Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Washington Pharmacy Advisory Committee Meeting

April 17th, 2019

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Agenda Topics

- Overview of Disease State
- Indications
- Dosage & Formulations
- Guideline Updates

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Patisiran (Onpattro™)

Overview of Disease State - Patisiran (Onpattro™) and Inotersen (Tegsedi™)

- Hereditary ATTR amyloidosis (hATTR)
  - Polyneuropathy of hATTR amyloidosis, previously referred to as transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare, progressive, and fatal disease
  - About 50,000 people worldwide have hATTR amyloidosis
  - An inherited disease (passed down through families) that often affects the liver, nerves, heart and kidneys
  - hATTR amyloidosis is characterized by the deposit of an abnormal protein called amyloid in multiple organs of the body where it should not be, which causes disruption of organ tissue structure and function
  - In hereditary amyloidosis, amyloid deposits most often occur in tissues of the nervous system, heart, and digestive tract
    - The first symptoms of hATTR amyloidosis typically appear between the mid-20s to the mid-60s, involve multiple tissues and organs and often seem unrelated
      - Ocular: Visual changes
      - Nephropathy: Damages to kidneys
      - Spinal Stenosis: Pain, tingling, or numbness along the spine caused by pressure of the nerves in the spine due to narrowing spinal cavity
      - Bilateral Carpal Tunnel Syndrome: Numbness and tingling in the hands and arms caused by a pinched nerve in the wrists
  - While there are other approved disease modifying agents in Europe and Japan, such as tafamidis, none are available in the US
    - Prior to the approval of patisiran (Onpattro) and Inotersen (Tegsedi) , treatment options for hATTR amyloidosis were limited and included mainly symptomatic management
      - For immediate resolution of neuropathic pain, analgesics (e.g., diflunisal) are recommended

Patisiran (Onpattro™) – Indication, Dosing/Availability

Drug	Indications
Patisiran (Onpattro™)	• Directed small interfering RNA (siRNA) and is indicated for the treatment of adults with polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults

Drug	Adult Dosing	Availability

Patisiran (Onpattro™)	**Dosing**
	• For patients weighing < 100 kg, the recommended dose is 0.3 mg/kg once every 3 weeks
	• For patients weighing ≥ 100 kg, the recommended dose is 30 mg once every 3 weeks
	• A healthcare professional should administer the intravenous (IV) infusion of patisiran
	• Patisiran should be administered as soon as possible in the event of a missed dose
	  • If administered ≤ 3 days of the missed dose, the patient's original dosing schedule should be continued
	  • If it has been > 3 days after the missed dose, dosing schedule should be continued every 3 weeks from the new administration date
	
	Premedication
	• Recommended at least 60 minutes prior to the start of the patisiran infusion to reduce the risk of IRRs
	• The premedications that should be administered include:
	  • IV corticosteroid (dexamethasone 10 mg or equivalent)
	  • oral acetaminophen (500 mg)
	  • IV H1 blocker (diphenhydramine 50 mg or equivalent)
	  • IV H2 blocker (ranitidine 50 mg or equivalent)
	• If certain premedications are not available or if the patient cannot tolerate them intravenously, medications that are equivalent may be given orally
	• If patients are tolerating their patisiran infusions but are experiencing adverse reactions to their corticosteroid premedication, the premedication can be reduced to a minimum dose of 5 mg IV dexamethasone (or equivalent) by 2.5 mg increments
	• Additional or higher doses of the premedications may be required in some patients to reduce their risk of IRRs
		Single-dose vial
		10 mg/5 mL
		(2 mg/ mL)

Patisiran (Onpattro™) – Additional Information

- Pediatrics
  - The safety and effectiveness of patisiran has not been established in pediatric patients
- Pregnancy
  - Data on patisiran use in pregnant women is not available
- Warnings/Contraindications
  - Infusion-related reactions (IRRs) have occurred in patients that have received treatment with patisiran
    - To reduce this risk of IRRs, all patients in clinical studies received premedication with a corticosteroid, acetaminophen, and antihistamines
    - Occurrence of IRRs lead to an infusion interruption in 5% of patients and further led to a permanent discontinuation of patisiran in <1% of patients
    - Most common symptoms of IRRs included flushing, back pain, nausea, abdominal pain, dyspnea, and headache
  - Patisiran infusion also may lead to a decrease in serum vitamin A levels
    - It is advised for patients receiving patisiran to take daily vitamin A supplements at the recommended allowance
    - Doses of vitamin A higher than the recommended daily allowance should not be given in order to achieve normal serum vitamin A levels, as serum vitamin A levels do not accurately depict the body's total vitamin A
    - If ocular symptoms occur that suggest vitamin A deficiency (e.g., night blindness), the patient should be referred to an ophthalmologist
  - The most commonly observed adverse reactions in clinical trials were upper respiratory tract infections and infusion-related reactions
    - Reactions occurred in at least 10% of patisiran-treated patients and this occurrence was 3% more frequent than in patients receiving placebo
- Hepatic and Renal Impairment
  - No dose adjustment is necessary
- Geriatric Patients
  - In patients ≥ 65 and older, there is no required dose adjustment
  - In the placebo-controlled study, a total of 62 patients that were ≥ 65 or older, including 9 patients that were ≥ 75 or older, received patisiran. There was no overall differences in safety or effectiveness, but some older patients did have greater sensitivity

Patisiran (Onpattro™) – Place In Therapy

- APOLLO Study
  - A multicenter, international, randomized, double-blind, placebo-controlled, phase 3 trial of patisiran in patients with polyneuropathy caused by hATTR amyloidosis
  - In this study, patients with hATTR amyloidosis with polyneuropathy were randomly assigned in a 2:1 ratio, to receive IV patisiran (0.3 mg/kg) (n=148) or placebo (normal saline 0.9%) (n=77) every 3 weeks for 18 months
  - Patients
    - Patients ranged from 18 to 85 years old and received premedications at least an hour before each infusion to reduce their risk of IRR
      - Premedications included dexamethasone, oral acetaminophen/parcetamol, an H2 blocker (ranitidine or famotidine), and an H1 blocker (diphenhydramine)
  - Endpoints
    - Primary endpoint was the change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7; range of 0 to 304 with higher scores indicating more impairment) at 18 months
    - Secondary endpoints included quality of life, motor strength, disability, gait speed, nutritional status, and patient-reported autonomic symptoms
    - At baseline, 9 months, and 18 months, all efficacy endpoints were assessed
    - At 18 months, change from baseline in the mNIS+7 was significantly lower with patisiran than with placebo
  - Results:
    - The mean (±SD) mNIS+7 at baseline was 80.9 ± 41.5 in the patisiran group and 74.6 ± 37 in the placebo group
    - At 18 months, the least-squares mean (±SE) change in mNIS+7 from baseline was −6 ± 1.7 with patisiran, as compared with 28 ± 2.6 with placebo (least-squares mean difference, −34 points; 95% confidence interval [CI], −39.9 to −28.1; **p<0.001**)
    - A positive effect of patisiran on mNIS+7 was observed as early as 9 months
    - Secondary endpoints, including quality of life, gait speed, and nutritional status were all statistically significant favoring the patisiran treatment
    - A total of 40 patients discontinued the trial, of which, 29 patients discontinued in the placebo group and 11 patients discontinued from the active treatment group
  - **A phase III multicenter, open-label, extension study that evaluates the long-term safety and efficacy of patisiran is currently enrolling. The estimated completion date is July 2019**

Patisiran (Onpattro)
Apple Health Policy

Washington State Health Care Authority

Indications and Products

- Hereditary transthyretin-mediated amyloidosis (hATTR)
  - patisiran (Onpattro)

- hATTR was previously known as transthyretin familial amyloid polyneuropathy (FAP)

hATTR Policy: Initial Criteria

- Patient is age 18 or older; **AND**
- Diagnosis of hATTR/FAP as documented by evidence of polyneuropathy and pathogenic TTR variant using molecular genetic testing; **AND**
- Documentation of baseline disease severity, such as using Neuropathic Impairment Score (NIS) or Polyneuropathy Disability (PND); **AND**
- Documentation of baseline disease severity as evidenced by other measurable factors (eg: quality of life, motor strength, disability, gait speed, etc…); **AND**
- Patisiran is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis; **AND**

hATTR Policy: Initial Criteria (continued)

- Patient is not currently taking inotersen, difunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid; **AND**
- Patient has no history of liver transplant or patient has planned liver transplant in the future; **AND**
- Patient does not have severe renal impairment, end-stage renal disease, or moderate-severe hepatic impairment.

- If ALL criteria are met, the request will be approved for 12 months.

hATTR Policy: Reauthorization Criteria

- Documentation of positive clinical response as provided by NIS or PND or other baseline measures of function.

- If ALL criteria are met, the request will be approved for 12 months.

Motion

- “I move that the Apple Health Medicaid Program implement the clinical criteria listed on slides 10-12 as recommended.”
  - Motion: Figueroa
  - 2nd: Buccola

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Inotersen (Tegsedi™)

Inotersen (Tegsedi™) – Indication, Dosing/Availability

Drug	Indications
Inotersen (Tegsedi™)	• A transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults

Drug	Adult Dosing	Availability
Inotersen (Tegsedi™)	**Recommended dose** • 284 mg via subcutaneous (SC) injection once weekly • Possible injection sites include clean, intact skin of the abdomen, upper thigh, or outer area of the upper arm, and injection sites should be rotated • Inotersen should be administered as soon as possible in the event of a missed dose. If inotersen is administered within 4 days of the missed dose, the patient's original dosing schedule should be continued • If it has been more than 4 days after the missed dose, the missed dose should be skipped and the dosing schedule should be resumed on the next scheduled administration date • Patients and/or caregivers can administer subsequent doses after being taught proper SC injection technique, and each dose of inotersen should be administered on the same day each week • A healthcare professional should administer the first SC dose of inotersen • While inotersen requires refrigeration, prefilled syringes should be removed at least 30 minutes prior to use to allow of injections at room temperature	**Single-dose vial** 284 mg/1.5 mL

Inotersen (Tegsedi™) – Additional Information

- Pediatrics
  - The safety and effectiveness of inotersen has not been established in pediatric patients
- Pregnancy
  - Data on inotersen use in pregnant women is not available
  - However, since inotersen therapy could cause a decrease in serum vitamin A levels, which is essential for normal embryofetal development, it is advised for patients to take vitamin A supplements
- Hepatic and Renal Impairment
  - Renal Impairment:
    - A dose adjustment is not required in patients who have mild to moderate renal impairment or mild hepatic impairment
    - The use of inotersen has not yet been studied in patients with severe renal impairment, end-stage renal disease (ESRD), or severe hepatic impairment
- Geriatric Patients
  - In patients ≥ 65 years old, there is no required dose adjustment
- Drug Interactions
  - Should be administered cautiously in patients who take medications that affect platelets including both prescription (e.g., antiplatelet drugs, such as, adenosine, clopidogrel, prasugrel, etc) and over-the-counter (e.g., aspirin, non-steroidal anti-inflammatory drugs [NSAIDs]) products, due to the risk of thrombocytopenia
  - In addition, patients who take nephrotoxic medications or medications which may impair renal function should use inotersen cautiously due to the risk of glomerulonephritis

Inotersen (Tegsedi™) – Additional Information

- Warnings/Contraindications
  - The most commonly observed adverse reactions in clinical trials were **injection site reactions**, **nausea**, **headache**, **fatigue**, **thrombocytopenia**, and **fever**
    - These adverse reactions occurred in at least 20% of patients treated with inotersen and more frequently than in patients who received placebo
  - Contraindicated in patients who have platelet counts less than 100 x 10^9/L, patients who have a history of acute inotersen-related glomerulonephritis, and in patients who have a known hypersensitivity to inotersen
  - Inotersen may cause a **stroke**, **liver problems**, and/or **serious allergic reactions**
    - Immediate medical attention should be sought for any signs or symptoms of stroke or hypersensitivity reactions
    - Prescribers should perform laboratory tests to assess hepatic function prior to initiation of inotersen and during treatment, and patients should inform their prescribers of any symptoms of hepatic injury or impairment
  - May also lead to a decrease in **serum vitamin A levels**
    - It is advised for patients receiving inotersen to take daily vitamin A supplements at the recommended allowance
    - Larger than recommended doses of vitamin A should not be given in order to achieve normal serum vitamin A levels, as serum vitamin A levels do not accurately depict the body's total vitamin A
    - If ocular symptoms occur that suggest vitamin A deficiency (e.g., night blindness), the patient should be referred to an ophthalmologist
- Black Box Warning: Risk of **thrombocytopenia** and **glomerulonephritis** and must be dispensed through REMS program
  - **Thrombocytopenia** caused by inotersen can be sudden, unpredictable, and potentially fatal
    - Treatment with inotersen requires laboratory monitoring to which patients must adhere
    - If a patient presents with signs or symptoms of thrombocytopenia, a platelet count should be obtained as soon as possible and the dose of inotersen should be held until results are available
    - In the event on uninterpretable results, which can be caused by inotersen, remeasure as soon as possible and only restart inotersen therapy once a confirmed normal platelet count is available
  - Inotersen may cause **glomerulonephritis** to the point of renal failure which requires dialysis
    - Some of these cases were also accompanied by nephrotic syndrome
    - Suspected cases of glomerulonephritis must be quickly diagnosed and treated with immunosuppressants

Inotersen (Tegsedi™) – Place In Therapy

- NEURO-TTR Study
  - An international, randomized, double-blind, placebo-controlled, phase 3 trial of patients with hATTR amyloidosis and symptoms of polyneuropathy (n=172)
  - Patients ranging from 18 to 82 years old were randomly assigned in a 2:1 ratio to receive SC inotersen 284 mg (n=113) or placebo (n=60) weekly for 65 weeks
  - Endpoints:
    - The co-primary endpoints for the trial were the change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7) and total score on the Norfolk Quality of Life–Diabetic Neuropathy (QOL-DN) at 66 weeks
  - Results
    - At 66 weeks, change from baseline in the mNIS+7 was significantly less in the inotersen group compared to the placebo group
    - The mean mNIS+7 at baseline was 80.2 in the inotersen group and 75.3 in the placebo group
    - At 66 weeks, the least-squares (LS) mean change in mNIS+7 from baseline was 5.8 with inotersen, compared to 25.5 with placebo (LS mean difference −19.7 points; 95% confidence interval [CI] −26.4, −13.0; **p<0.001**)
    - In terms of Norfolk QOL-DN, change from baseline was significantly less in the inotersen group compared to the placebo group at 66 weeks
    - The mean Norfolk QOL-DN at baseline was 48.7 in the inotersen group and 48.7 in the placebo group
    - At 66 weeks, the least-squares (LS) mean change in Norfolk QOL-DN from baseline was 1.0 with inotersen, compared to 12.7 with placebo (LS mean difference −11.7 points; 95% CI −18.3, −5.1; **p<0.001**)
    - Treated patients experienced similar benefit regardless of subgroups such as age, sex, race, region, NIS Score, Val30Met mutation status, and disease stage
  - **A phase III open-label extension (OLE) study is also being conducted to evaluate the long-term efficacy and safety of inotersen. The results of the OLE are expected after study completion in September, 2022**

Inotersen (Tegsedi)
Apple Health Policy

Washington State Health Care Authority

Indications and Products

- Hereditary transthyretin-mediated amyloidosis (hATTR)
  - inotersen (Tegsedi)

hATTR Policy: Initial Criteria

- Patient is age 18 or older; **AND**
- Diagnosis of hATTR/FAP as documented by evidence of polyneuropathy and pathogenic TTR variant using molecular genetic testing; **AND**
- Documentation of baseline disease severity, such as using Neuropathic Impairment Score (NIS) or Polyneuropathy Disability (PND); **AND**
- Documentation of baseline disease severity as evidenced by other measurable factors (eg: quality of life, motor strength, disability, gait speed, etc…); **AND**
- Patisiran is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis; **AND**

hATTR Policy: Initial Criteria (continued)

- Patient is not currently taking patisiran, difunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid; **AND**
- Patient has no history of liver transplant or patient has planned liver transplant in the future; **AND**
- Patient does not have severe renal impairment, end-stage renal disease, or moderate-severe hepatic impairment.

