

## **Drug Class Update with New Drug Evaluation: Drugs for Paroxysmal Nocturnal Hemoglobinuria**

**Date of Review:** December 2021

**Date of Last Review:** April 2021

**Generic Name:** Pegcetacoplan

**Dates of Literature Search:** 01/01/2020 – 07/20/2021

**Brand Name (Manufacturer):** EMPAVELI

**Dossier Received:** yes

### **Current Status of PDL Class:**

See **Appendix 1**.

### **Purpose for Class Update:**

To define place in therapy for a new immunosuppressive agent, pegcetacoplan, which is Food and Drug Administration (FDA)-approved for treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH). In addition, assess recently published evidence for 2 additional agents, eculizumab and ravulizumab, which are also indicated for management of PNH.

### **Research Questions:**

1. What is the comparative efficacy or effectiveness of drugs indicated for the treatment of PNH in adults?
2. What are the comparative harms of drugs indicated for the treatment of PNH in adults?
3. Are there certain sub-populations (based on age, gender, race, ethnicity, comorbidities, disease duration or severity) in which pegcetacoplan, eculizumab or ravulizumab may be beneficial or cause more harm in adults with PNH?

### **Conclusions:**

#### *Pegcetacoplan*

- The safety and efficacy of pegcetacoplan were evaluated in a 48-week, prospective, randomized, multicenter, open-label, active-comparator controlled trial (PEGASUS).<sup>1</sup> During the 16-week randomized phase of the study, pegcetacoplan was compared with eculizumab in 80 adults with PNH who continued to have hemoglobin levels less than 10.5 g/dL despite treatment with eculizumab.<sup>1</sup> The open-label study design of the trial introduced risk for performance and detection biases.
- The primary efficacy endpoint in the trial was change from baseline in hemoglobin level at week 16.<sup>1</sup> During 16 weeks of treatment, patients in the pegcetacoplan group had an adjusted least squares (LS) mean change from baseline increase in their hemoglobin of 2.4 g/dL, while patients in the eculizumab group had an average decrease in their hemoglobin of 1.5 g/dL; with an LS mean difference of 3.84 g/dL (95% confidence interval [CI], 2.33 to 5.34; P<0.0001), based on low quality evidence.<sup>1</sup>

- Key secondary endpoints were the proportion of patients who did not require a transfusion during the randomized, controlled period and the change from baseline to week 16 in absolute reticulocyte count (ARC), lactate dehydrogenase (LDH) level, and score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale.<sup>1</sup> Low-quality evidence showed pegcetacoplan met noninferiority to eculizumab on transfusion avoidance (pegcetacoplan: 85% patients vs. eculizumab 15% patients; difference, 62.5%; 95% CI 48.3 to 76.8%).<sup>1</sup> Pegcetacoplan was also noninferior to eculizumab for change in ARC, based on low quality evidence (pegcetacoplan –135.8 vs. eculizumab 27.8; LS mean difference –163.6 × 10<sup>9</sup> cells/L; 95% CI, –189.9 to –137.3 × 10<sup>9</sup> cells/L).<sup>1</sup> For change in LDH level, the adjusted mean change from baseline was –15 U/L in the pegcetacoplan group and –10 U/L in the eculizumab group and the noninferiority criterion of -20 U/L change was not met.<sup>1</sup> Scores on the FACIT-F scale were not tested for noninferiority because the between-group difference in LDH level did not meet the noninferiority criterion, thereby causing a break in the hierarchal testing strategy.<sup>1</sup>
- The most common adverse events that occurred during 16-week treatment in the pegcetacoplan and eculizumab groups, respectively, were injection site reactions (39% vs. 3%), infections (29% vs. 26%), diarrhea (22% vs. 3%), headache (7% vs. 23%), and fatigue (12% vs. 23%).<sup>1</sup> Systemic hypersensitivity reactions (e.g., facial swelling, rash, urticaria) have occurred in patients treated with pegcetacoplan. One patient (less than 1% in clinical studies) experienced a serious allergic reaction which resolved after treatment with antihistamines. There are insufficient data to assess the long-term safety of pegcetacoplan.
- Serious infections can occur in patients taking pegcetacoplan that can become life-threatening or fatal if not treated early.<sup>2</sup> Pegcetacoplan is available only through a restricted program under a risk evaluation and mitigation strategy (REMS) because of the risk of severe side effects.<sup>2</sup>
- There is insufficient evidence to evaluate the use of pegcetacoplan in the treatment of specific subpopulations based on age, gender, race, ethnicity, comorbidities, disease duration or severity.

