A et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. N Engl J Med. 2022 Dec 15;387(24):2232-2244. doi: 10.1056/NEJMoa2204591. Epub 2022 Dec 10. PMID: 36507686. NCT03399799
3. Schinke C et al. Pivotal Phase 2 MonumenTAL-1 Results of Talquetamab, a GPRC5D×CD3 Bispecific Antibody, for Relapsed/Refractory Multiple Myeloma. Poster presentation (#8036) at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting. June 2023.

Tarlatamab (Imdelltra) 1 mg and 10 mg vials
EBRx PA Criteria

is FDA-approved for:
Treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy

Criteria for new users
1. Diagnosis of extensive stage small cell lung cancer (SCLC)
2. SCLC has progressed on or after platinum-based chemotherapy (e.g. cisplatin or carboplatin plus etoposide)
Approve if both criteria met. Therapy continues until disease progression or unacceptable toxicity.
Dose: 1 mg IV infusion step-up dose followed by 10 mg IV infusion biweekly on day 1 and 15 of each cycle. Treat until disease progression or unacceptable toxicity. First 2 doses require monitoring for 24 hours. Reference: Ahn, Myung-Ju, et al. "Tarlatamab for patients with previously treated small-cell lung cancer." New England Journal of Medicine 389.22 (2023): 2063-2075.

Quantity Limits: n/a (medical benefit drug)

Tislelizumab (Tevimbra) 100 mg/10 mL single-dose vial
EBRx PA Criteria

is FDA-approved for:

- the treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor

Criteria for new users (Esophageal Squamous Cell Carcinoma)
1. Diagnosis of metastatic or unresectable esophageal squamous cell carcinoma
2. Progression on or after prior systemic chemotherapy that did not include a PD-1 or PD-L1 inhibitor
3. Lack of active brain or leptomeningeal metastases (stable or treated metastasis are acceptable)
If all of the above criteria are met, approve for 1 year

Notes:
Tislelizumab was compared to investigator's choice of chemotherapy (paclitaxel, docetaxel, or irinotecan) in patients with metastatic or unresectable esophageal squamous cell carcinoma who had progressed after prior systemic chemotherapy without previous PD-1 or PD-L1 inhibitor exposure (n=512). Patients in the tislelizumab group had improved overall survival (OS) (8.6 vs. 6.3 months; HR 0.7; p=0.0001). The OS rate at 12 months was 37.4% in the tislelizumab arm vs. 23.7% in the chemotherapy arm. This benefit was seen regardless of PD-L1 expression. Patients in the tislelizumab group also exhibited lower rates of grade 3 or higher adverse events compared to chemotherapy (18.8% vs. 55.8%).[1]

Dose: 200 mg IV once every 3 weeks until disease progression or unacceptable toxicity

References:

1. Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-302): A Randomized Phase III Study. J Clin Oncol. 2022 Sep 10;40(26):3065-3076. doi: 10.1200/JCO.21.01926. Epub 2022 Apr 20. Erratum in: J Clin Oncol. 2024 Feb 1;42(4):486. doi: 10.1200/JCO.23.02629. PMID: 35442766; PMCID: PMC9462531.

Toripalimab (Loqtorzi) 240 mg/6 mL (40 mg/mL) single-dose vial
EBRx PA Criteria

is FDA-approved for:

- in combination with cisplatin and gemcitabine, for first-line treatment of adults with metastatic or with recurrent locally advanced nasopharyngeal carcinoma (NPC)
- as a single agent for the treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy

Criteria for new users
1. Diagnosis of nasopharyngeal carcinoma (NPC)
2. NPC is metastatic or recurrent
3. If disease has progressed on or after previous platinum-based therapy, toripalimab will be used as monotherapy
4. If no prior NPC treatment, toripalimab will be used in combination with cisplatin and gemcitabine. Note: if carboplatin is being used instead of cisplatin, ok to approve if there is documentation of reason (e.g. not a good candidate for cisplatin due to age or baseline renal dysfunction)
If 1, 2 and EITHER 3 OR 4 are met, approve for 12 months.