- If ALL criteria are met, the request will be approved for 12 months.

hATTR Policy: Reauthorization Criteria

- Documentation of positive clinical response as provided by NIS or PND or other baseline measures of function.
- If ALL criteria are met, the request will be approved for 12 months.

Motion

- "I move that the Apple Health Medicaid Program implement the clinical criteria listed on slides 21-23 as recommended."
  - Motion: Chew
  - 2nd: Huynh

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Ocrelizumab (Ocrevus™)

Overview of Disease State - Ocrelizumab (Ocrevus™)

- Multiple sclerosis (MS)
  - A complex human autoimmune-type inflammatory disease of the central nervous system (CNS)
  - More than 2.3 million people worldwide have MS
  - Although the etiology is predominantly unknown, the pathology of MS is characterized by demyelination and subsequent axonal degeneration
  - The nerve degeneration associated with MS can result in a wide variety of symptoms, including sensory disturbances (numbness, paresthesias, burning, and pain) in the limbs, optic nerve dysfunction, ataxia, fatigue, bladder, bowel, sexual dysfunction, and, ultimately, partial and complete paralysis

- At onset of the disease, MS can be categorized as
  - Either relapsing-remitting MS (observed in 85% to 90% of patients)
  - Primary progressive MS (observed in 10% to 15% of patients)

  - Relapses or “attacks” typically present subacutely, with symptoms developing over hours to several days, persisting for several days or weeks, and then gradually dissipating
  - The attacks are likely caused by the migration of activated, myelin-reactive T-cells into the CNS, causing acute inflammation with associated edema
  - The use of high-dose corticosteroids to quickly relieve MS symptoms suggests that the acute edema and its subsequent resolution underlie the clinical relapse and remission, respectively

Ocrelizumab (Ocrevus™) – Indication, Dosing/Availability

Drug	Indications
Ocrelizumab (Ocrevus™)	• Indicated for the treatment of adult patients with relapsing multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS)

Drug	Adult Dosing	Availability

Ocrelizumab (Ocrevus™)	• Initial dose of ocrelizumab is 300 mg as an IV infusion followed 2 weeks later by a second 300 mg IV infusion
	• Maintenance dose thereafter is 600 mg as an IV infusion every 6 months beginning 6 months after the first infusion
	
	• The initial 2 doses should be diluted as 300 mg in 250 mL of 0.9% sodium chloride (final concentration of 1.2 mg/mL)
	  • The infusion should start at 30 mL/hour and may be increased by 30 mL/hour every 30 minutes to a maximum rate of 180 mL/hour for a total duration of 2.5 hours or longer
	
	• Subsequent doses should be diluted as 600 mg in 500 mL of 0.9% sodium chloride (final concentration of 1.2 mg/mL). The infusion should start at 40 mL/hour and may be increased by 40 mL/hour every 30 minutes to a maximum rate of 200 mL/hour for a total duration of 3.5 hours or longer
	
	• Premedicate with 100 mg IV methylprednisolone (or an equivalent corticosteroid) 30 minutes prior to each ocrelizumab infusion and an antihistamine (e.g., diphenhydramine) 30 to 60 minutes prior to each infusion.
	  • Addition of an antipyretic (e.g., acetaminophen) may also be considered as part of the regimen
	
	• All patients should be observed for at least 1 hour following the completion of every infusion.
	
	• If a dose is missed, administer the dose as soon as possible. Subsequent doses should be administered 6 months following the rescheduled dose. Doses must be separated by at least 5 months
	  • Immediately stop infusion and permanently discontinue ocrelizumab should a life-threatening or disabling infusion reaction occur
		Injection: 300 mg/10 mL (30 mg/mL) in a single-dose vial

Ocrelizumab (Ocrevus™) – Additional Information

- Pediatrics
  - Safety and effectiveness have not been established in patients < 18 years old
- Geriatrics
  - Clinical trials did not include a sufficient population of patients ≥ 65 years old to determine if older adults respond differently from younger adults
  - Key clinical trials limited the population to adults ≤ 55 years
- Pregnancy
  - No data in pregnant women receiving ocrelizumab to inform of the drug-related risk
  - Lymphocytopenia and transient peripheral B-cell depletion have been reported in infants whose mothers were exposed to other CD20 antibodies during pregnancy
  - Ocrevus is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placenta
  - Women of childbearing potential should use contraception while undergoing treatment and for 6 months following the last Ocrevus infusion
- Warnings/Contraindications
  - Hepatitis B (HBV)
    - No cases of hepatitis B virus (HBV) reactivation in patients in clinical trials, reactivation has been reported with other anti-CD20 antibodies
    - HBV screening prior to initiation is required and contraindicated in patients with active HBV infection
  - Infusion reactions
    - Contraindicated in patients with a history of life-threatening infusion reactions
    - Include pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, pharyngeal or laryngeal edema, dyspnea, oropharyngeal pain, flushing, pyrexia, fatigue, headache, dizziness, nausea, hypotension, and tachycardia
    - HCP should:
      - Administer pre-medication (e.g., methylprednisolone or equivalent corticosteroid and an antihistamine) prior to the infusion, and use of an antipyretic may also be considered
      - Observe patients for at least 1 hour following infusion completion and inform patients that infusion reactions can occur up to 24 hours
      - Immediately and permanently stop infusion in patients with life-threatening infusion reactions

Ocrelizumab (Ocrevus™) – Additional Information

- Warnings/Contraindications (Continued)
  - Infections
    - In clinical trials, a higher proportion of patients treated with Ocrevus experienced infections compared to patients treated with placebo or interferon ß-1a (Rebif)
    - Ocrevus increased the risk of both upper and lower respiratory tract infections, skin infections, and herpes-related infections; however, no increased risk in serious infections was found
  - Progressive Multifocal Leukoencephalopathy (PML)
    - An opportunistic viral infection of the brain caused by the John Cunningham (JC) virus that primarily occurs in patients who are immunocompromised and usually leads to death or severe disability
    - No cases have not been reported with Ocrevus
      - However, cases of PML could occur as these have been reported with other anti-CD20 antibodies and other MS therapies
      - A full evaluation and work-up should occur in any patient presenting with signs and symptoms suggestive of PML
  - Live-attenuated vaccines
    - The safety of immunization with live or live-attenuated vaccines following Ocrevus use has not been evaluated
    - Administer all immunizations ≥ 6 weeks prior to initiation of Ocrevus
    - Vaccination with live-attenuated or live vaccines is not recommended during treatment and until B cell repletion upon discontinuation of Ocrevus
  - Malignancies
    - A higher rate of malignancies, including breast cancer, occurred in patients treated with Ocrevus in clinical trials compared to the active comparator (interferon ß-1a [Rebif]) or placebo
    - Patients should adhere to standard breast cancer screening guidelines
  - Additional MS Therapy
    - Ocrevus has not been studied in combination with other MS therapies
    - Additive immunosuppressive effects should be considered when using with other immunosuppressive therapy

Ocrelizumab (Ocrevus™)– Place In Therapy

- Prior to the approval of ocrelizumab, there was no pharmacologic agent FDA-approved for the treatment of PPMS
  - Thus, current treatment guidelines focus on the use of these agents for RMS

- Subcommittee of the American Academy of Neurology (AAN) and the MS Council for Clinical Practice Guidelines, which were reaffirmed in 2003 and 2008
  - Interferon beta has been demonstrated to reduce the attack rate, whether measured clinically or by MRI, in patients with MS or with clinically isolated syndromes who are at high risk for developing MS
  - It is appropriate to consider interferon beta for treatment in any patient who is at high risk for developing clinically definite MS, or who already has RMS or secondary progressive MS and is still experiencing relapses, but the effectiveness of interferon beta in patients with SPMS but without relapses is uncertain
  - These guidelines also state that glatiramer acetate has reduced the attack rate, whether measured clinically or by MRI, in patients with RMS and is appropriate to be considered for treatment in any patient who has RMS
  - Based on trial evidence, interferons and glatiramer acetate have similar clinical utility in RMS
    - Other agents were not available at the time of these statements but have since demonstrated efficacy in RMS treatment in clinical trials
  - While the AAN guidelines state no one agent has consistent data supporting its use for PPMS, other agents recommended based on their potential for benefit (possibly in select patients) include cladribine, cyclophosphamide, methotrexate, and cyclosporine
  - An update to this guideline is in progress

  - Newer agents not addressed in the clinical guidelines, with the exception of dalfampridine, have demonstrated improvement over placebo-controlled trials in ARR and other endpoints (e.g., MRI measures, disease progression); however, comparative trials are limited with MS agents to make any definitive conclusions that any one agent is superior to another. Another oral agent, dalfampridine, improves walking speed but it has no effect on the underlying disease
  - The role of ocrelizumab in the treatment of RMS has yet to be fully determined. While it has demonstrated efficacy over interferon ß-1a (Rebif) in the OPERA trials, its utility may be limited due to competition in this class and tolerability (e.g., infusion-related reactions, potential for PML)
  - As ocrelizumab is the first drug FDA-approved for PPMS and has demonstrated a benefit in disease progression in a condition for which treatment is primarily symptomatic, it will likely to play a significant role in the treatment of patients with this condition

Ocrelizumab (Ocrevus) Apple Health Policy

Washington State Health Care Authority

Indications and Products

- Relapsing remitting multiple sclerosis (RRMS)
  - ocrelizumab (Ocrevus)
- Primary progressive multiple sclerosis (PPMS)
  - ocrelizumab (Ocrevus)

RRMS Policy: Initial Criteria

- Diagnosis of RRMS; **AND**
- Patient is 18 years of age or older; **AND**
- The patient must have an inadequate response to two or more medications FDA-approved for the same indication and/or medications that are considered the standard of care; **AND**
- The patient is not concurrently taking other disease-modifying therapies for multiple sclerosis (MS); **AND**
- Test results for hepatitis B viral infection are negative;**AND**
- Dose does not exceed FDA or compendia supported limitations; **AND**

RRMS Policy: Initial Criteria (continued)

- For patients previously treated with disease-modifying drugs with long-lasting treatment effects (e.g., natalizumab, alemtuzumab), an appropriate wash-out period has elapsed prior to planned treatment with ocrelizumab.
- For patients with Expanded Disability Status Scale (EDSS) 6.5 or greater:
  - Imaging evidence of active disease; **AND**
  - Documentation of at least ONE relapsing event in the last 2 years; **AND**
  - Documentation that the provider has discussed the benefits and risks of continuing disease-modifying therapy.
- If ALL criteria are met, request will be approved for 12 months.

RRMS Policy: Reauthorization Criteria

- Documentation of clinical benefit as determined by prescriber.

- If ALL criteria are met, request will be approved for 12 months.

PPMS Policy: Initial Criteria

- Patient has a diagnosis of PPMS according to the revised McDonald Criteria; **AND**
- Patient is 18 years of age or older; **AND**
- Documentation of oligoclonal IgG bands in cerebral spinal fluid; **AND**
- T2 lesions on brain or spinal cord imaging; **AND**
- Ambulatory stage of disease (EDSS < 7); **AND**

PPMS Policy: Initial Criteria (continued)

- The patient is not concurrently taking other disease-modifying therapies for multiple sclerosis (MS); **AND**
- Test results for hepatitis B viral infection are negative;**AND**
- Dose does not exceed FDA or compendia supported limitations.

- If ALL criteria are met, request will be approved for 12 months.

PPMS Policy: Reauthorization Criteria

- Documentation of clinical benefit as determined by prescriber.

- If criteria are met, request will be approved for 12 months.

Motion

- “I move that the Apple Health Medicaid Program implement the clinical criteria listed on slides 33-38 as recommended.”
  - Motion: Flatebo
  - 2nd: Brown

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Thrombopoiesis Stimulating Proteins

Overview of Disease State – Thrombopoiesis Stimulating Proteins

- Platelets
  - Small, circulating cell particles that do not contain a nucleus and are released into the bloodstream by megakaryocytes that reside in the bone marrow and function to maintain hemostasis by aggregating and forming platelet plugs at sites of injury to limit blood loss

- Thrombocytopenia
  - Generally defined as a platelet count of $< 100 \times 10^9/L$
  - Can result in bruising, bleeding, and fatal hemorrhaging
  - Causes of thrombocytopenia include decreased bone marrow production of megakaryocytes, splenic sequestration of platelets, and increased destruction of platelets

- Immune Thrombocytopenia (ITP)
  - Previously known as “immune thrombocytopenic purpura” and “idiopathic thrombocytopenic purpura”
  - Platelet count of $< 100 \times 10^9/L$
  - An immune-mediated disorder in which platelets are opsonized by autoreactive antibodies and prematurely destroyed by the reticuloendothelial system

Overview of Disease State – Thrombopoiesis Stimulating Proteins

- Immune Thrombocytopenia (ITP)
  - In children, ITP is usually an acute, self-limiting disease that often occurs 2 to 3 weeks after a viral infection or immunization
    - Spontaneous remission in children typically occurs within 2 to 8 weeks
  - In adults, ITP has an insidious onset with no preceding viral or other illness and typically has a chronic course
    - Many adult cases of ITP are diagnosed incidentally after a routine complete blood count (CBC)
    - Signs and symptoms of ITP are highly variable and range from asymptomatic with mild bruising or mucosal bleeding to frank hemorrhage from any site
    - Severity of ITP in adults is dependent on the presence of active bleeding; platelet count; patient age; patient's lifestyle related to risk of bleeding; and presence of additional risk factors for bleeding, such as uremia or chronic liver diseases

- Primary ITP
  - Defined as an autoimmune disorder with isolated thrombocytopenia ($< 100 \times 10^9$/L) in the absence of other causes or disorders that might cause thrombocytopenia
  - Diagnosis of primary ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy
    - Primary ITP is also defined by the length of time since diagnosis – newly diagnosed (< 3 months), persistent (between 3 and 12 months), and chronic (≥ 12 months)
  - The main clinical problem of primary ITP is an increased risk of bleeding, although bleeding symptoms may not always be present
  - Secondary causes of ITP include drug-induced, autoimmune diseases such as systemic lupus erythematosus (SLE), and viral infections such as human immunodeficiency virus (HIV) and Hepatitis C
  - Severe ITP, occurring at any time, indicates bleeding which requires treatment or the occurrence of new bleeding symptoms, which requires additional treatment or increased dose to control bleeding

Overview of Disease State – Thrombopoiesis Stimulating Proteins

- Thrombocytopenia secondary to chronic liver disease (CLD)
  - Occurs in 64% to 84% of CLD patients with cirrhosis or fibrosis and 6% of CLD patients without cirrhosis
  - Liver disease-related thrombocytopenia is thought to generally be caused by decreased production (e.g., reduced thrombopoietin), splenic sequestration, and increased destruction of platelets
  - Patients with CLD often require invasive procedures and are at increased risk of bleed related to the procedures