#### *Eculizumab/Ravulizumab*

- National Institute for Health and Care Excellence (NICE) guidance for the use of ravulizumab for treating PNH was issued May 2021.<sup>3</sup> Ravulizumab is recommended as an option for treating PNH in adults: 1) with hemolysis and clinical symptoms suggesting high disease activity, or 2) whose disease is clinically stable after receiving eculizumab for at least 6 months.<sup>3</sup>
- In June 2021 the FDA expanded the approved indications for ravulizumab to include treatment of pediatric patients one month of age and older and weighing 5 kg or greater with PNH and atypical hemolytic-uremic syndrome (aHUS).<sup>4</sup> Ravulizumab was previously approved only for use in adults with PNH or aHUS and pediatric patients less than 18 years of age with aHUS.
- No new head-to-head trials have been published to evaluate the comparative safety and efficacy of eculizumab, ravulizumab or pegcetacoplan therefore comparative evidence remains insufficient.

#### **Recommendations:**

- Revise ravulizumab prior authorization (PA) criteria to reflect expanded indication for use in pediatric patients aged 1 month and older with PNH or aHUS. Revise dosing (**Table 1**) to reflect updated indications.
- Add pegcetacoplan to the “Biologics for Rare Diseases” drug class on the Preferred Drug List (PDL).
- Maintain pegcetacoplan as non-preferred on the PDL.
- Implement clinical prior authorization criteria for pegcetacoplan (**Appendix 4**) to ensure appropriate utilization in FDA-approved indications funded by Oregon Health Plan (OHP).
- After evaluation of costs in executive session, no PDL changes were recommended. Maintain pegcetacoplan as non-preferred.

## Summary of Prior Reviews and Current Policy

At the April 2021 Pharmacy & Therapeutics (P & T) Committee meeting, the P & T Committee reviewed evidence supporting the FDA approval of eculizumab and ravulizumab for the treatment of PNH. A new class of drugs entitled “Biologics for Rare Diseases” was added to the Preferred Drug List (PDL). Eculizumab and ravulizumab were included in this new PDL class. To ensure appropriate utilization in FDA-approved indications funded by OHP, clinical PA criteria were implemented for eculizumab and ravulizumab (**Appendix 4**). Besides PNH, eculizumab is FDA-approved for 3 additional indications including: 1) inhibiting complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS, 2) managing generalized myasthenia gravis (MG) and 3) treatment of adults with neuromyelitis optica spectrum disorder (NMOSD).<sup>5</sup> Ravulizumab is also FDA-approved for treatment of aHUS.<sup>4</sup> After executive session, ravulizumab was designated as a preferred agent on the PDL and eculizumab was designated as non-preferred. Other monoclonal antibodies that are included in the Biologic for Rare Diseases class are listed in **Appendix 1**. In the first quarter of 2021, 2 claims in Fee-for-Service (FFS) population were submitted for eculizumab. No claims were received for other drugs in the Biologics for Rare Disease drug class.