Note:
Toripalimab 240 mg IV every 3 weeks or 3 mg/kg IV every 2 weeks is given until disease progression or unacceptable toxicity.

The JUPITER-02 trial treated NPC patients with no prior therapy with toripalimab in combination with cisplatin/gemcitabine OR to cisplatin/gemcitabine alone. Overall survival was improved in the toripalimab arm (HR0.63).

The POLARIS-02 trial studied toripalimab monotherapy in NPC patients who had progressed on or after platinum-containing chemotherapy. Results compared favorably with alternatives in this setting.

Ustekinumab (Stelara) PA Criteria
45 mg/0.5mL (0.5mL), 90mg/mL (1mL)

FDA approved indications:

- **Plaque Psoriasis:** indicated for the treatment of adult and pediatric patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
- **Psoriatic arthritis**: indicated for the treatment of active psoriatic arthritis in adult and pediatric patients aged 6 years or older. Ustekinumab may be used alone or in combination with methotrexate).
- **Crohn's Disease**: indicated for the treatment of moderately to severely active Crohn disease in adults who failed or were intolerant to treatment with 1 or more tumor necrosis factor blockers or the treatment of moderately to severely active Crohn disease in adults who failed or were intolerant to immunomodulator or corticosteroid therapy, but never failed treatment with a tumor necrosis factor blocker
- **Ulcerative colitis**: indicated for the treatment of moderately to severely active ulcerative colitis in adults

Plaque psoriasis	
Initial request	
1. The patient has 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.	
2. The patient had an inadequate response despite 3 months of methotrexate 25mg per week **OR** The patient experience intolerance to methotrexate **OR** The patient has a contraindication to methotrexate.	
3. The patient had an inadequate response despite at least 3 months of treatment with at least 1 other conventional systemic agents for psoriasis (cyclosporine, or psoralen plus ultraviolet A). **OR** The patient is intolerant to or have a contraindication to at least 1 of those treatments	
4. The patient must have tried and failed Humira (for a minimum of 12 weeks) AND must have tried and failed Enbrel (for a minimum of 12 weeks) prior seeking ustekinumab.	
If the answer to 1, 2, AND 3 is yes, approve coverage for 28 weeks (4 doses).	
Responders maintenance therapy	
The patient has achieved a reduction in PASI of at least 50%	
If the answer was yes, patient is approved for therapy for 1 year (4 doses).	

References:
1. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371:1665-74.
2. Lin VW, Ringold S, Devine EB. Comparison of ustekinumab with other biological agents for the treatment of moderate to severe plaque psoriasis, A Bayesian Network Meta-analysis. Arch Dermatol. Oct 2012; E1-E8.
3. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675-84.
4. Griffiths CE, Strober BE, Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010;362:118-28.

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

Psoriatic Arthritis (must be used in combo with DMARD)
Med Impact: Preferred
1. The patient must have a diagnosis of psoriatic arthritis
2. The patient must have failed 3 months of a DMARD therapy (examples: methotrexate, sulfasalazine, penicillamine, azathioprine, leflunomide).
3. Trial of adalimumab for 12 weeks

References:
1. DERP. Report on Targeted Immune Modulators Update 3/8/12.
2. Treatment of Psoriatic Arthritis. UpToDate. http://www.uptodate.com/contents/treatment-of-psoriatic-arthritis?source=search_result&search=psoriatic+arthritis&selectedTitle=2%7E105#H18 . Accessed 7/3/12.
3.Treatment of Psoriatic Arthritis: UpToDate. https://www-uptodate-com.libproxy.uams.edu/contents/treatment-of-psoriatic-arthritis?search=treatment%20of%20psoriatic%20arthritis&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1. Accessed 08/12/24

Note: Dose for psoriatic arthritis is 45 mg. Drug is dosed at weeks 0 and 4, then every 12 weeks thereafter.