- Treatment
  - Interventional management (e.g., partial splenic embolization [PSE], surgical splenectomy) have been used in an attempt to correct splenomegaly-associated thrombocytopenia; however, the only non-invasive tool to increase platelet count is platelet transfusion, which has risks for allergic reaction, infection, and iron overload if used chronically
  - While there are guidelines available for platelet transfusions in adults and thrombocytopenia treatment recommendations for patients with cancer or immune (idiopathic) thrombocytopenia (ITP), there are no specific guidelines for the treatment of thrombocytopenia in CLD patients who are undergoing an invasive procedure
  - Avatrombopag and lusutrombopag have been proven efficacious for the treatment of thrombocytopenia in adults with CLD who are scheduled to undergo a procedure

Thrombopoiesis Stimulating Proteins – Indications

Drugs	Generic	Indications
avatrombopag (Doptelet)	---	Treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure
eltrombopag (Promacta)	---	Treatment of thrombocytopenia in adult and pediatric patients ≥ 1 year of age with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy ▪ Eltrombopag should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding Treatment of thrombocytopenia in patients with chronic hepatitis C (HCV) to allow the initiation and maintenance of interferon-based therapy ▪ Eltrombopag should be used only in patients with chronic HCV whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy ▪ Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic HCV genotype 1 infection Treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy Eltrombopag is not indicated for the treatment of myelodysplastic syndrome (MDS)
fostamatinib disodium hexahydrate (Tavalisse)	---	Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment

Thrombopoiesis Stimulating Proteins – Indications

Drugs	Generic	Indications
Lusutrombopag (Mulpleta)	---	Treatment of thrombocytopenia in adult patients with CLD who are scheduled to undergo a procedure
romiplostim (Nplate)	---	Treatment of thrombocytopenia in patients with chronic ITP who have failed to achieve an adequate response with corticosteroids, immunoglobulins, or splenectomy ▪ Romiplostim should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increases their risk for bleeding ▪ Romiplostim is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP ▪ Romiplostim should not be used in an attempt to normalize platelet counts

Thrombopoiesis Stimulating Proteins – Dosing and Availability

Drug	Initial Dosing	Titration and/or Dosage timing	Availability
avatrombopag (Doptelet)	For patients with a platelet count of < 40 × 109/L: 60 mg dose (3 tablets) orally once daily for 5 consecutive days For patients with a platelet count of 40 × 109/L to < 50 × 109/L: 40 mg (2 tablets) orally once daily for 5 consecutive days	Begin treatment 10 to 13 days prior to the scheduled procedure The procedure should occur 5 to 8 days following the last dose of avatrombopag	20 mg tablet
fostamatinib (Tavalisse)	Initial dose is 100 mg orally twice daily	After 1 month, increase to 150 mg twice daily if platelet count is < 50 × 109/L Use the lowest dose to achieve and maintain platelet count ≥ 50 × 109/L Dosage should be reduced interrupted, or discontinued based on tolerability; a dose-reduction schedule provided in the product label Discontinue after 12 weeks if platelet count is not adequate to avoid clinically important bleeding	100 mg, 150 mg tablets
lusutrombopag (Mulpleta)	3 mg orally once daily for 7 days	Begin treatment 8 to 14 days prior to the scheduled procedure The procedure should occur 2 to 8 days following the last dose of lusutrombopag	3 mg tablet
romiplostim (Nplate)	1 mcg/kg (based on actual body weight) weekly given by subcutaneous injection Syringes used for injection should have 0.01 mL graduations	Adjust the weekly dose by increments of 1 mcg/kg until the patient achieves a platelet count ≥ 50 × 109/L as necessary to reduce the risk for bleeding; do not exceed a maximum weekly dose of 10 mcg/kg; median dose is 2 mcg/kg weekly; do not dose if platelet count > 400 × 109/L Discontinue if platelet count does not increase after 4 weeks at the maximum dose of 10 mcg/kg; avoid shaking single-use vial during reconstitution, and protect from light Administer prepared solution within 24 hours using a syringe with 0.01 mL graduations	250 mcg, 500 mcg vial

Thrombopoiesis Stimulating Proteins – Dosing and Availability

Drug	Initial Dosing	Titration and/or Dosage timing	Availability
eltrombopag (Promacta)	<u>ITP</u> patients ≥ 6 years of age: 50 mg orally once daily ▪ For patients of Asian descent or with hepatic impairment (Child Pugh A, B, C): initiate with 25 mg once daily ▪ For patients of Asian descent and hepatic impairment (Child Pugh A, B, C): initial dose of 12.5 mg once daily may be considered patients 1-5 years of age: 25 mg orally once daily <u>Chronic HCV-associated thrombocytopenia</u> 25 mg orally once daily <u>Aplastic Anemia</u> 50 mg orally once daily ▪ For patients of Asian descent or with hepatic impairment (Child Pugh A, B, C): initiate with 25 mg once daily	Use the lowest dose to achieve and maintain platelet count ≥ 50 × 109/L as needed to reduce the risk for bleeding If platelet > 400 × 109/L, stop eltrombopag until platelet < 150 × 109/L; reinitiate at a 25 mg dose reduction (or at 12.5 mg if the patient was already on 25 mg daily) Discontinue if platelet count is > 400 × 109/L after 2 weeks of treatment using the lowest dose <u>ITP</u> Increase or decrease the daily dose by 25 mg For patient taking 25 mg once daily increase or decrease the daily dose by 12.5 mg Do not exceed a dose of 75 mg daily Discontinue if platelet count does not increase to a sufficient level to avoid clinically important bleeding after 4 weeks of using 75 mg daily <u>Chronic HCV-associated thrombocytopenia</u> Adjust dose in 25 mg increments every 2 weeks to achieve target platelet count necessary to initiate antiviral therapy Do not exceed 100 mg daily Discontinue eltrombopag when antiviral therapy is stopped <u>Aplastic Anemia</u> Adjust dose in 50 mg increments every 2 weeks as needed to achieve platelet count ≥ 50 × 109/L Do not exceed 150 mg daily May reduce dose by 50% in patients who attain transfusion independence for ≥ 8 weeks; if platelet level remains stable after 8 weeks after dose reduction, then discontinue eltrombopag and monitor platelet count Reinitiate at the previous effective dose for platelets < 30 × 109/L or absolute neutrophil count (ANC) < 0.5 × 109/L Discontinue if hematologic response is not seen within 16 week of initiating therapy	12.5 mg 25 mg 50 mg 75 mg tablets

Thrombopoiesis Stimulating Proteins – Guidelines

- The American Society of Hematology (ASH), 2011
  - For adults, treatment for a newly diagnosed patient is considered at a platelet count of < 30×10^9/L (grade 2C)
  - Treatment decisions should consider the presence and severity of bleeding, the rapidity of desired platelet count rise, and the possible adverse effects
  - In the management of adults with ITP
    - First-line treatment includes longer courses of corticosteroids (such as prednisone 1 mg/kg orally for 21 days then tapered off) over shorter courses of corticosteroids or IVIG as first-line treatment (grade 2B)
    - IVIG may be used with corticosteroids when a more rapid increase in platelet count is necessary (grade 2B)
    - Either IVIG or anti-D (in appropriate patients) may be used as a first-line therapy if corticosteroids are contraindicated (grade 2C)
      - If IVIG is used, the dose should initially be 1 g/kg as a one-time dose
      - IVIG may be repeated if necessary (grade 2B)
    - Recommend splenectomy for patients who are unresponsive to or relapse after initial corticosteroid therapy (grade 1B)
      - Thrombopoietin receptor agonists may be considered for patients at risk for bleeding who have failed at least 1 other therapy and who relapse after splenectomy or have a contraindication to splenectomy (grade 1B)
      - Thrombopoietin receptor agonists may also be considered in patients at risk for bleeding who have not had a splenectomy and who have failed one line of therapy such as corticosteroids or IVIG (grade 2C)
      - For adult patients after splenectomy, no treatment is recommended if the platelet count exceeds 30×10^9/L (grade 1C)
  - Fostamatinib was not available at the time of this guideline development

Thrombopoesis Stimulating Agents (TPO) Apple Health Policy

Washington State Health Care Authority

Indications and Products

- Chronic Immune Idiopathic Thrombocytopenic Purpura (ITP)
  - eltrombopag olamine (Promacta)
  - fostamatinib (Tavalisse)
  - romiplostim (Nplate)
- Aplastic Anemia
  - eltrombopag olamine (Promacta)
- Chronic Hepatitis C-associated Thrombocytopenia
  - eltromopag olamine (Promacta)
- Thrombocytopenia in Patients with Chronic Liver Disease
  - avatrombopag (Droptelet)
  - lusutrombopag (Mulpleta)

ITP Policy: Initial Criteria

- Patient has diagnosis of chronic immune thrombocytopenia purpura (ITP); **AND**
- Documentation of platelet count less than $30x10^9$/L (30,000/mm^3); **AND**
- Patient has history of failure, contraindication, or intolerance to at least ONE of the following:
  - corticosteroids; **OR**
  - immunoglobulin; **OR**
  - rituximab; **OR**
  - previous history of splenectomy

- If ALL criteria are met, the request will be approved for 12 months.

ITP Policy: Reauthorization Criteria

- Documentation of positive clinical response (e.g., increase in platelet count).

- If ALL criteria are met, the request will be approved for 12 months.

Aplastic Anemia Policy: Initial Criteria

- Patient has a diagnosis of aplastic anemia; **AND**
- Patient has history of failure, contraindication, or intolerance to at least ONE course of immunosuppressive therapy. Appropriate immunosuppressive therapy include but are not limited to:
  - antithymocyte globulin equine (Atgam)
  - antithymocyte globulin rabbit (Thmoblobulin)
  - cyclosporine
- If ALL criteria are met, the request will be approved for 6 months.

Aplastic Anemia Policy: Reauthorization Criteria

- Documentation of positive clinical response (e.g., increase in platelet count).

- If ALL criteria are met, the request will be approved for 12 months.

HCV-associated Thrombocytopenia: Initial Criteria

- Patient has diagnosis of chronic hepatitis C-associated thrombocytopenia; **AND**
- Thrombocytopenia is preventing the initiation of interferon-based therapy or limiting the ability to maintain interferon-based therapy; **AND**
- Patient has ONE of the following:
  - A reason why they cannot use direct acting antivirals for hepatitis C; **OR**
  - Planning to initiate and maintain interferon-based treatment; **OR**
  - Currently receiving interferon-based treatment
- If ALL criteria are met, the request will be approved for 6 months.

HCV-associated Thrombocytopenia: Reauthorization Criteria

- Documentation of positive clinical response (e.g., increase in platelet count); **AND**
- Patient is currently on interferon-based therapy for the treatment of chronic hepatitis C

- If ALL criteria are met, the request will be approved for 6 months.

Chronic Liver Disease Policy: Criteria

- Age 18 or older; **AND**
- Used for the treatment of thrombocytopenia in a patient with chronic liver disease who is scheduled to undergo a procedure;
  - Patient should undergo their procedure within 8 days after the last dose
- If ALL criteria are met, the request will be approved

Motion

- "I move that the Apple Health Medicaid Program implement the clinical criteria listed on slides 51-57 as recommended."
  - Motion: Figueroa
  - 2nd: Lee

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Erythropoiesis Stimulating Agents

Overview of Disease State – Erythropoiesis Stimulating Agents

- Anemia
  - A frequent complication, affecting over 3 million Americans
  - Associated with a number of serious diseases, such as chronic kidney disease (CKD), diabetes, heart disease, and cancer, as well as chronic inflammatory conditions like rheumatoid arthritis or inflammatory bowel disease
  - These conditions can cause anemia by interfering with the production of oxygen-carrying red blood cells (RBCs). Sometimes, as in the case of cancer chemotherapy, anemia can be caused by the treatment itself

- Erythropoietin
  - A glycoprotein produced in the kidneys that stimulates RBC production from bone marrow
  - Acts on the erythroid progenitor cells in the bone marrow to cause late differentiation and maturity of the RBCs
  - Endogenous production of erythropoietin by the kidney is normally regulated by the level of tissue oxygenation
  - Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis
  - In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 units/mL and may increase 100- to 1,000-fold during hypoxia or anemia
  - In contrast, patients with CKD have impaired production of erythropoietin, which is the primary cause of their anemia.[1] Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents

Erythropoiesis Stimulating Agents – Indications

Drugs	Generic	Indications
darbepoetin (Aranesp)	---	▪ Treatment of anemia associated with chronic kidney disease (CKD) including patients on dialysis and patients not on dialysis ▪ Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and, upon initiation, a minimum of 2 additional months chemotherapy is planned – Darbepoetin is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure or in in whom anemia can be managed by transfusion – Darbepoetin is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy – Darbepoetin is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia – Darbepoetin use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being
PEG-EPO (Mircera)	---	▪ Treatment of anemia associated with chronic renal failure (CRF) in o Adult patients on dialysis and adult patients not on dialysis o Pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an o Erythropoiesis stimulating agent (ESA) – PEG-EPO use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being – PEG-EPO is not indicated for treatment of anemia in patients receiving cancer chemotherapy – PEG-EPO is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia

Erythropoiesis Stimulating Agents – Indications

Drugs	Generic	Indications
rHuEPO (Epogen)	---	• Treatment of anemia associated with CRF including patients on dialysis and patients not on dialysis to decrease the need for red blood cell (RBC) transfusion • Treatment of anemia related to therapy with zidovudine (≤ 4,200 mg per week) in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL • Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and, upon initiation, hemoglobin < 10 g/dL and there is a minimum of 2 additional months of planned chemotherapy • Indicated to reduce the need for allogenic RBC transfusion among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery – rHuEPO is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy – rHuEPO is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure or in in whom anemia can be managed by transfusion – rHuEPO is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia – rHuEPO is not indicated in patients undergoing cardiac or vascular surgery – rHuEPO is not indicated for patients who are willing to donate autologous blood pre-operatively – rHuEPO use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being
rHuEPO (Procrit)	---	

Erythropoiesis Stimulating Agents – Indications

Drugs	Generic	Indications
rHuEPO-epbx (Retacrit)	---	• Treatment of anemia associated with CKD including patients on dialysis and patients not on dialysis to decrease the need for red blood cell (RBC) transfusion • Treatment of anemia due to zidovudine administered at ≤ 4,200 mg per week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL • Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and, upon initiation, there is a minimum of 2 additional months of planned chemotherapy • Reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery – Epoetin alfa-epbx is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy – Epoetin alfa-epbx is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure or in in whom anemia can be managed by transfusion – Epoetin alfa-epbx is not indicated as a substitute for RBC transfusion in patients who require immediate correction of anemia – Epoetin alfa-epbx is not indicated in patients undergoing cardiac or vascular surgery – Epoetin alfa-epbx is not indicated for patients who are willing to donate autologous blood pre-operatively – Epoetin alfa-epbx use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being