## Background:

Paroxysmal nocturnal hemoglobinuria is a rare disease characterized by uncontrolled complement activation, which leads to a variety of symptoms, including hemolytic anemia, fatigue, and shortness of breath.<sup>6</sup> Other findings associated with PNH include thrombosis, renal insufficiency, and in the later course of the disease, bone marrow failure.<sup>6</sup> PNH results from the expansion of abnormal hematopoietic clones that lack cell-surface complement inhibitory proteins attached to the membrane through glycosylphosphatidylinositol anchors.<sup>7</sup> The rarity of the disease and nonspecific symptoms can result in significant delays in diagnosis.<sup>6</sup> The condition is genetic, with the mutations occurring on the X-linked gene.<sup>6</sup> This mutation of the X-linked gene phosphatidylinositol glycan class A (PIGA) produces a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of erythrocytes.<sup>6</sup> Proteins responsible for the regulation of complement activity, specifically CD55 and CD59, are thereby prevented from attaching to affected cells.<sup>6</sup> This leads to activation of C3, C5, and the terminal pathway of complement culminating in the formation of the membrane attack complex (MAC).<sup>8</sup> Under normal conditions, formation of the MAC is under the regulation of CD59.<sup>8</sup> The absence of CD59 on erythrocytes leads to uncontrolled formation of the MAC resulting in complement-mediated intravascular hemolysis.<sup>8</sup> This chronic state of hemolysis can be exacerbated if the complement system is activated by stress due to surgery, trauma, infection, or other triggers for inflammation.<sup>6</sup> As a result of intravascular hemolysis, the circulating levels of LDH are increased. Lactate dehydrogenase is released upon cell or tissue damage, and an elevated serum LDH level is a measure of erythrocyte injury from ongoing hemolysis.<sup>9</sup> In patients with PNH, LDH is usually elevated and used both as a diagnostic tool and to monitor the severity of hemolysis.<sup>9</sup> LDH levels can be up to 10-times the upper limit of normal (ULN) in untreated PNH.<sup>8</sup> Patients with hemolytic PNH have an average LDH level of  $2,201 \pm 105$  U/L, compared with the normal LDH range of 103 to 223 U/L.<sup>8</sup>

Anemia in PNH is often multifactorial and may result from a combination of hemolysis and bone marrow failure.<sup>8</sup> Intravascular hemolysis with moderate to severe anemia, an elevated reticulocyte count, and up to a 10-fold increase in LDH is common in classic PNH.<sup>8</sup> Patients with classic PNH often have a high percentage of PNH granulocytes (greater than 50%).<sup>8</sup> PNH in the context of other primary marrow disorders usually refers to acquired aplastic anemia.<sup>8</sup> Thrombosis leads to severe morbidity and is the most common cause of mortality in PNH.<sup>8</sup> Thrombosis in PNH may occur at any site; however, venous thrombosis is more common than arterial thrombosis.<sup>8</sup> Abdominal pain, esophageal spasm, dysphagia, and erectile dysfunction are common symptoms associated with classic PNH and are a direct consequence of hemolysis and the release of free hemoglobin.<sup>8</sup> Free hemoglobin is normally cleared by haptoglobin, CD163, and hemopexin.<sup>8</sup> These clearing mechanisms are overwhelmed in PNH and lead to accumulation of high levels of free hemoglobin in the plasma and consequently, depletion of nitric oxide.<sup>8</sup> Renal tubular damage is caused by microvascular thrombosis and accumulation of iron deposits. Raised pulmonary pressures and reduced right ventricular function caused by subclinical microthrombi and hemolysis-associated nitric oxide scavenging contribute to symptoms of fatigue and dyspnea.<sup>8</sup> A classification scheme, proposed by the International PNH Interest Group, includes 3 main categories of PNH: (1) classic

PNH, which includes hemolytic and thrombotic patients; (2) PNH in the context of other primary bone marrow disorders, such as aplastic anemia or myelodysplastic syndrome; and (3) subclinical PNH, in which patients have clones, but no clinical or laboratory evidence of hemolysis or thrombosis.<sup>10</sup> This classification scheme has resulted in some confusion because varying degrees of bone marrow failure underlie virtually all cases of PNH; thus, the distinction between 3 categories may be difficult in some cases.<sup>8</sup>

PNH is rare, with occurrence estimated as 15.9 individuals per million worldwide.<sup>11</sup> Some authors indicate that this number is probably low as the disease remains undiagnosed in individuals with limited symptomatology, or with comorbid conditions that obscure the PNH diagnosis.<sup>12</sup> Typically most patients are diagnosed at 30 years to 40 years of age.<sup>6</sup> Children can be affected by PNH, but it is uncommon.<sup>6</sup> According to an analysis of 1,610 patients registered in the International PNH Registry in 2012, the median age of all registered patients was 42 years, with the disease duration of 4.6 years.<sup>13</sup> The age range of patients in the registry was 3 to 99 years.<sup>13</sup> While the occurrence of PNH has no apparent ethnic or geographic distribution, there is an increased risk of thrombosis in the United States (US) and Europe.<sup>6</sup> About 30 to 40% of PNH cases are reported in the US and Europe, whereas less than 10% of PNH cases are reported from Asia.<sup>6</sup> Consequently, the incidence of thromboembolism due to PNH is higher in the US and Europe compared to Japan.<sup>14</sup> Patients affected by PNH in the US demonstrate differences in complications according to ethnic groups. African-Americans with PNH have a 73% incidence of thromboembolism and Latin Americans have about a 50% incidence.<sup>6</sup> White and Asian Americans have a 36% incidence of thromboembolism complications.<sup>6</sup> Bone marrow failure also varies with ethnicity and geography.<sup>6</sup> It is more common in residents of Asia, the Pacific Islands, and Latin America.<sup>6</sup> The reasons for these variations are not clear.<sup>6</sup>