Crohns Disease
1. The patient must have the diagnosis of Crohns disease.
2. The patient must have a Crohn's Disease Activity Index of 220-450 (out of 600).
3. The patient must have tried and failed Humira (for a minimum of 12 weeks) prior seeking ustekinumab.
If the patient satisfies the criteria above, PA is approved for 1 year.
References: 1. Feagan, Brian G., et al. "Ustekinumab as induction and maintenance therapy for Crohn's disease." *New England Journal of Medicine* 375.20 (2016): 1946-1960.

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:

1. Drug Effectiveness Review Project. Targeted Immune Modulators Update 3/8/12.
2. Kornbluth A, Sachar DB, The Practice Parameters Committee of the American College of Gastroenterology. Ulcerative Colitis practice guidelines in adults: ACG, Practice Parameters Committee. *Am J Gastroenterol* 2010; 105:501–523.

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).

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

is FDA-approved for:

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

Crohn's Disease indication **Criteria for new users**
The patient must have the diagnosis of active, moderate to severe Crohn's disease.
The patient must be age 18y+.
The patient must have failed treatment with, or is dependent on corticosteroids, as defined by the following: a. Signs and symptoms of persistent, active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily, PO for two weeks or IV for 1 week ***OR*** b. 2 failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily PO on 2 separate occasions ***OR*** c. History of intolerance of corticosteroids (including, but not limited to: Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, or infection)
The patient must have tried and failed combination TNF inhibitor + immunomodulator (eg, azathioprine, 6-mercaptopurine, or methotrexate)
The patient should not be on combination biologic drugs.

Ulcerative Colitis indication **Criteria for new users**
The patient must have the diagnosis of moderate to severe ulcerative colitis.
The patient must be age 18y+.
The patient must not be taking concurrent combination biologic drugs.
Note: Vedolizumab may be used for induction of remission in UC as initial therapy.

References:
1. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 369;8. Aug 22, 2013. Accessed July 17, 2014.
2. Sands BE, Feagan BG, et al. Effects of vedolizumab induction therapy for patients with CD in whom TNF treatment failed. (GEMINI3) Gastroenterology. 2014;147:618-27.
3. UpToDate. Management of moderate to severe UC in adults.

Zolbetuximab-clzb (Vyloy) 100 mg lyophilized powder single dose vial
EBRx PA Criteria

is FDA-approved for:

- first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA-approved test, in combination with fluoropyrimidine- and platinum-containing chemotherapy.

Criteria for new users (locally advanced or metastatic gastric or GEJ adenocarcinoma)
1. Diagnosis of locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma
2. Has not received prior treatment for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma
3. Tumor is negative for HER2 and positive for CLDN-18.2
4. No central nervous system metastases
If all above criteria are met, approve for 1 year. May renew annually until progression or intolerance.
Note: Dose: 800 mg/m^2 x1, then 600 mg/m^2 every 3 weeks or 400 mg/m^2 every 2 weeks Compared to chemotherapy alone, zolbetuximab-clzb in combination with chemotherapy significantly improved overall survival in 2 different studies. 1. SPOTLIGHT (zolbetuximab-clzb + mFOLFOX6) – HR 0.75 (0.60-0.94) – 18.2 months vs. 15.5 months 2. GLOW (zolbetuximab-clzb + CAPOX) – HR 0.77 (0.62-0.97) – 14.4 months vs. 12.2 months References: 1. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomized, double-blind, phase 3 trial. Lancet. 2023 May 20;401(10389):1655-1668. doi: 10.1016/S0140-6736(23)00620-7. Epub 2023 Apr 15. PMID: 37068504 2. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med. 2023 Aug;29(8):2133-2141. Doi: 10.1038/s41591-023-02465-7. Epub 2023 Jul 31. PMID: 37524953.