Erythropoiesis Stimulating Agents – Dosing

Drug	CRF		Zidovudine-treated HIV-infected Patients	Chemotherapy-associated Anemia in Cancer Patients		Surgery
	Starting Dose		Starting Dose	Starting Dose	Target Hb (g/dL)	Starting Dose
darbepoetin (Aranesp)	Dialysis: Adults: 0.45 mcg/kg IV or SC once weekly or 0.75 mcg/kg every 2 weeks Pediatrics: 0.45 mcg/kg IV or SC once weekly	Not on dialysis: Adults: 0.45 mcg/kg IV or SC every 4 weeks Pediatrics: 0.45 mcg/kg IV or SC once weekly or 0.75 mcg/kg every 2 weeks	--	2.25 mcg/kg SC once weekly or 500 mcg SC every 3 weeks	Sufficient to avoid RBC transfusion	--
PEG-EPO (Mircera)	All Adults: 0.6 mcg/kg IV or SC once every 2 weeks Pediatrics: IV administration once every 4 weeks at the dose based on the total weekly ESA dose at time of conversion		--	--	--	--
rHuEPO (Epogen, Procrit)	Dialysis: Adults: 50-100 units/kg IV or SC 3 times weekly Pediatrics: 50 units/kg IV or SC 3 times weekly	Not on dialysis Adults: 50-100 units/kg IV or SC 3 times weekly	Adults: 100 units/kg IV or SC 3 times weekly	Adults: 150 units/kg SC 3 times weekly or 40,000 units SC once weekly* Pediatrics: 600 units/kg IV weekly (max 60,000 units weekly)*	Sufficient to avoid RBC transfusion	Adults: 300 units/kg SC daily for 10 days prior to surgery, day of surgery, and 4 days after surgery OR 600 units/kg once weekly starting 3 weeks prior to, and on day of surgery
rHuEPO-epbx (Retacrit)	Adults: 50-100 units/kg IV or SC 3 times weekly Pediatrics: 50 units/kg 3 times weekly		Adults: 100 units/kg IV or SC 3 times weekly	Adults: 150 units/kg SC 3 times weekly or 40,000 units SC once weekly Pediatrics: 600 units/kg IV weekly (max 60,000 units weekly)	Sufficient to avoid RBC transfusion	Adults: 300 units/kg SC daily for 10 days prior to surgery, day of surgery, and 4 days after surgery OR 600 units/kg once weekly starting 3 weeks prior to, and on day of surgery

Erythropoiesis Stimulating Agents – Availability

Drug	Single-Dose Vials	Multiple Dose Vials	Prefilled Syringe and SureClick Autoinjectors
darbepoetin (Aranesp)	25, 40, 60, 100, 200, 300 mcg/mL in 1 mL vials	--	10 mcg/0.4 mL, 25 mcg/0.42 mL, 40 mcg/0.4 mL, 60 mcg/0.3 mL, 100 mcg/0.5 mL, 150 mcg/0.3 mL, 200 mcg/0.4 mL, 300 mcg/0.6 mL, 500 mcg/1 mL
PEG-EPO (Mircera)	--	--	30 mcg/0.3 mL, 50 mcg/0.3 mL, 75 mcg/0.3 mL, 100 mcg/0.3 mL, 150 mcg/0.3 mL, 200 mcg/0.3 mL
rHuEPO (Epogen, Procrit)	2,000, 3,000, 4,000, 10,000 units/mL in 1 mL vials (Epogen) 2,000, 3,000, 4,000, 10,000, 40,000 units/mL in 1 mL vials (Procrit)	10,000 units/mL in 2 mL vial 20,000 units/mL in 1 mL vial (Contains preservative)	--
rHuEPO-epbx (Retacrit)	2,000, 3,000, 4,000, 10,000 units/mL, 40,000 units/mL in 1 mL vials	--	--

Erythropoiesis Stimulating Agents – Guidelines

- National Comprehensive Cancer Network (NCCN), 2018 Guidelines
  - State that erythropoiesis stimulating agents (ESAs) are associated with an increased risk of thrombosis, decreased survival, and shortened time to tumor
  - Physicians are advised to use the lowest ESA dose possible to maintain hemoglobin (Hb) levels sufficient to avoid blood transfusions, to prescribe according to Food and Drug Administration (FDA) guidelines, and to obtain patient consent
  - ESAs should be discontinued once the course of chemotherapy has been completed and anemia resolves
  - There is not enough evidence to support the use of ESAs for the treatment of anemia related to myelosuppressive chemotherapy with curative intent, patients receiving non-myelosuppressive therapy, or patients with cancer not receiving therapy
- National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), 2007
  - Each ESA is effective in achieving and maintaining target Hb levels
  - KDOQI recommends Hb of 11 to 12 g/dL for dialysis or nondialysis patients with CKD with avoidance of Hb levels exceeding 13 g/dL
  - FDA published a safety communication regarding a more conservative dosing approach to ESAs in patients with CKD due to increased risks of cardiovascular (CV) events
    - The FDA warned of an increased risk of death, CV events, and strokes in CKD patients when their HB levels were greater than 11 g/dL. However, no clinical trials have been performed which have identified a HB target level or ESA dose that would not increase these risks
  - Methoxy polyethylene glycol epoetin beta (PEG-EPO, Mircera) is approved for the treatment of anemia due to CKD in adult patients that are both receiving and not receiving dialysis. It is not indicated for the correction of anemia in cancer patients
  - Epoetin alfa-epbx (Retacrit), or rHuEPO-epbx, is the first FDA-approved biosimilar to epoetin-alfa (Epogen, Procrit)
    - Approved for the treatment of anemia due to CKD in patients on dialysis and not on dialysis, use of zidovudine in patients with HIV infection, and the effects of concomitant myelosuppressive chemotherapy
    - Approved for the reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery

Erythropoiesis Stimulating Agents – Guidelines

- American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH), 2010 Joint Guidelines
  - Before initiating therapy for anemia in a patient with cancer, consideration should be given to the risks of thromboembolism, the possibility of death, and minimizing ESA use, particularly in patients with malignancy being treated with curative intent
  - While the FDA label now limits the indication for ESA use to patients receiving chemotherapy for palliative intent, no study has evaluated outcomes of ESA therapy by subgroups defined by chemotherapy intent
  - The optimal Hb level at which to initiate ESA therapy in patients with chemotherapy-associated anemia and Hb between 10 and 12 g/dL cannot be definitively determined
    - As a result, the decision to initiate ESA therapy in patients with anemia and Hb between 10 and 12 g/dL should be guided by clinical judgment, consideration of the risks and benefits of ESAs, and patient preferences
  - When warranted by clinical conditions, RBC transfusion is an option
    - Evidence does not exist to support improved effectiveness or safety with alternative starting doses, dose schedules, or dose-modifying schedules, starting and modifying doses should follow the FDA dosing guidelines outlined in the product information of each ESA
  - ESAs should be discontinued when chemotherapy is concluded
    - Assuming an appropriate dose increase has been attempted in non-responders as outlined in the FDA-approved label, ESA therapy should be discontinued if there is less than a 1 to 2 g/dL increase in Hb or no decrease in transfusion requirements after 6 to 8 weeks of therapy
    - Non-responders should be investigated for underlying tumor progression, iron deficiency, or other etiologies for anemia
  - Recommends against the use of ESAs for the treatment of anemia associated with malignancy in patients who are not receiving concurrent myelosuppressive chemotherapy, except for patients with lower risk of myelodysplastic syndrome to avoid transfusions
  - Maintains that all ESAs are equivalent with respect to effectiveness and safety

Erythropoiesis Stimulating Agents (ESA) Apple Health Policy

Washington State Health Care Authority

Indications

- Anemia associated with chronic kidney disease (CKD)
- Anemia of prematurity (AOP) for less than 6 months of age
- General anemia policy:
  - Anemia associated with zidovudine-treated HIV-infected patients
  - Anemia of cancer patients on chemotherapy, where the intent of treatment ispalliative
  - Anemia associated with myelodysplastic syndrome to reduce transfusion dependency
  - Anemia after allogeneic bone marrow transplantation
  - Anemia due to ribavirin in patients who did not experience an improvement in hemoglobin level with ribavirin dose reduction
  - To reduce the need for blood transfusions in anemic participants scheduled to undergo high-risk surgery who are at increased risk or intolerant to transfusions
  - Special circumstance patients who will not or cannot receive whole blood or components as replacement for traumatic or surgical loss

Products

- darbepoetin alfa (Aranesp)
- epoetin alfa (Epogen)
- epoetin alfa (Procrit)
- epoetin alfa-epbx (Retacrit)
- methoxy peg-epoetin beta (Mircera)

Anemia associated with CKD Policy: Initial Criteria

- Diagnosis of chronic kidney disease (CKD); **AND**
- Most recent hemoglobin (Hb) level less than 10 g/dL; **AND**
- Documentation of adequate iron stores as indicated by current (within the last 3 months) serum ferritin level greater than or equal to 100 mcg/L or serum transferrin saturation greater than or equal to 20%.

- If ALL criteria are met, the request will be approved for 6 months.

Anemia associated with CKD Policy: Reauthorization Criteria

- Hemoglobin (Hb) level less than 11 g/dL documented in the previous 3 months; **AND**
- Documentation of positive clinical response (eg: as evidence by decrease in blood transfusions) submitted by the prescriber.

- If ALL criteria are met, the request will be approved for 12 months.

Anemia of Prematurity Policy: Initial Criteria

- Documentation of refusal of transfusion due to religious or cultural reasons; **AND**
- Patient is less than 6 months of age; **AND**
- Most recent hemoglobin level is less than 10 g/dL.

- If ALL criteria are met, the request will be approved for 3 months.

Anemia of Prematurity Policy: Reauthorization Criteria

- Patient is less than 6 months of age; **AND**
- Hemoglobin level is less than 11 g/dL; **AND**
- Documentation of positive clinical response submitted by the prescriber.

- If ALL criteria are met, the request will be approved for 3 months.

General Anemia Policy: Initial Criteria

- Patient must have at least ONE of the following conditions:
  - Anemia associated with zidovudine-treated HIV-infected patients; **OR**
  - Anemia of cancer patients on chemotherapy, where the intent of treatment is palliative; **OR**
  - Anemia associated with myelodysplastic syndrome to reduce transfusion dependency; **OR**
  - Anemia after allogeneic bone marrow transplantation; **OR**
  - Anemia due to ribavirin in patients who did not experience an improvement in hemoglobin level with ribavirin dose reduction; **OR**
  - To reduce the need for blood transfusions in anemic participants scheduled to undergo high-risk surgery who are at increased risk or intolerant to transfusions; **OR**
  - Special circumstance patients who will not or cannot receive whole blood or components as replacement for traumatic or surgical loss; **AND**

General Anemia Policy: Initial Criteria (continued)

- Most recent hemoglobin level is less than 10 g/dL
- If ALL criteria met, the request will be approved for 3 months.

General Anemia Policy: Reauthorization Criteria

- Hemoglobin (Hb) level less than 11 g/dL documented in the previous 3 months; **AND**
- Documentation of positive clinical response (eg: as evidence by decrease in blood transfusions) submitted by the prescriber.

- If ALL criteria are met, the request will be approved for 6 months.

Motion

- "I move that the Apple Health Medicaid Program implement the clinical criteria listed on slides 71-77 as recommended."
  - Motion: Lee
  - 2nd: Huynh

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Granulocyte Colony Stimulating Factors (G-CSF)

Colony Stimulating Factors

Overview of Disease State – Granulocyte Colony Stimulating Factors (G-CSF)

- Febrile neutropenia
  - Myelosuppressive chemotherapy can induce neutropenia (< 500 neutrophils/µL or < 1,000 neutrophils/µL and a predicted decline to ≤ 500/µL during the 48 hours after the dose) and febrile neutropenia (≥ 38.3°C orally or ≥ 38°C over 1 hour) which is a dose-limiting toxicity of chemotherapy
  - Can cause increased diagnostic and treatment costs, prolonged hospitalizations, and broad-spectrum antibiotic use which may necessitate chemotherapy dose reductions, treatment delays, and may ultimately compromise treatment outcomes
  - The risk of febrile neutropenia is dependent on treatment and dose intensity, which is often underreported
- Colony stimulating factors (CSF) are hematopoietic growth factors that have been shown to decrease the likelihood of neutropenic complications resulting from chemotherapy and to improve relative chemotherapy dose intensity
- Biosimilars
  - In 2018, the FDA approved the biosimilars Nivestym and Fulphila; the reference products are Neupogen and Neulasta, respectively
  - Biosimilars must demonstrate there are no clinically meaningful differences in safety or effectiveness from the reference product; however, small differences in clinically inactive compounds are permissible in biosimilar products. Currently, biosimilars are not considered interchangeable products
- Prophylactic CSF use can reduce the severity, risk, and duration of febrile neutropenia and decrease rates of infection
  - Neupogen, Nivestym, Zarxio, Neulasta, Fulphila, and Granix are granulocyte colony-stimulating factors (G-CSF)
  - Leukine is a granulocyte-macrophage colony stimulating factor (GM-CSF)
    - Colony stimulating factors act on hematopoietic cells and stimulate proliferation, differentiation commitment, and some end-cell functional activation

Granulocyte Colony Stimulating Factors (G-CSF) – Indications

Drug	Generic	Cancer patients receiving myelosuppressive chemotherapy (To reduce incidence of infection (febrile neutropenia)	Acute Myeloid Leukemia (AML) patients receiving chemotherapy (Following induction or consolidation chemotherapy to reduce time to neutrophil recovery and the duration of fever in adults)	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia (To reduce the incidence and duration of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia)	Hematopoietic Syndrome of Acute Radiation Syndrome (To Increase survival in patients acutely exposed to myelosuppressive doses of radiation)
filgrastim (Neupogen)	--	X	X	X	X	X	X
filgrastim-aafi (Nivestym)	--	X	X	X	X	X	--
filgrastim-sndz (Zarxio)	--	X	X	X	X	X	--
pegfilgrastim (Neulasta)	--	X	--	--	--	--	X
pegfilgrastim-jmdb (Fulphila)	--	X	--	--	--	--	--
sargramostim (Leukine)	--	--	X	X	X	--	X
tbo-filgrastim (Granix)	--	X	--	--	--	--	--

Granulocyte Colony Stimulating Factors (G-CSF) – Dosing/Availability

Drug	Cancer patients receiving myelosuppressive chemotherapy	Acute Myeloid Leukemia (AML) patients receiving chemotherapy	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia	Hematopoietic Syndrome of Acute Radiation Syndrome	Availability
filgrastim (Neupogen)	5 mcg/kg/day, administered as a single daily injection by SC bolus, by short IV infusion (15 to 30 minutes), or continuous IV infusion; doses may be increased by increments of 5 mcg/kg for each chemotherapy cycle according to the duration and severity of the ANC nadir	5 mcg/kg/day as single daily injection by SC injection, short IV infusion (15 to 30 minutes), or continuous IV infusion; doses may be increased by increments of 5 mcg/kg for each chemotherapy cycle according to the duration and severity of the ANC nadir	10 mcg/kg/day given as an IV infusion no longer than 24 hours; during periods of neutrophil recovery, the daily dose should be titrated against the neutrophil response dosing schedule	10 mcg/kg/day SC; give for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis	Starting Dose: Congenital Neutropenia: 6 mcg/kg SC twice daily Idiopathic or Cyclic Neutropenia: 5 mcg/kg SC daily	10 mcg/kg as single daily SC injection; administer as soon as possible after suspected/ confirmed exposure to radiation doses > 2 gray (Gy)	Single-dose vials: 300 mcg/1 mL, 480 mcg/1.6 mL Prefilled single-use syringes (SingleJect®): 300 mcg/0.5 mL, 480 mcg/0.8 mL
filgrastim-aafi (Nivestym)						--	Prefilled syringe: 300 mcg/0.5 mL, 480 mcg/0.8 mL
filgrastim-sndz (Zarxio)						--	Prefilled single-dose syringes: 300 mcg/0.5 mL 480 mcg/0.8 mL
tbo-filgrastim (Granix)	5 mcg/kg/day as a SC injection until expected neutrophil nadir is passed and neutrophil count is in normal range; administer no earlier than 24 hours following myelosuppressive chemotherapy	--	--	--	--	--	Single-use, preservative-free: prefilled syringes: 300 mcg/0.5 mL, 480 mcg/0.8 mL with needle guard (HCP-administered) Without needle guard (self- or caregiver-administered) vials: 300 mcg/1 mL, 480 mcg/1.6 mL