In the past, PNH treatment was mostly supportive.<sup>6</sup> Patients were given a blood transfusion and iron supplementation for anemia from recurrent hemolysis and anti-thrombosis prophylaxis was initiated to prevent thrombosis.<sup>6</sup> For severe, life-threatening bone marrow complications, an allogeneic bone marrow transplant was offered.<sup>6</sup> The mainstay of current therapy for PNH includes the C5 inhibitors eculizumab and ravulizumab.<sup>6</sup> These agents prevent cleavage and the formation of the MAC which averts complement-mediated intravascular hemolysis. Although C5 inhibitor therapies control intravascular hemolysis and have improved the disease trajectory for patients with PNH, some patients continue to have suboptimal C5 blockade, resulting in a potential risk of continued extravascular hemolysis, elevated LDH, and sustained risk of thromboembolic events.<sup>8</sup> Surviving PNH erythrocytes become opsonized with C3 fragments and are removed by extravascular hemolysis in the liver and spleen.<sup>1</sup> Extravascular hemolysis is observed in most patients with PNH who are being treated with C5 inhibitors and leads to reduced erythrocyte half-life (10 to 13 days).<sup>1</sup> Low hemoglobin levels, elevated reticulocyte counts, elevated bilirubin levels, continued need for red blood cell (RBC) transfusions, and persistent patient-reported fatigue are indicators of ongoing disease activity despite treatment with C5 inhibitors.<sup>15</sup> Other novel therapy development projects are focusing on targets upstream in the complement pathway, such as C1, C3, and Factor D inhibitors.<sup>6</sup>

#### **Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

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**Systematic Reviews:** No new systematic reviews have been published since the last class update.

**New Guidelines:**

**High Quality Guidelines**

***National Institute for Health and Care Excellence***

NICE guidance for the use of ravulizumab in treating PNH was issued May 2021.<sup>3</sup> Paroxysmal nocturnal hemoglobinuria is currently treated with eculizumab infusions every 2 weeks. Clinical trial evidence shows that ravulizumab and eculizumab are similarly safe and effective.<sup>3</sup> Ravulizumab is administered less often than eculizumab. Ravulizumab is recommended as an option for treating PNH in adults when: 1) hemolysis and clinical symptoms suggest high disease activity, or 2) disease is clinically stable after eculizumab treatment for at least 6 months.<sup>3</sup>

**New Formulations or Indications:**

In June 2021, the FDA expanded the approved indications for ravulizumab to treatment of pediatric patients one month of age and older and weighing 5 kg or greater with PNH and aHUS.<sup>4</sup> Ravulizumab was previously approved only for use in adults with PNH or aHUS and pediatric patients less than 18 years of age with aHUS. The expanded pediatric indication was based upon extrapolation of evidence from RCTs in adults and patients aged 9 to 17 years.<sup>4</sup> The manufacturer of ravulizumab, Alexion Pharmaceuticals, supplies the product in 2 concentrations: 100 mg/mL and 10 mg/mL.<sup>4</sup>

**New FDA Safety Alerts:** No new safety alerts focused on eculizumab or ravulizumab have been issued in the past year.

**Randomized Controlled Trials:**

A total of 5 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

**NEW DRUG EVALUATION: Pegcetacoplan**

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

**Clinical Efficacy:**

Pegcetacoplan received FDA approval May 2021 for the treatment of adult patients with PNH.<sup>2</sup> Pegcetacoplan binds to complement protein C3, which prevents intravascular and extravascular hemolysis.<sup>1</sup> In contrast, protein C5 inhibition only targets intravascular hemolysis. The recommended pegcetacoplan dosage is 1,080 mg by subcutaneous infusion twice weekly via a commercially available pump.<sup>2</sup> Pegcetacoplan is intended for use under the guidance of a healthcare professional (HCP).<sup>2</sup> After proper training, a patient may self-administer the drug, or the patient's caregiver may administer pegcetacoplan if the HCP determines that is appropriate.<sup>2</sup>

Pegcetacoplan was approved based upon results from the phase 3 PEGASUS study and two phase 2 trials in patients naïve to anti-complement therapy.<sup>16</sup> The PEGASUS study details are described and evaluated below in **Table 4**. PEGASUS was a 48-week randomized, multicenter, open-label, active-comparator controlled study that evaluated the efficacy and safety of pegcetacoplan compared with eculizumab in 80 adults with PNH who continued to have hemoglobin levels less than 10.5 g/dL despite treatment with eculizumab.<sup>1</sup> The treatment period of the study consisted of three parts: 1) a 4-week run-in period in which

patients received both pegcetacoplan and their current eculizumab dose, 2) a 16-week randomized controlled period in which patients were randomized to receive either pegcetacoplan or eculizumab monotherapy, and 3) a 32-week open-label pegcetacoplan-only period. The 4 week run-in period was for safety purposes to avoid abruptly switching patients from eculizumab to pegcetacoplan. Patients were randomized 1:1 to receive either 1,080 mg of pegcetacoplan twice weekly (n=41) or their current dosage of eculizumab (n=39) during the 16-week randomized controlled period.<sup>1</sup> If a patient did not respond sufficiently to the twice weekly dosing regimen (LDH greater than 2-times the ULN), the dose of pegcetacoplan could be adjusted to 1,080 mg every 3 days.<sup>1</sup> In the pegcetacoplan arm, 2 patients required every 3-day dosing.<sup>1</sup>

Treatment groups were generally balanced with regard to baseline characteristics, including transfusions in the previous 12 months and baseline hemoglobin levels (~8.7 g/dL in both groups).<sup>1</sup> The most common eculizumab dosing regimen was 900 mg every 2 weeks (70% of patients), consistent with the FDA-approved label.<sup>1</sup> Thirty percent of patients on eculizumab were on a dose greater than the FDA-approved dose.<sup>1</sup> Specifically, these patients received 1,200 mg every 2 weeks (26.3%), 1,500 mg every 2 weeks (2.5%), or 900 mg every 11 days (1.3%).<sup>1</sup> If a patient required a transfusion during the 16-week randomized period, their data collected after the transfusion was excluded from descriptive statistics for all efficacy endpoints.<sup>1</sup> If a patient discontinued study treatment, any values collected after discontinuation continued to be used in analyses.<sup>1</sup> Data from patients who withdrew from the study were handled in the same manner as for patients who received transfusions.<sup>1</sup>

The primary efficacy endpoint was change from baseline in hemoglobin level at week 16 after randomization to pegcetacoplan or eculizumab.<sup>1</sup> The between-treatment group comparison for the primary efficacy endpoint was performed using a mixed-effect model for repeated measures.<sup>1</sup> Pegcetacoplan was superior to eculizumab with regard to change from baseline in hemoglobin level: the adjusted LS mean change from baseline was 2.4 g/dL for pegcetacoplan and -1.5 g/dL for eculizumab, with an adjusted LS mean difference of 3.84 g/dL (95% CI, 2.33 to 5.34; P<0.0001).<sup>1</sup>

Key secondary end points were the proportion of patients who did not require a transfusion during the 16 week randomized period and the change from baseline to week 16 in ARC, LDH level, and score on the FACIT-F scale (scores range from 0 to 52, with higher scores indicating less fatigue).<sup>1</sup> A FACIT-F score of 43.6 is considered normal for a healthy adult.<sup>1</sup> Secondary end-point analyses were based on hierarchical assessments and prespecified noninferiority margins.<sup>1</sup> For the proportion of patients who avoided transfusions, if the lower bound of the 95% CI for the difference was greater than the noninferiority margin of -20%, pegcetacoplan was considered noninferior to eculizumab and testing proceeded with the 16-week change in ARC.<sup>1</sup> For the change in ARC, if the upper bound of the 95% CI for the difference between the treatment groups was less than the noninferiority margin of  $10 \times 10^9/L$ , pegcetacoplan was considered noninferior to eculizumab and testing proceeded with the 16-week change in LDH level.<sup>1</sup> For the change in LDH from baseline to week 16, if the upper bound of the 95% CI for the difference between the treatment groups was less than the noninferiority margin of 20 U/L, pegcetacoplan was considered noninferior to eculizumab and testing proceeded with the 16-week change in FACIT-F score.<sup>1</sup>