Granulocyte Colony Stimulating Factors (G-CSF) – Dosing/Availability

Drug	Cancer patients receiving myelosuppressive chemotherapy	Acute Myeloid Leukemia (AML) patients receiving chemotherapy	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia	Hematopoietic Syndrome of Acute Radiation Syndrome	Availability
pegfilgrastim (Neulasta)	6 mg SC once per chemotherapy cycle; pediatric (weight < 45 kg) dosing is weight-based per dosing schedule in drug PI	--	--	--	--	2 doses, 6 mg each, given SC 1 week apart; pediatric (weight < 45 kg) dosing is weight based per dosing schedule in drug PI; first dose given as soon as possible after suspected / confirmed radiation exposure of > 2 gray; second dose given 1 week after	**Neulasta** Single-use prefilled syringe for manual use: 6 mg/0.6 mL **Neulasta Onpro** Delivery Kit: single-use delivery kit: 1 prefilled syringe copackaged with 1 on-body injector for HCP administration
pegfilgrastim-jmdb (Fulphila)						--	Single-dose prefilled syringe: 6 mg/0.6 mL

Granulocyte Colony Stimulating Factors (G-CSF) – Dosing/Availability

Drug	Cancer patients receiving myelosuppressive chemotherapy	Acute Myeloid Leukemia (AML) patients receiving chemotherapy	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia	Hematopoietic Syndrome of Acute Radiation Syndrome	Availability
sargramostim (Leukine)	--	- 250 mcg/m2/day given IV over 4 hours starting approximately day 11 or 4 days following completion of induction chemotherapy, if the day 10 bone marrow is hypoplastic with < 5% blasts	- 250mcg/m2/day given IV over 2 hours beginning 2 to 4 hours after bone marrow infusion, and not < 24 hours after the last dose of chemotherapy or radiotherapy - Therapy should not begin until post-marrow infusion ANC is < 500 cells/mm3 and continued until ANC is > 1,500 cells/mm3 for 3 consecutive days - Treatment of BMT failure or engraftment delay: 250 mcg/m2/day given IV over 2 hours for 14 days	- Mobilization/collection: 250 mcg/m2/day IV over 24 hours or SC once daily - Continue at same dose through PBPC collection, usually after 5 days - If WBC > 50,000 cells/mm3 reduce dose by 50% **<u>Transplantation:</u>** - 250 mcg/m2/day IV over 24 hours or SC once daily until ANC > 1,500 cells/mm3 for 3 consecutive days	--	- Administer weight-based dose as SC injection once daily after suspected or confirmed exposure to radiation doses > 2 gray - Continue until ANC > 1,000/mm3 for 3 consecutive CBCs or exceeds 10,000/mm3 after radiation induced nadir - Adults/pediatrics > 40 kg: 7 mcg/kg - Pediatrics 15 kg to 40 kg: 10 mcg/kg - Pediatrics < 15kg: 12 mcg/kg	Vial: 250 mcg single-dose

Granulocyte Colony Stimulating Factors (G-CSF) – Guidelines

- National Comprehensive Cancer Network (NCCN), 2018
  - There is less evidence available to support the therapeutic use of CSF for febrile neutropenia as an adjunct to antibiotics compared to prophylactic use
  - The NCCN guidelines recommend therapeutic treatment based on the patient's prophylactic therapy use
  - Safety data appear similar between Neupogen and Neulasta, and the subcutaneous (SC) route is preferred for all 5 agents
  - To date, there are insufficient head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs
  - Subcutaneous Neupogen, Zarxio, Granix, and Neulasta have a category 1 and there is uniform NCCN consensus that they prophylactically reduce the risk of febrile neutropenia
    - Neupogen, Zarxio, and Granix can be administered the day after chemotherapy, up to 3 to 4 days after chemotherapy, and through post-nadir recovery
    - Neulasta
      - Based on data from clinical trials, should be administered the day after chemotherapy (category 1); however, administration up to 3 to 4 days after chemotherapy is also reasonable according to the NCCN guidelines
      - There is evidence to support the use of chemotherapy regimens every 3 weeks with Neulasta (category 1)
      - Efficacy data exist for Neuasta in chemotherapy regimens given every 2 weeks (category 2A)
      - Insufficient data to support dose/schedule of weekly chemotherapy regimens; therefore, the use of Neulasta should not be used
      - Since Neulasta is long-acting, patients who received prophylactic Neulasta should not receive additional CSF
      - For patients who have not received prophylactic CSF, the guidelines recommend an evaluation of risk factors related to infection complications or poor clinical outcomes; if risk factors are present then CSF should be considered
    - Leukine
      - No longer recommended for prophylactic use and prophylactic use of CSF in patients taking chemotherapy and radiation concurrently has not been studied; therefore, the NCCN guidelines do not recommend CSF use in such patients

Granulocyte Colony Stimulating Factors (G-CSF) – Guidelines

- National Comprehensive Cancer Network (NCCN), 2018
  - Neupogen, Zarxio, and Leukine have a 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate) for therapeutic use and can be used until post-nadir absolute neutrophil count (ANC) recovery to normal or near-normal levels
  - Granix and Neulasta have only been studied for prophylactic use.
  - Guidelines stratify patients into 3 risk groups based on the chemotherapy regimen and patient-related risk factors:
    - High risk (> 20% risk of developing febrile neutropenia)
      - Recommend patients receive prophylactic CSF regardless of the intent of treatment (category 1)
    - Intermediate risk (10% to 20% risk of developing febrile neutropenia)
      - Recommend individualized consideration of CSF based on the likelihood of developing febrile neutropenia, consequences of developing febrile neutropenia, and the implications of interfering with chemotherapy treatments
    - Low risk (< 10% risk of developing febrile neutropenia)
      - Does not recommend the routine use of CSF in patients with low risk of developing febrile neutropenia due to lack of cost effectiveness and availability of alternative treatments
      - However, choosing to administer a CSF may be considered if the treatment is curative or adjuvant and the patient is at serious medical consequences of febrile neutropenia
  - Biosimilars
    - In general, NCCN recommends Zarxio in the same instances as Neupogen; however, they do not recommend switching between the biosimilar and the originator product, filgrastim, during treatment
    - The guidelines recommend Neupogen (2A recommendation), Zarxio (2B recommendation), or Granix (category 2B) for allogeneic hematopoietic cell mobilization and for granulocyte transfusion
    - The NCCN guidelines state there is insufficient data for consideration with regard to Nivestym and Fulphila; therefore, no recommendations will be made on their use at this time

Granulocyte Colony Stimulating Factors (G-CSF) – Guidelines

- American Society of Clinical Oncology (ASCO), 2015
  - They note the ability of these agents to reduce the duration and severity of neutropenia and febrile neutropenia
  - No recommendation regarding the equivalency of the 2 colony-stimulating agents, granulocyte CSFs, and granulocyte-macrophage CSFs
  - Neulasta, Neupogen, Zarxio, and Granix can be used for the prevention of treatment-related febrile neutropenia
    - The choice of agent should be based on the clinical situation, convenience, and cost
  - The recommendations for the use of CSF for primary prophylaxis include the prevention of febrile neutropenia in patients who are at high risk based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen
    - Recommend the use of CSF when the risk of febrile neutropenia is ≥ 20% starting with the first cycle and continuing through subsequent cycles of chemotherapy
    - Take factors into consideration concerns such as the optimal chemotherapy regimen, individual patient risk factors, and the intention of treatment, that is, curative, prolongation of life, or symptom control and palliation
    - Recommends secondary prophylaxis with CSF for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free, overall survival, or treatment outcome
  - CSF should not be routinely used for patients with neutropenia who are afebrile
  - CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia
    - However, CSF should be considered in patients with fever and neutropenia who are at high-risk for infection-related complications or who have prognostic factors that are predictive of poor clinical outcomes
    - High-risk features include expected prolonged (> 10 days) and profound (< 0.1 x 10^9/L) neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever

Granulocyte Colony Stimulating Factors (G-CSF) – Guidelines

- American Society of Clinical Oncology (ASCO), 2015
  - CSFs can be used during or after chemotherapy or with plerixafor to mobilize peripheral-blood progenitor cells (PBPC) depending on the type of cancer and transplantation
  - CSF should be administered after autologous stem-cell transplantation and may be administered after allogenic stem-cell transplantation
  - They recommend Zarxio; future biosimilars may be used for the prevention of neutropenia
  - ASCO recommends that the choice of agent depend on convenience, cost, and clinical situation
  - ASCO's dosing and administration recommendations for Zarxio are identical to those for Neupogen

Granulocyte Colony Stimulating Factors (G-CSF) Apple Health Policy

Washington State Health Care Authority

Indications

- Indications for short-acting G-CSF products:
  - decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
  - reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
  - reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT)
  - mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
  - reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
  - increase survival in patients acutely exposed to myelosuppresive doses of radiation (hematopoietic syndrome of acute radiation syndrome)

Indications

- Indications for long-acting G-CSF products:
  - decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
  - increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic subsyndrome of acute radiation syndrome)

Products

- Short-acting G-CSF products
  - filgrastim (Neupogen)
  - filgrastim-aafi (Nivestym)
  - filgrastim-sndz (Zarxio)
  - tbo-filgrastim (Granix)

- Long-acting G-CSF products
  - pegfilgrastim (Neulasta)
  - pegfilgrastim-cbqv (Udenyca)
  - pegfilgrastim-imdb (Fulphila)

Acute myeloid leukemia (AML) Policy Criteria

Filgrastim may be approved for patients set to receive induction or consolidation chemotherapy for acute myeloid leukemia (AML)

Primary prevention of febrile neutropenia Policy Criteria

Filgrastim may be approved for the primary prevention of febrile neutropenia if ONE of the following criteria is met:

- The chemotherapy regimen has a greater than 20% risk for febrile neutropenia; **OR**
- The chemotherapy regimen has a 10 - 20% risk for febrile neutropenia and the member meets ONE of the following:
  - Extensive prior chemotherapy or radiation therapy to pelvis or other areas important for bone marrow reserve
  - Persistent neutropenia (ANC 1000/mm3 or less)
  - Bone marrow involvement by tumor
  - Recent surgery and/or open wounds
  - Liver dysfunction (bilirubin > 2.0 mg/dL)
  - Renal dysfunction (eGFR < 50 mL/min/1.73m^2)
  - Age > 65 years and receiving full chemotherapy dose intensity
  - Poor performance status; **OR**
- The member has experienced treatment delay of curative chemotherapy due to a dose-limiting neutropenic event, with the same dose and schedule planned for future cycles

Primary prevention of febrile neutropenia Policy Criteria (continued)

Pegfilgrastim may be approved for the primary prevention of febrile neutropenia if there is a documented treatment failure or an inability to complete course of treatment with a preferred short-acting G-CSF **AND** ONE of the following criteria is met:

- The chemotherapy regimen has a greater than 20% risk for febrile neutropenia;**OR**
- The chemotherapy regimen has a 10 - 20% risk for febrile neutropenia and the member meets ONE of the following:
  - Extensive prior chemotherapy or radiation therapy to pelvis or other areas important for bone marrow reserve
  - Persistent neutropenia (ANC 1000/mm3 or less)
  - Bone marrow involvement by tumor
  - Recent surgery and/or open wounds
  - Liver dysfunction (bilirubin > 2.0 mg/dL)
  - Renal dysfunction (eGFR < 50 mL/min/1.73m^2)
  - Age > 65 years and receiving full chemotherapy dose intensity
  - Poor performance status; **OR**
- The member has experienced treatment delay of curative chemotherapy due to a doselimiting neutropenic event, with the same dose and schedule planned for future cycles

Secondary prevention of febrile neutropenia Policy Criteria

Filgrastim may be approved for the secondary prevention of febrile neutropenia if ONE of the following criteria is met:

- The member has experienced febrile neutropenia with a previous cycle of similar chemotherapy, with the same dose and schedule planned for future cycles; **OR**
- The member has experienced treatment delay of curative chemotherapy due to a dose-limiting neutropenic event, with the same dose and schedule planned for future cycles; **OR**
- The member has experienced treatment delay of palliative chemotherapy due to a dose-limiting neutropenic event, and dose reduction or a delay in frequency of subsequent chemotherapy cycles is not recommended

Secondary prevention of febrile neutropenia Policy Criteria (continued)

Pegfilgrastim may be approved for the secondary prevention of febrile neutropenia if there is a documented treatment failure or failure to complete course of treatment with a preferred short-acting G-CSF **AND** ONE of the following criteria is met:

- The member has experienced febrile neutropenia with a previous cycle of similar chemotherapy, with the same dose and schedule planned for future cycles; **OR**
- The member has experienced treatment delay of curative chemotherapy due to a dose-limiting neutropenic event, with the same dose and schedule planned for future cycles; **OR**
- The member has experienced treatment delay of palliative chemotherapy due to a dose-limiting neutropenic event, and dose reduction or a delay in frequency of subsequent chemotherapy cycles is not recommended

Treatment of febrile neutropenia: Policy Criteria

Filgrastim may be approved for the treatment of febrile neutropenia if BOTH of the following criteria is met:

- The member has been diagnosed with febrile neutropenia; **AND**
- The patient has ONE or more of the following high-risk factors:
  - Age greater than 65 years
  - Hospitalized for febrile neutropenia
  - Sepsis syndrome
  - Invasive fungal infection
  - Clinically documented infection such as pneumonia
  - Prolonged or profound neutropenia
  - History of prior episodes of febrile neutropenia

Bone marrow transplant (BMT): Policy Criteria

Filgrastim may be approved if BOTH are met:

- Filgrastim is administered at least 24 hours after:
  - cytotoxic chemotherapy; OR
  - bone marrow infusion; **AND**
- CBC & platelet counts are monitored daily during neutrophil recovery.

Autologous peripheral blood progenitor cell collection and therapy: Policy Criteria

Filgrastim may be approved if BOTH are met:

- Filgrastim is administered for at least 4 days before the first leukapheresis procedure; **AND**
- Filgrastim is continued until the last leukapheresis.

Severe chronic neutropenia: Policy Criteria

Filgrastim may be approved after confirmation of diagnosis of SCN by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype.

- Filgrastim can only be approved after confirmation of a correct diagnosis of SCN.

Acute radiation exposure: Policy Criteria

Filgrastim or **pegfilgrastim** may be approved for hematopoietic subsyndrome of acute radiation syndrome when patients are exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death as a result of injury to other organs. This includes accidental or intentional total body radiation of doses of 3 to 10 Gy.

Motion

- "I move that the Apple Health Medicaid Program implement the clinical criteria listed on slides 93-102 as recommended."
  - Motion: Flatebo
  - 2nd: Huynh

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Alpha-Proteinase Inhibitors

Enzyme Inhibitors, Systemic

Overview of Disease State – Alpha-Proteinase Inhibitors

- Alpha-1-antitrypsin deficiency (AATD)
  - 1 of the 3 most common fatal genetic diseases in Caucasian adults
    - Severe AATD affects ~70,000 to 100,000 individuals, and an estimated 25 million people have at least 1 deficient gene
    - In adults, AATD leads to chronic liver disease in the fifth decade
  - AATD may present in neonates as jaundice and hepatitis, in infants as cholestatic jaundice, and in children as hepatic cirrhosis or liver failure
    - It is the leading cause of pediatric liver transplantation
  - Approximately 1% to 5% of patients with a diagnosis of chronic obstructive pulmonary disease (COPD) are predicted to have AATD
    - As a cause of emphysema, it is seen in nonsmokers in the fifth decade of life and during the fourth decade of life in smokers
    - Disease onset is accelerated by approximately 10 years by cigarette smoking
    - Patients with AATD frequently develop dyspnea 20 to 30 years earlier (at age 30 to 45 years) compared to smokers with emphysema with normal AAT levels
  - The primary manifestation is early-onset panacinar emphysema
    - It most often manifests as slowly progressive dyspnea; although, many patients initially demonstrate symptoms of cough, sputum production, or wheezing
    - Patients with AATD can experience emphysema, hepatitis, liver fibrosis, and cirrhosis

Overview of Disease State – Alpha-Proteinase Inhibitors

- Alpha-1-antitrypsin deficiency (AATD)
  - Pathophysiology
    - The genetic mutation in the SERPINA1 gene modifies the configuration of the AAT molecule and inhibits AAT release from hepatocytes
    - This leads to low alveolar AAT concentrations, where the AAT molecule would typically protect against antiproteases
    - In AATD, protease excess in the alveoli damage alveolar walls resulting in emphysema
    - The accumulation of excess AAT in the liver can also lead to destruction of hepatocytes and, ultimately, clinical liver disease
    - Since the major biochemical activity of the AAT molecule is inhibition of several neutrophil-derived proteases, the protein has been termed alpha-1-antiprotease
  - Approximately, 24 variants of the alpha-1-antiprotease molecule have been identified, all of which are codominant alleles
  - The most common form of AATD is associated with allele Z, or homozygous PiZ (ZZ)
    - Individuals with the PiZ (ZZ) allele have a 16% likelihood of surviving to age 60 years compared to an 85% likelihood for the general U.S. population
    - Other genotypes associated with severe AATD include PiSZ, PiZ/Null, and PiNull
  - The *S* gene is more commonly found in people of Spanish or Portuguese descent, while the *Z* gene is detected more often in individuals of Northern or Western European descent

Alpha-Proteinase Inhibitors – Indications

Drug	Generic	FDA Indications
		Congenital Alpha-1–Proteinase Inhibitor Deficiency with Emphysema
Aralast NP	--	X
Glassia	--	X
Prolastin-C/ Prolastin-C Liquid	--	X
Zemaira	--	X

Alpha-Proteinase Inhibitors – Dosing/Availability

Drug	Dose	Availability	Storage	Stability
Aralast NP	60 mg/kg via IV infusion once weekly	0.5 gm and 1 gm single use vials lyophilized powder for IV injection	Store at up to 25°C (77°F) Do not freeze	Use within 3 hours of reconstitution
Glassia	60 mg/kg via IV infusion once weekly	1 gm in 50 mL solution for IV injection	Store at 2 to 8°C (36 to 46°F) Do not freeze	Per expiration dating
Prolastin-C / Prolastin-C Liquid	60 mg/kg via IV infusion once weekly	1 gm single use vials lyophilized powder for IV injection 1 gm single use vials solution for IV injection	Lyophilized powder - Store at up to 25°C (77°F) Do not freeze Liquid – Store at 2 to 8°C (36 to 46°F) Do not freeze	Lyophilized powder - Use within 3 hours of reconstitution
Zemaira	60 mg/kg via IV infusion once weekly	1 gm single use vials lyophilized powder for IV injection	Store at up to 25°C (77°F) Do not freeze	Use within 3 hours of reconstitution

Alpha-Proteinase Inhibitors – Guidelines

- American Thoracic Society and the European Respiratory Society (ATS/ERS) AAT Deficiency Task Force
  - Do not recommend fetal testing or population screening unless the prevalence of AATD is high (> 1 case per 1,500 population), smoking is prevalent, and adequate counseling services are available
  - Phenotyping is required to confirm AATD and it is recommended that AAT replacement therapy not be initiated without testing
    - Patients and healthcare providers can obtain a free Alpha-1 Test Kit (finger-stick test) from the Alpha-1 Research Registry
    - The test screens for the most common *Z* and *S* genotypes and if more extensive testing is needed to determine an AAT level, both the patient and physician are notified
    - Test kits capable of detecting *S* and *Z* alleles on samples from mouth swabs have made genetic testing easier. These tests will not, however, detect the rare null alleles
  - The clinical efficacy of any A1-PI in influencing the frequency, duration, or severity of pulmonary exacerbations has not been demonstrated
  - Clinical trial data suggest that A1-PI augmentation therapy may slow the progression of emphysema when lung density is measured by computerized tomography (CT) scan
  - Recommend therapy with A1-PIs for patients who are deficient in AAT (defined as serum concentration < 11 micromoles) with obstructive lung disease, where obstructive lung disease is defined as a FEV_1 of 30% to 65% of predicted, or a rapid decline in lung function defined as a change in FEV_1 of > 120 mL/year
    - The guidelines further state that A1-PIs do not confer benefit in, and are not recommended for, patients who have A1-PI deficiency-associated liver disease
    - In addition, A1-PIs are not indicated in patients with lung disease in whom congenital A1-PI deficiency has not been established

Alpha-Proteinase Inhibitors – Guidelines

- Medical and Scientific Advisory Committee of the Alpha-1 Foundation Guidelines, 2016
  - These were intended to simplify the 2003 American Thoracic Society (ATS) and the European Respiratory Society guidelines on the diagnosis and management of AATD
  - Recommend the following:
    - AATD testing in individuals with COPD, regardless of age or ethnicity
    - AATD testing in individuals with unexplained chronic liver disease
    - AATD testing in individuals with necrotizing panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis
    - Parents, siblings, and children, as well as extended family members of persons with AATD or others with an abnormal alpha-1 gene, should receive genetic counseling and be offered testing for AATD
    - For diagnostic testing in symptomatic patients, genotyping is recommended for at least the S and Z alleles
      - Any advanced or confirmatory testing should include Pi-typing, AAT level testing, and/or expanded genotyping
  - Recommends augmentation therapy for all AAT deficient patients who have AAT-related lung disease and a score of ≤ 65% on pulmonary function tests and anyone with necrotizing panniculitis
    - For those with a FEV_1 > 65% predicted, the recommendation is to discuss on an individual basis the potential benefits of reducing lung function decline while considering therapy cost and lack of evidence for such benefit
    - Providers should stress efforts to prevent exposure to tobacco smoke and facilitate cessation in individuals who currently smoke
    - The group does not suggest intravenous (IV) augmentation therapy for individuals with the following: MZ genotype of AATD, lung disease due to AATD who continue to smoke, AATD and emphysema/bronchiectasis who do not have airflow obstruction, status post liver transplant, or liver disease due to AATD
    - Lung volume reduction surgery is not recommended in individuals with COPD related to AATD

Alpha-Proteinase Inhibitors Apple Health Policy

Washington State Health Care Authority

Indications and Products

- Alpha-1-antitrypsin deficiency (AATD)
  - Alpha-1-proteinase inhibitor, Human (alpha-1-antitrypsin)
    - Aralast NP
    - Glassia
    - Prolastin-C
    - Zemaira

AATD Policy: Initial Criteria

- An FDA approved indication for augmentation and maintenance therapy of patients 18 years of age or older with severe hereditary deficiency of alpha-1-antitrypsin with clinical evidence of emphysema;
- Diagnosis confirmed by **ALL** of the following:
  - Genetic confirmation of PiZZ, PiZ(null), or Pi(null, null) phenotype alpha-1-antitrypsin deficiency (AATD) or other alleles determined to increase risk of AATD
  - Test levels of AAT less than 11µmol/L (or less than the threshold level considered protective for the assay* used)
    - *Other assays and thresholds equivalent to 11µmol/L, provided for reference (Laboratory-specific reference cut-offs may vary):
    - Immunoturbidimetry – less than or equal to 57 mg/dL
    - Nephelometry – less than or equal to 57 mg/dL
    - Radial Immunodiffusion – less than or equal to 80 mg/dL
  - Documented emphysema with airflow obstruction;

AATD Policy: Initial Criteria (continued)

- Prescriber must document that member's forced expiratory volume in one second (FEV_1) is less than or equal to 65% predicted;
- The prescriber must verify that patient is a non-smoker;
- The prescriber must verify the patient does not have antibodies to IgA;
- The diagnosis was established by, or in consultation with, a specialist in pulmonology;
- The patient's recent weight must be provided in order to authorize the appropriate amount of drug required according to package labeling
  - Dose limit: 60 mg/kg every week

- If **ALL** criteria are met, the request will be approved for 6 months.

AATD Policy: Reauthorization Criteria

- Documentation of a positive clinical response from pretreatment baseline to alpha-1-proteinase inhibitor treatment;
- The prescriber must verify that patient is a non-smoker or initiating smoking cessation;
- The patient's recent weight must be provided in order to authorize the appropriate amount of drug required according to package labeling;
  - Dose limit: 60 mg/kg every week

- If **ALL** criteria are met, the request will be approved for 12 months.

Motion

- “I move that the Apple Health Medicaid Program implement the clinical criteria listed on slides 113-115 as recommended.”
  - Motion: Buccola
  - 2nd: Flatebo

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

nitazoxanide (Alinia®)

Overview of Disease State

- Giardiasis
  - The most frequently diagnosed intestinal parasitic disease in the United States (U.S.) and is caused by ***G. lamblia***
  - Diagnosis is done by detection of cysts or trophozoites in the feces, trophozoites in the small intestine, or by detection of ***Giardia*** antigens in the feces
  - Patients with Giardiasis may experience mild or severe diarrhea or, in some instances, no symptoms at all
    - Fever is rarely present
    - Onset of symptoms is generally 1 to 2 weeks after inoculation
    - Occasionally, some will have chronic diarrhea over several weeks or months, with significant weight loss
  - Giardiasis can cause failure to absorb fat, lactose, vitamin A, and vitamin B12. Giardia is passed from the feces of an infected person or animal and may contaminate water or food
  - ***G. lamblia*** can also be transmitted through anal-genital, oral-anal, or digital-anal contact
  - Person-to-person transmission may occur in daycare centers or other settings where hand washing practices are poor
  - Effective treatments for ***Giardia*** infection include metronidazole, tinidazole, and **nitazoxanide (Alinia)**

- Cryptosporidiosis
  - Caused by the protozoan, ***Cryptosporidium parvum***
  - Intestinal cryptosporidiosis is characterized by severe watery diarrhea but may also be asymptomatic and is self-limiting in most otherwise healthy people
  - Some infected people are asymptomatic; in others, symptoms may range from mild to profuse diarrhea, with passage of 3-6 liters of watery stool per day
    - In some outbreaks involving day-care centers, diarrhea has lasted from 1 to 4 weeks
  - Dehydration is a major concern, particularly for pregnant women and young children and immunocompromised people in whom the infection becomes chronic
  - Immune status has a strong influence on the severity and duration of symptoms and illness. In people with HIV/AIDS or other immunocompromising conditions, ***C. parvum*** infections may be severe, lifelong, and may contribute to their death
    - The FDA has approved **nitazoxanide** for the treatment of cryptosporidiosis in immunocompetent people

nitazoxanide (Alinia) – Indication, Dosing/Availability

Drug	Indications
nitazoxanide (Alinia®)	Diarrhea caused by *Giardia lamblia* • Oral tablet is indicated for patients ≥ 12 years old • Oral suspension is indicated for patients ≥ 1 year old Diarrhea caused by *Cryptosporidium parvum* • Oral suspension is indicated for patients 1 to 11 years of age

Drug	Adult Dosing	Pediatric Dosing	Availability
nitazoxanide (Alinia®)	**Diarrhea caused by G. lamblia or C. parvum (> 12 years):** 500 mg tablet every 12 hours with food for 3 days OR 500 mg (25 mL) of oral suspension every 12 hours with food for 3 days	**Diarrhea caused by *G. lamblia* or *C. parvum* – oral suspension:** 1-3 years: 100 mg (5 mL) of oral suspension every 12 hours with food for 3 days 4-11 years: 200 mg (10 mL) of oral suspension every 12 hours with food for 3 days ≥ 12 years: 500 mg (1 tablet) every 12 hours for 3 days OR 500 mg (25 mL) of oral suspension every 12 hours with food for 3 days	500 mg tablet 100 mg/5 mL oral suspension

nitazoxanide (Alinia®) - Additional Information

- Pediatrics
  - Nitazoxanide (Alinia) tablets have not been studied in children < 12 years of age
  - A single nitazoxanide tablet contains a greater amount of nitazoxanide than is recommended for pediatric patients ≤ 11 years and should not be used in this age group
  - Nitazoxanide oral suspension has not been studied in children < 1 year of age

- Pregnancy
  - Product labeling for nitazoxanide was revised to comply with the current Pregnancy and Lactation Labeling Rule (PLLR) and advises that there are no data for nitazoxanide use in pregnancy women to inform of a drug-associated risk. Previously, it was considered Pregnancy Category B

- Warnings/Contraindications
  - Nitazoxanide (Alinia) is contraindicated in patients with prior hypersensitivity to nitazoxanide or any of the product components
  - Tizoxanide, the active metabolite of nitazoxanide (Alinia), is highly bound to plasma protein (> 99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, such as warfarin

- Hepatic and Renal Impairment
  - Pharmacokinetic studies of nitazoxanide have not been performed in patients with renal or hepatic insufficiency
    - Use caution when administering nitazoxanide to patients with hepatic impairment

- Geriatric Patients
  - Studies with nitazoxanide, rifaximin for traveler's diarrhea, and tinidazole did not include a sufficient number of patients aged ≥ 65 years

nitazoxanide (Alinia)
Apple Health Policy

Washington State Health Care Authority

Indications and Products

- Giardiasis
  - nitazoxanide (Alinia)

- Cryptosporidosis
  - nitazoxanide (Alinia)

Nitazoxanide Policy Criteria

- Patient has a diagnosis of infectious diarrhea caused by ONE of the following:
  - *Giardia lamblia*;
    - Patient has failed prior treatment with metronidazole for this episode (defined as no improvement or resolution of symptoms 5 days after completing regimen) or has contraindication to, intolerance to, or culture/sensitivity testing showing antibiotic resistance to metronidazole; **OR**
  - *Cryptosporidium parvum*;
    - Patients must not be immunodeficient or infected with HIV; **AND**
- Maximum dose as follows:
  - Patient greater than or equal to 1 year of age but less than 4 years of age
    - Dose is less than or equal to 200 mg per day for 3 days
  - Patient is greater than or equal to 4 years of age but less than 12 years of age
    - Dose is less than or equal to 400 mg per day for 3 days
  - Patient is greater than or equal to 12 years of age
    - Dose is less than or equal to 1,000 mg per day for 3 days
- If ALL criteria are met, the request will be approved for a 3-day supply.