Pegcetacoplan was noninferior to eculizumab in transfusion avoidance and ARC.<sup>1</sup> Eighty-five percent of pegcetacoplan patients and 15% of eculizumab patients were transfusion-free over the 16-week randomized controlled period (difference: 62.5%; 95% CI 48.3 to 76.8%).<sup>1</sup> The change at 16 weeks from baseline in ARC was  $-136 \times 10^9$  cells/L for pegcetacoplan and  $28 \times 10^9$  cells/L for eculizumab arms with an LS mean difference of  $-163.6 \times 10^9$  cells/L (95% CI  $-189.9 \times 10^9$  cells/L to  $-137.3 \times 10^9$  cells/L).<sup>1</sup> For change at 16 weeks from baseline in the endpoint of LDH level, the noninferiority criterion of -20 U/L change was not met; the adjusted mean change from baseline was -15 U/L in the pegcetacoplan group and -10 U/L in the eculizumab group.<sup>1</sup> Changes in fatigue levels as measured by the FACIT-F scale, were not tested for noninferiority because the between-group difference in LDH level did not meet the noninferiority criterion, thereby causing a break in the hierarchical testing strategy.<sup>1</sup> FACIT-F scores increased with pegcetacoplan by 9.2 points and decreased with eculizumab by 2.7 points.<sup>1</sup> A 3-

point change in FACIT-F score is considered clinically significant.<sup>1</sup> The adjusted mean difference in FACIT-Fatigue scores between pegcetacoplan and eculizumab was 11.9 points (95% CI, 5.49-18.25) at 16 weeks.<sup>1</sup> These are numerical differences, and no comparisons can be drawn between the two arms.<sup>1</sup>

The Pegasus study has several biases that impact the quality of the data. The study population was limited to a subset of patients with PNH with a hemoglobin level of less than 10.5 g/dL despite 3 months of eculizumab treatment. Data from this trial cannot be extrapolated to treatment-naïve adults. The study was not double-blinded for patients or investigators, and the open-label trial design does not exclude the potential for performance or detection bias.<sup>1</sup> Differences in underlying disease severity may have played a role in a small subgroup of patients (n=2) who required dose adjustments in pegcetacoplan after cessation of eculizumab.<sup>1</sup> The PRINCE study, a phase 3 open-label, multicenter, randomized, controlled study is currently ongoing. The study is evaluating the efficacy and safety of pegcetacoplan in adults with PNH who are C5 treatment-naïve. The results of this study will be reported upon study completion.

**Clinical Safety:**

The most common adverse events that occurred during treatment over 16 weeks in the pegcetacoplan and eculizumab groups, respectively, were injection site reactions (39% vs. 5%), infections (29% vs. 26%), diarrhea (22% vs. 3%), headache (7% vs. 23%), and fatigue (12% vs. 23%).<sup>1</sup> The majority of injection-site reactions were mild and occurred early in the trial; none resulted in discontinuation.<sup>1</sup> Systemic hypersensitivity reactions (e.g., facial swelling, rash, urticaria) have occurred in patients treated with pegcetacoplan.<sup>2</sup> One patient (less than 1% in clinical studies) experienced a serious allergic reaction which resolved after treatment with antihistamines.<sup>2</sup> Long term safety data for pegcetacoplan is insufficient. The adverse reactions reported during the PEGASUS trial are summarized in **Table 2**.