Motion

- “I move that the Apple Health Medicaid Program implement the clinical criteria listed on slide 123 as recommended.”
  - Motion: Lee
  - 2nd: Figueroa

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

rifaximin (Xifaxan®)

Overview of Disease State

- Traveler's diarrhea
  - Characterized by more than 2 to 5 loose stools per day
    - Symptoms can range from mild cramps and urgent loose stools to severe abdominal pain, fever, vomiting, and bloody diarrhea
  - If untreated, most bacterial illnesses will resolve spontaneously over 3 to 7 days and viral infections in 2 to 3 days
  - Most often caused by ***enterotoxigenic E. coli***, followed by Campylobacter *jejuni*, *Shigella* species, and *Salmonella* species. Ingesting contaminated food or water is the most common mode of acquisition
    - Approximately 10% of traveler's diarrhea is caused by parasitic infections, which can persist for weeks to months, with giardiasis being the most common

  - Treatment
    - Antibiotic chemoprophylaxis for traveler's diarrhea is discouraged for most travelers due to mounting bacterial resistance
    - Symptomatic self-treatment of traveler's diarrhea includes replacement of fluid losses, although traveler's diarrhea in adults is not usually dehydrating
    - Symptomatic treatment with bismuth subsalicylate reduces the number of stools by approximately 50%
    - Other self-treatment options include synthetic opiates, such as loperamide and diphenoxylate
    - Antibiotic therapy includes fluoroquinolones (however, increasing microbial resistance may limit their use), azithromycin, and rifaximin (Xifaxan)
    - Agents no longer recommended due to drug resistance include neomycin, sulfonamides, ampicillin, doxycycline, tetracycline, and trimethoprim

Overview of Disease State

- Irritable bowel syndrome (IBS)
  - A functional bowel disorder which can be chronic, relapsing, and often lifelong
  - Occurs in up to 15% of the population and is up to 2.5 times more common in women than men
  - Patients present with a combination of symptoms that are typically constipation predominant (IBS-C), diarrhea predominant (IBS-D), and/or alternating between both, or mixed (IBS-M)
  - Characterized by symptoms of abdominal pain or discomfort associated with abnormal stool frequency, abnormal stool form, abnormal stool passage, and/or bloating or abdominal distension, which may or may not be relieved by defecation at least 3 days per month in the past 3 months
  - IBS is a chronic condition without a cure. Therefore, treatment of IBS is based on management of the patient's symptoms and may require a combination of modalities to achieve relief
  - The 2014 American Gastroenterological Association (AGA) guidelines on the treatment of IBS recommend rifaximin (Xifaxan) and loperamide over no drug treatment in patients with IBS-D
- Hepatic encephalopathy
  - Occurs in patients with cirrhosis and is characterized by altered consciousness, behavior (apathy, irritability, disinhibition), and motor function
  - Caused by accumulation of nitrogenous substances, primarily ammonia, in the blood
  - In advanced stages, it is referred to as hepatic coma which may be preceded by seizures
  - The treatment goal is to reduce nitrogen load from the GI tract and to improve central nervous system (CNS) status
    - Treatment options include lactulose administered orally or by nasogastric tube or enema, non-absorbable antibiotics, such as rifaximin, and protein-restricted diets
    - Antibiotics are usually second-line therapy
      - Neomycin or paromomycin can suppress the normal bacterial flora in the intestines that produce urease, an enzyme which breaks down urea to carbon dioxide and ammonia
    - Rifaximin is minimally absorbed and affects the normal bacterial flora of the intestines. In severe cases of hepatic encephalopathy, combination therapy can be considered
    - In clinical trials with rifaximin, 91% of patients also received concurrent lactulose therapy for the management of hepatic encephalopathy

rifaximin (Xifaxan®) – Indication, Dosing/Availability

Drug	Indications
rifaximin (Xifaxan®)	• Treatment of traveler's diarrhea caused by noninvasive strains of ***Escherichia coli*** *(*patients ≥ 12 years of age). Rifaximin should not be used in patients with diarrhea complicated by fever or blood in stool or diarrhea due to pathogens other than *E. coli* • Reduction in the risk of overt hepatic encephalopathy recurrence in patients ≥ 18 years of age • Treatment of irritable bowel syndrome (IBS) with diarrhea in adults

Drug	Adult Dosing	Pediatric Dosing	Availability
rifaximin (Xifaxan®)	**Traveler's diarrhea**: 200 mg 3 times daily for 3 days taken with or without food **Reduction in risk of overt hepatic encephalopathy**: 550 mg twice daily taken with or without food **Irritable Bowel Syndrome with Diarrhea**: 550 mg 3 times daily for 14 days May repeat course twice more with recurrence for a maximum of 3 treatment cycles	--	200 mg, 550 mg tablets

rifaximin (Xifaxan®) – Additional Information

- Pediatrics
  - For traveler's diarrhea, safety and effectiveness have not been established in children < 12 years of age
  - For hepatic encephalopathy, safety and effectiveness have not been established in patients < 18 years of age
  - For IBS with diarrhea, safety and effectiveness have not been established in patients < 18
- Pregnancy
  - No available data of use in pregnant women; teratogenic effects have been observed in some animal reproduction studies
- Warnings/Contraindications
  - Should not be used to treat patients with diarrhea complicated by fever or blood in the stool or diarrhea secondary to pathogens other than *E. coli* due to a lack of proven effectiveness
  - Has not been shown to be effective in cases of traveler's diarrhea due to and should not be used if one of these organisms may be suspected as the causative pathogen: ***Campylobacter jejuni, Shigella species,*** and ***Salmonella species***
  - Should be discontinued if diarrhea symptoms worsen or persist more than 24 to 48 hours
  - Is poorly absorbed into the systemic circulation and should not be used to treat systemic infections
  - Caution should be used when administering rifaximin along with a P-glycoprotein (P-gp) inhibitor due to the possibility of a substantial increase in exposure to rifaximin
- Hepatic and Renal Impairment
  - Since rifaximin acts locally in the GI tract, no dosage adjustment is necessary in patients with hepatic impairment
    - However, there is potential for increased systemic exposure of rifaximin with severe hepatic impairment; therefore, caution should be used when prescribing rifaximin to patients with severe hepatic impairment (Child-Pugh C)
  - Pharmacokinetic studies of rifaximin have not been performed in patients with renal insufficiency

rifaximin (Xifaxin)
Apple Health Policy

Washington State Health Care Authority

Indications and Products

- Prophylaxis of hepatic encephalopathy
  - rifaximin (Xifaxan)
- Treatment of irritable bowel syndrome with diarrhea (IBS-D)
  - rifaximin (Xifaxan)
- Treatment of traveler's diarrhea caused by noninvasive strains of*E. coli*
  - rifaximin (Xifaxan)

Hepatic encephalopathy policy: Initial Criteria

- Patient has a history of overt hepatic encephalopathy OR liver cirrhosis
- Patient has **ONE** of the following:
  - Currently stabilized on and will continue to use lactulose at maximally tolerated dose; **OR**
  - History of failure of lactulose, at a maximally tolerated dose for at least 30 days, or contraindication or intolerance to lactulose; **AND**
- Patient is greater than or equal to 18 years of age; **AND**
- Dose less than or equal to 1,100mg per day
- Baseline documentation of serum ammonia and any other measure for which the provider will evaluate the effectiveness of rifaximin for hepatic encephalopathy

- If ALL criteria are met, the request will be approved for 12 months.

Hepatic encephalopathy policy: Reauthorization Criteria

- Documentation of improvements in mental status, a decrease in serum ammonia levels from baseline, decrease in hospitalizations or emergency department visits, or other predefined clinical criteria as specified by the provider

- If ALL criteria are met, the request will be approved for 12 months.

IBS-D Policy: Initial Criteria

- Patient has a history of failure, contraindication or intolerance to **TWO** prior therapies for the treatment of IBS-D:
  - Antidiarrheal (e.g., loperamide); **OR**
  - Antispasmodics (e.g., dicyclomine (Bentyl); **OR**
  - Tricyclic antidepressants (e.g., amitriptyline); **AND**
- Patient is greater than or equal to 18 years of age; **AND**
- Dose less than or equal to 1,650mg per day for 14 days
- Patient has not used more than 2 courses of treatment for IBS-D in lifetime

- If ALL criteria are met, the request will be approved for 14 day supply.

IBS-D Policy: Reauthorization Criteria

- Documentation of improvement in IBS-D related symptoms from previous course(s) of treatment; **AND**
- Documentation with rationale for continued use of rifaximin; **AND**
- Patient has not used more than 2 courses of treatment for IBS-D in lifetime

- If ALL criteria are met, the request will be approved for up to 2 more 14 day supplies.

Noninvasive strains of *E coli* policy: Initial Criteria

- Confirm E coli, patient has failed prior antibiotic treatment for this episode (defined as no improvement or resolution of symptoms after 5 days of completing regimen) or contraindication or intolerance to TWO of the following:
  - Azithromycin; **AND**
  - Ciprofloxacin; **AND**
  - Levofloxacin; **OR**
- Culture/sensitivity testing showing antibiotic resistance to all THREE of the following:
  - Azithromycin; **AND**
  - Ciprofloxacin; **AND**
  - Levofloxacin; **AND**
- Patient has not previously failed rifaximin for current episode or has culture/sensitivity testing showing antibiotic resistance to rifaximin; **AND**
- Patient is greater than or equal to 12 years of age; **AND**
- Dose is less than or equal to 600 mg per day for 3 days

- If ALL criteria are met, the request will be approved for 3 days supply.

Noninvasive strains of *E coli* policy: Reauthorization Criteria

- Requests for renewal or extension beyond the authorized amount for rifaximin for the same treatment episode will be denied as not medically necessary, except:
  - when all other treatment options have been ruled out; **AND**
  - culture/sensitivity testing shows no antibiotic resistance to rifaximin

Motion

- “I move that the Apple Health Medicaid Program implement the clinical criteria listed on slides 132-137 as recommended.”
  - Motion: Flatebo
  - 2nd: Brown

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Burosumab-twza (Crysvita®)

Overview of Disease State - Burosumab-twza (Crysvita®)

- X-linked Hypophosphatemia (XLH) – AKA Phosphate regulating Endopeptidase on the X chromosome (PHEX)
  - A dominant genetic disorder and is due to mutations of chromosome Xp22.1
    - This gene is expressed predominantly in bone and teeth
  - Mutations in PHEX indirectly alter the degradation and production of FGF23 by osteocytes and osteoblasts
    - Excess levels of FGF23 act as a counter-regulatory hormone and decrease renal phosphate resorption and renal production of 1, 25-dihydroxy vitamin D
    - This results in an excess of phosphate excretion and a decrease in intestinal phosphate absorption leading to hypophosphatemia
    - These abnormally low phosphate levels lead to defective mineralization and delayed ossification resulting in a multitude of symptoms, but most notably rickets and/or osteomalacia

- Adult XLH
  - Affects approximately 9,000 to 12,000 adults
  - Experience symptoms such as arthritis, decreased mobility, bone/joint/muscle pain, ligament/tendon attachment abnormalities, fractures, and softening of the bone
  - In contrast to therapy in children, for adults with XLH, once a patient reaches adult height and their epiphyses has fused, the goal of therapy is to manage generalized bone pain and enhance limited mobility

- Crysvita®
  - The approval of Crysvita represents the first therapy that is directed at the underlying disease process of renal phosphate wasting
  - Crysvita acts as an FGF23-blocking antibody by binding to and inhibiting the action of FGF23; therefore, restoring renal phosphate resorption and increasing the serum concentration of 1, 25-dihydroxy vitamin D

Overview of Disease State - Burosumab-twza (Crysvita®)

- Pediatric XLH
  - Estimated that XLH affects about 1 in 20,000 newborns
    - Most cases of XLH are diagnosed in childhood with clinical presentation in the first 2 years of life
  - Diagnosis of XLH can be made by a combination of familial history of the disease, clinical presentation, as well as a classic biochemical profile that consists of: low serum-phosphorus, elevated alkaline phosphatase and low 1, 25-dihydroxy vitamin D levels
  - Testing for FGF23 and genetic testing for PHEX is also available, however these tests are also very inconclusive and not widely used

  - Clinical presentation
    - Poor bone health, abnormal bone formation, bone pain, low bone density, fractures, short stature, tooth abscesses, tinnitus, bow or knock-knee leg deformities, muscle pain/weakness, and waddling gait
    - **The aim of therapy in pediatric XLH patients is to correct or minimize rickets/osteomalacia and to achieve normal growth**
    - Use of oral phosphates transiently increases the serum phosphate concentration, lowering the plasma ionized calcium concentration, which further reduces the plasma calcitriol concentration
      - However, this can also lead to secondary hyperparathyroidism due to both hypocalcemia and removal of the inhibitory effect of calcitriol on parathyroid hormone (PTH) synthesis, thereby aggravating bone disease and increasing urinary phosphate excretion. Therefore, administration of calcitriol is necessary to increase intestinal absorption of calcium and phosphate, and to suppress PTH release directly

Burosumab-twza (Crysvita®) – Indication, Dosing/Availability

Drug	Indications
Burosumab-twza (Crysvita®)	• A fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older

Drug	Adult Dosing	Availability

Burosumab-twza (Crysvita®)	Burosumab-twza is a subcutaneous (SC) injection that should be administered by a healthcare provider
	
	<u>Pediatric XLH patients</u>
	• Starting dose regimen is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered every two weeks
	  • The minimum starting dose is 10 mg up to a maximum dose of 90 mg
	  • Dose may be increased up to approximately 2 mg/kg (maximum 90 mg), administered every two weeks to achieve normal serum phosphorus
	
	<u>Adult XLH patients</u>
	• Starting dose is 1 mg/kg of body weight (rounded up to the nearest 10 mg) SC given every 4 weeks
	• A minimum starting dose of 10 mg with a maximum dose of 90 mg
	• Serum phosphorous should be monitored monthly for the first 3 months of therapy with measurements taken 2 weeks after each dose
	  • Therapy at the same dose may be continued if the patient's serum phosphorous is within a normal range, however if the patient's serum phosphorous measurement is above the normal range, the next dose should be withheld and reassessment completed in 4 weeks
	  • If the serum phosphorous falls below the normal range, the patient is able to reinitiate therapy with Crysvita at half of the initial starting dose up to a maximum of 40 mg every 4 weeks with reassessment of serum phosphorous 2 weeks after any change in dose
		Injection (single-dose vial):
		10 mg/mL
		20 mg/mL
		30 mg/mL

Burosumab-twza (Crysvita®) – Additional Information

- Pediatrics
  - The safety and efficacy of Crysvita have been established in patients of 1 years of age and older
- Pregnancy
  - There is no available data on Crysvita use during pregnancy and any drug-associated risk of adverse developmental outcomes. If pregnancy occurs, serum phosphorous levels should be monitored throughout the pregnancy
- Warnings/Contraindications
  - Crysvita is contraindicated with concomitant use of oral phosphate and active vitamin D analogs; therapy with these agents should be discontinued 1 week prior to initiation
  - Patients who have normal or elevated serum phosphorous levels, as well as those patients with severe renal impairment or end-stage renal disease, are contraindicated for use as these conditions are associated with abnormal mineral metabolism
  - Crysvita carries a warning/precaution for hypersensitivity reactions (e.g. rash, urticarial) as well as severe injection site reactions, and therapy should be discontinued if these severe events occur
  - Based on the mechanism of action, Crysvita can also cause elevations of serum phosphorus to above the upper limit of normal, and increasing the risk of nephrocalcinosis. Therefore, dose interruptions and/or dose reductions may be required based on the patient's serum phosphorus levels
- Adverse Effects
  - The most common (incidence ≥ 10%) adverse effects reported in clinical trials in pediatric patients were: headache (60%), injection site reactions (59%), vomiting (48%), pyrexia (48%), extremity pain (42%), decrease in vitamin D (32%), rash (23%), toothache (22%), tooth abscess (17%), myalgia (15%), and dizziness (12%)
- Hepatic and Renal Impairment
  - The effect of hepatic and renal impairment is unknown
- Geriatric Patients
  - Due to the limited number of patients ≥ 65 years of age in clinical trials, study results should be viewed with caution in this age group

burosumab-twza (Crysvita) Apple Health Policy

Washington State Health Care Authority

Indications and Products

- X-linked hypophosphatemia (XLH)
  - burosumab-twza (Crysvita)

XLH Policy: Initial Criteria

- Diagnosis of X-linked hypophosphatemia confirmed by
  - Genetic testing for PHEX-gene mutations **OR**
  - Serum FGF23 level > 30 pg/mL; **AND**
- Patient age 1 year or older; **AND**
- Serum phosphorus is below normal range for age;**AND**
- Patient has not received oral phosphate or active vitamin D analogs in the previous week;**AND**
- Patient must have an inadequate response or intolerance to oral phosphate and vitamin D treatment for at least 6 months; **AND**
- Patient does not have severe renal impairment, defined as GFR < 30 mL/min; **AND**
- Documentation of clinical signs and/or symptoms of the disease (e.g rickets, growth retardation, musculoskeletal pain, bone fractures) for patients ≥ 18 years old; **AND**
- Prescribed by or in consultation with a specialist experienced in the treatment of metabolic bone disorders.

- If ALL criteria are met, the request will be approved for 6 months.

XLH Policy: Reauthorization Criteria

- Current serum phosphorus level is below the upper limit of lab normal range; **AND**
- Positive clinical response to drug defined as:
  - Increase in serum phosphorus levels, **OR**
  - Improvement in symptoms (e.g. skeletal pain, linear growth, improvement in skeletal deformities, reduction of fractures), **OR**
  - Reduction in serum alkaline phosphatase activity, **OR**
  - Improvement in radiographic imaging of Rickets/osteomalacia; **AND**
- Prescribed by or in consultation with a specialist experienced in the treatment of metabolic bone disorders.

- If ALL criteria are met, the request will be approved for 12 months.

Motion

- "I move that the Apple Health Medicaid Program implement the clinical criteria listed on slides 146-147 as recommended."
  - Motion: Figueroa
  - 2nd: Lee

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Pegvaliase-pqpz (Palynziq™)

Overview of Disease State - Pegvaliase-pqpz (Palynziq™)

- Phenylketonuria (PKU)
  - An inherited disorder that increases the body's levels of phenylalanine and is typically caused by phenylalanine hydroxylase deficiency
    - Humans cannot make phenyalanine, but it is a natural byproduct of the foods consumed
    - People with PKU cannot properly break down the extra phenylalanine to convert it to tyrosine. This means phenylalanine builds up in the person's blood, urine, and body. If PKU is not treated, phenylalanine can build up to harmful levels in the body
    - As an orphan condition, the incidence of PKU is 1 in 13,500 to 19,000 births in the United States (US)
  - PKU varies from mild to severe
    - Severe form is known as classic PKU
      - Without treatment, children with classic PKU develop permanent intellectual disability. Light skin and hair, seizures, developmental delays, behavioral problems, and psychiatric disorders are also common
    - Mild PKU AKA "variant PKU" and "non-PKU hyperphenylalaninemia"
      - Have a smaller risk of brain damage
    - Mothers who have PKU and no longer follow a phenylalanine-restricted diet have an increased risk of having children with an intellectual disability, because their children may be exposed to very high levels of phenylalanine before birth
  - Treatment
    - Dietary restriction of phenylalanine is the cornerstone of therapy in PKU
    - Usually treated with a strict low protein diet and phenylalanine-free medical foods
      - Oral sapropterin (Kuvan) can be used in adults and pediatrics as an adjunct to diet, in patients responsive to tetrahydrobiopterin (BH4)
- Pegvaliase-pqpz (Palynziq)
  - An enzyme therapy for adult PKU patients who have uncontrolled blood phenylalanine concentrations with their current therapy along with a specialized diet
  - Self-administered SC, after initial HCP administration
  - Has a boxed warning for anaphylaxis, requires that patients carry epinephrine auto-injectors, and has a long dose initiation/titration process
  - Widespread adoption of Palynziq may be limited by the high rates of anaphylaxis associated with its use as seen in clinical trials

Pegvaliase-pqpz (Palynziq™) – Indication, Dosing/Availability

Drug	Indications
Pegvaliase-pqpz (Palynziq™)	• A phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management

Drug	Adult Dosing	Availability
Pegvaliase-pqpz (Palynziq™)	**Obtain baseline blood phenylalanine concentration before initiating treatment** • The recommended initial dosage is 2.5 mg subcutaneously once weekly for 4 weeks • Titrate dosage in a step-wise manner over at least 5 weeks based on tolerability to achieve a dosage of 20 mg SQ once daily • Assess patient tolerability, blood phenylalanine concentration, and dietary protein and phenylalanine intake throughout treatment • Consider increasing the dosage to a maximum of 40 mg subcutaneously once daily in patients who have been on 20 mg once daily continuously for at least 24 weeks and who have not achieved either a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to 600 micromol/L • Discontinue Palynziq in patients who have not achieved at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to 600 micromol/L after 16 weeks of continuous treatment with the maximum dosage of 40 mg once daily • Reduce the dosage and/or modify dietary protein and phenylalanine intake, as needed, to maintain blood phenylalanine concentrations within a clinically acceptable range and above 30 micromol/L **Blood Phenylalanine Monitoring and Diet** • Obtain blood phenylalanine concentrations every 4 weeks until a maintenance dosage is established • After a maintenance dosage is established, periodically monitor blood phenylalanine concentrations • Counsel patients to monitor dietary protein and phenylalanine intake, and adjust as directed by their healthcare provider **Premedication** • Consider premedication for hypersensitivity reactions **Administration Instructions** • Rotate injection sites. If more than one injection is needed for a single dose, the injection sites should be at least 2 inches away from each other	Injection (single-dose prefilled syringe): 2.5 mg/0.5 mL 10 mg/0.5 mL 20 mg/mL

Pegvaliase-pqpz (Palynziq™) – Additional Information

- Pediatrics
  - Safety and effectiveness in this patient population has not been established
- Geriatric Patients
  - Clinical trials and studies did not include any patients 65 years old or older
- Pregnancy
  - Insufficient and limited data available for use in pregnant women to determine a drug-associated risk of adverse fetal outcomes
  - Studies of pregnant animals without PKU who were given Palynziq, showed that its use may cause fetal harm when administered
  - Therefore, phenylalanine concentrations need to be closely monitored in women with PKU during pregnancy
  - Pregnant women should be advised of the potential risks to the fetus in either scenario
- Warnings/Contraindications
  - Boxed warning for the risk of **anaphylaxis** which may occur at any time during treatment
    - Measures to reduce the potential for anaphylaxis should be based on the severity of the reaction, recurrence, and clinical judgement, and may include dosage adjustment, temporary drug interruption, or treatment with antihistamines, antipyretics, and/or corticosteroids
    - As a result of the anaphylaxis risk, there is also a Risk Evaluation and Mitigation Strategies (REMS) program for Palynziq requiring provider (prescriber and pharmacy) and patient enrollment
    - In addition, an epinephrine auto-injector must be prescribed for all patients treated with Palynziq
  - As with all therapeutic protein medications, there is potential for the development of immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay
- Adverse Effects
  - The most commonly observed adverse reactions reported in at least 20% of patients taking part in clinical trials were injection site reactions, arthralgia, hypersensitivity reactions, headache, generalized skin reactions, pruritis, nausea, abdominal pain, oropharyngeal pain, vomiting, cough, diarrhea, and fatigue

pegvaliase-pqpz (Palnyziq)
Apple Health Policy

Washington State Health Care Authority

Indications and Products

- Phenylketonuria (PKU)
  - pegvaliase-pqpz (Palnyziq)

PKU Policy: Initial Criteria

- Patient has confirmed diagnosis phenylketonuria (PKU) established by a metabolic specialist; **AND**
- Patient has uncontrolled blood phenylalanine (PHE) concentrations greater than 600 micromol/L over the last 6 months prior to starting pegvaliase; **AND**
- Treatment with sapropterin (Kuvan) has been ineffective, not tolerated, or is contraindicated
  - Ineffectiveness is defined as a decrease in blood PHE levels of less than 30% from baseline after one month of treatment; **AND**
- Patient is greater than or equal to 18 years of age; **AND**
- Palynziq® is not to be used in combination with Kuvan.

- If ALL criteria are met, the request will be approved for 6 months.

PKU Policy: Reauthorization Criteria

- Blood PHE level should have decreased at least 20% from baseline or is less than or equal to 600 µmol/L at the maximum dose of 40 mg/day.

- If ALL criteria are met, the request will be approved for 12 months.

Motion

- “I move that the Apple Health Medicaid Program implement the clinical criteria listed on slides 155-156 as recommended.”
  - Motion: Schwilke
  - 2nd: Buccola

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Cerliponase alfa (Brineura™)

Overview of Disease State - Cerliponase alfa (Brineura™)

- CLN2 disease
  - Belongs to a group of disorders known as Batten disease
  - Occurs in approximately 1 in 200,000 births worldwide
  - A lysosomal storage disorder (LSD), in which genetic mutations disrupt the cells ability to dispose of wastes
    - Mutations in the TPP1/CLN2 gene cause a deficiency of the TPP1 enzyme
    - Results in abnormal storage of proteins and lipids in neurons and other cells and impairs cellular function and motor function
  - Neurodegeneration occurs and is as characterized by seizures, loss of motor function, cognitive decline, and speech and visual impairment
    - The first symptoms usually appear between the ages of 2 and 4 years, typically starting with seizures, followed by regression of developmental milestones
    - Visual impairment appears at age 4 to 6 years and progresses rapidly
    - Most patients lose their ability to walk and talk by 6 years of age
    - Life expectancy is 6 to 12 years
  - Some patients may have a milder form of CLN2, with the first symptoms evident after age 4 years and life expectancy into adulthood

- Cerliponase alfa (Brineura™)
  - A recombinant form of human TPP1
  - It is the only medication approved by the Food and Drug Administration to slow disease progression in patients with CLN2 disease
    - There are no other approved treatment options for CLN2 disease. Current care focuses on symptom management, prevention, treatment of complications, and quality of life
  - Administration requires an implanted device and must occur under sterile conditions by an HCP knowledgeable in intraventricular administration
  - Approval is based on efficacy in a very small non-randomized trial
    - A long-term study is ongoing to evaluate the long-term safety and effectiveness

Cerliponase alfa (Brineura™) – Indication, Dosing/Availability

Drug	Indications
Cerliponase alfa (Brineura™)	• A hydrolytic lysosomal N-terminal tripeptidyl peptidase indicated to slow the loss of ambulation in symptomatic pediatric patients ≥ 3 years of age with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency

Drug	Adult Dosing	Availability
Cerliponase alfa (Brineura™)	• The recommended dosage is 300 mg administered once every other week as an intraventricular infusion followed by infusion of Intraventricular Electrolytes over approximately 4.5 hours • Pre-treatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of infusion • Aseptic technique must be strictly observed during preparation and administration • Should be administered by, or under the direction of a physician knowledgeable in intraventricular administration • Administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter • For complete information on preparation, specific intraventricular access device for use, and administration, see the full prescribing information.	Solution for intraventricular administration Kit contains: • cerliponase alfa injection (2 single-use vials of 150 mg/5 mL) • intraventricular electrolytes injection (1 single-use vial of 5 mL) • two 20 mL syringes • two 21 G syringe needles • one extension line • one infusion set with 0.2 micron inline filter • one 22 G port needle

Cerliponase alfa (Brineura™) – Additional Information

- Pediatrics
  - Safety and effectiveness have not been established in patients younger than 3 years of age
- Hepatic/Renal Impairment
  - There are no data reported in the product labeling regarding use with hepatic or renal impairment
- Pregnancy
  - No data available in women during pregnancy or in animal reproductive studies to inform of a drug-associated risk of harm to the fetus or mother
- Warnings/Contraindications
  - Contraindicated in patients with ventriculoperitoneal (VP) shunts and in patients with acute intraventricular access device-related complications, such as leakage, device failure, or device-related infection
- Adverse Effects
  - If an intraventricular access device complication occurs, discontinue the Brineura infusion and refer to the device labeling for appropriate action
  - Hypotension has been reported during or up to 8 hours after the dose in 8% of patients treated with cerliponase alfa
  - In clinical trials, 46% of patients experienced hypersensitivity reactions, (e.g., pyrexia, vomiting, pleocytosis, irritability) during or within 24 hours after the infusion. Pre-medication with antihistamines with or without corticosteroids is recommended. Anaphylaxis may also occur
  - In clinical studies, the most commonly reported adverse reactions (≥ 10%) include pyrexia (71%), ECG abnormalities (71%), decreased cerebrospinal fluid (CSF) protein (71%), vomiting (63%), seizures (50%), hypersensitivity (46%), increased CSF protein (21%), hematoma (21%), headache (17%), irritability (17%), and pleocytosis (17%)
  - Additional AE can be found in NDU
- Monitoring Parameters
  - Cerebral spinal fluid should be routinely tested to detect subclinical infection of the device
  - Blood pressure and heart rate should be monitored before, during, and after the infusion
  - Electrocardiogram (ECG) should be performed every 6 months; in patients with a history of bradycardia, or a structural heart disease, ECG should be performed during the cerliponase alfa administration

cerliponase alfa (Brineura)
Apple Health Policy

Washington State Health Care Authority

Indications and Products

- Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)
  - cerliponase alfa (Brineura)

- CLN2 is also known as tripeptidyl peptidase 1 (TPP1) deficiency

CLN2 Policy: Initial Criteria

- Patient is 3 years of age or older; **AND**
- Patient has documented diagnosis of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) confirmed by TPP1 deficiency and/or genetic testing to show mutation of the TPP1 gene on chromosome 11p15; **AND**
- Documentation of baseline CLN2 Clinical Rating Scale score; **AND**
- Medication is prescribed by or in consultation with a specialist with expertise in the treatment of CLN2 (e.g. pediatric neurologist, pediatric epileptologist, or geneticist); **AND**
- Patient is ambulatory; **AND**
- Documentation of no acute intraventricular access device-related complications (for example, leakage, device failure, or device-related infection) or ventriculoperitoneal shunt.

- If ALL criteria are met, the request will be approved for 6 months.

CLN2 Policy: Reauthorization Criteria

- Documentation of positive clinical improvement (e.g. no decline in the CLN2 Clinical Rating Scale); **AND**
- Medication is prescribed by or in consultation with a specialist with expertise in the treatment of CLN2 (e.g. pediatric neurologist, pediatric epileptologist, or geneticist); **AND**
- Patient is ambulatory; **AND**
- Documentation of no acute intraventricular access device-related complications (for example, leakage, device failure, or device-related infection) or ventriculoperitoneal shunt.

- If ALL criteria are met, the request will be approved for 12 months.

Motion

- “I move that the Apple Health Medicaid Program implement the clinical criteria listed on slides 164-165 as recommended.”
  - Motion: Huynh
  - 2nd: Brown