**Table 2. Adverse Reactions Reported In 5% Or More Of Patients Treated With Pegcetacoplan Compared With Eculizumab<sup>2</sup>**

Adverse Reactions	Pegcetacoplan n=41	Eculizumab n=39
Injection-site reaction	39%	5%
Infections	29%	26%
Diarrhea	22%	3%
Abdominal Pain	20%	10%
Respiratory tract infection	15%	13%
Viral Infection	12%	8%
Fatigue	12%	23%
Back Pain	7%	10%
Chest Pain	7%	3%
Headache	7%	23%
Hypertension	7%	3%

Due to complement inhibition, meningococcal infections may occur in patients treated with pegcetacoplan and may become rapidly life-threatening or fatal if not recognized and treated early.<sup>2</sup> Use of pegcetacoplan may predispose individuals to serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B.<sup>2</sup> There were no cases of meningitis reported in either treatment arm of the PEGASUS trial.<sup>1</sup> Patients were vaccinated against encapsulated bacteria prior to study enrollment to reduce the risk of serious

infection.<sup>1</sup> Pegcetacoplan is available only through a restricted REMS program. An FDA black boxed warning in the manufacturer’s prescribing information contains the following guidance:

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria in patients with altered immunocompetence associated with complement deficiencies.<sup>2</sup>
- Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of pegcetacoplan unless the risks of delaying therapy with pegcetacoplan outweigh the risk of developing a serious infection.<sup>2</sup>
- Vaccination reduces, but does not eliminate, the risk of serious infections. Monitor patients for early signs of serious infections and evaluate immediately if infection is suspected.<sup>2</sup>

Look-alike / Sound-alike Error Risk Potential: No issues have been reported.

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Decrease hemolysis as measured by change in LDH level
- 2) Stabilize anemia requiring blood transfusions
- 3) Reduce fatigue that impacts quality of life
- 4) Improve survival
- 5) Serious adverse events
- 6) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Change in hemoglobin level from baseline to week 16

**Table 3. Pharmacology and Pharmacokinetic Properties<sup>2</sup>**

Parameter	
Mechanism of Action	Complement protein C3 inhibitor
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 3.9 L; Protein Binding N/R
Elimination	Clearance is 0.37 L/day
Half-Life	8 days
Metabolism	Pegcetacoplan is expected to be metabolized into small peptides and amino acids by catabolic pathway

Abbreviations: L=Liters; N/A=not applicable; N/R=not reported



				Difference: 11.9 95% CI 5.49 to 18.25 NI not assessed	NA			
<p><b>Abbreviations:</b> AC = active comparator; ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; dL = deciliter; FACIT-F scale = Functional Assessment of Chronic Illness Therapy-Fatigue; Hgb = hemoglobin; IRT = interactive response technology; ITT = intention to treat; IV = intravenous; L = liter; LDH = lactate dehydrogenase; LSM = least squares mean; MC = multi-center; MD = mean difference; MI = myocardial infarction; mo = months; N = number of subjects; NA = not applicable; NI = noninferiority; NIM = noninferiority margin; NNH = number needed to harm; NNT = number needed to treat; OL = open label; PNH = postural nocturnal hemoglobinuria; PP = per protocol; PRBC = packed red blood cells; RCT = randomized clinical trial; SC = subcutaneous; y = years; U = units; ULN = upper limits of normal; US = United States</p>								

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## Appendix 1: Current Preferred Drug List

### Biologics for Rare Conditions

Generic	Brand	Route	Form	PDL
ravulizumab-cwvz	ULTOMIRIS	INTRAVEN	VIAL	Y
inebilizumab-cdon	UPLIZNA	INTRAVEN	VIAL	Y
satralizumab-mwge	ENSPRYNG	SUB-Q	SYRINGE	Y
eculizumab	SOLIRIS	INTRAVEN	VIAL	N

Medications highlighted in grey are indicated for PNH within this drug class.

### Uncategorized Medication

Generic	Brand	Route	Form	PDL
pegcetacoplan	EMPAVELI	SQ	VIAL	

## Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 2 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 20, 2021

1. *exp Hemoglobinuria, Paroxysmal/* 1829
2. *eculizumab.mp.* 1674
3. *ravulizumab.mp.* 48
4. *complement C3/or pegcetacoplan.mp* 4795
5. *2 or 3 or 4* 6377
6. *1 and 5* 381
7. *limit 6 to (english language and humans)* 329
8. *limit 7 to (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial or controlled clinical trial or guideline or meta-analysis or randomized controlled trial or "systematic review")* 5

## Appendix 3: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EMPAVELI safely and effectively. See full prescribing information for EMPAVELI.

EMPAVELI™ (pegcetacoplan) injection, for subcutaneous use  
Initial U.S. Approval: 20XX

#### WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

See full prescribing information for complete boxed warning.

Meningococcal infections may occur in patients treated with EMPAVELI and may become rapidly life-threatening or fatal if not recognized and treated early. Use of EMPAVELI may predispose individuals to serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B. (5.1).

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria. (5.1)
- Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of EMPAVELI unless the risks of delaying EMPAVELI therapy outweigh the risks of developing a serious infection. See *Warnings and Precautions* (5.1) for additional guidance on managing the risk of serious infections.
- Vaccination reduces, but does not eliminate, the risk of serious infections. Monitor patients for early signs of serious infections and evaluate immediately if infection is suspected. (5.1)

EMPAVELI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the EMPAVELI REMS, prescribers must enroll in the program. (5.2)

#### INDICATIONS AND USAGE

EMPAVELI is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). (1)

#### DOSAGE AND ADMINISTRATION

- Recommended dosage is 1,080 mg by subcutaneous infusion twice weekly via a commercially available pump. (2.2)
- See Full Prescribing Information for instructions on preparation and administration. (2.2, 2.3)

#### DOSAGE FORMS AND STRENGTHS

- Injection: 1,080 mg/20 mL (54 mg/mL) in a single-dose vial. (3)

#### CONTRAINDICATIONS

EMPAVELI is contraindicated in:

- Patients with hypersensitivity to pegcetacoplan or any of the excipients. (4)
- Patients who are not currently vaccinated against certain encapsulated bacteria unless the risks of delaying EMPAVELI treatment outweigh the risks of developing a serious bacterial infection with an encapsulated organism. (4, 5.1)
- Patients with unresolved serious infection caused by encapsulated bacteria. (4)

#### WARNINGS AND PRECAUTIONS

Use caution when administering EMPAVELI to patients with:

- Serious infections caused by encapsulated bacteria. (5.1)
- Infusion-Related Reactions: Monitor patients for infusion-related reactions and institute appropriate medical management as needed. (5.3)
- Interference with Laboratory Tests: Use of silica reagents in coagulation panels may result in artificially prolonged activated partial thromboplastin time (aPTT). (5.5)

#### ADVERSE REACTIONS

Most common adverse reactions in patients with PNH (incidence  $\geq 10\%$ ) were injection-site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, viral infection, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apellis Pharmaceuticals, Inc. at 1-833-866-3346 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2021

Appendix 4: Prior Authorization Criteria

**Eculizumab (Soliris®)**

**Goal(s):**

- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Eculizumab is approved by the FDA for the following indications:
  - Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody positive
  - Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)
  - Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)
  - Treatment of generalized myasthenia gravis (MG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive

**Length of Authorization:**

Up to 12 months

**Requires PA:**

- Soliris® (eculizumab) pharmacy and physician administered claims

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
3. Is this request for continuation of therapy?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #4

## Approval Criteria

<p>4. Has the patient been vaccinated against <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i> type B, and <i>Neisseria meningitidis</i> serogroups A, C, W, and Y and serogroup B according to current Advisory Committee on Immunization Practice (ACIP) recommendations for vaccination in patients with complement deficiencies?</p> <p>Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2 week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.</p>	<p><b>Yes:</b> Go to #5</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>
<p>5. Is the diagnosis one of the following:</p> <ul style="list-style-type: none"> <li>• Neuromyelitis Optica Spectrum Disorder (NMOSD) in an adult who is anti-aquaporin-4 (AQP4) antibody positive,</li> <li>• Paroxysmal Nocturnal Hemoglobinuria (PNH),</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>• atypical Hemolytic Uremic Syndrome (aHUS)? (Note: Eculizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).</li> </ul>	<p><b>Yes:</b> Go to #6</p>	<p><b>No:</b> Go to #7</p>
<p>6. Does the requested dosing align with the FDA- approved dosing (<b>Table 1</b>)?</p>	<p><b>Yes:</b> Approve for 12 months</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>
<p>7. Is the request for a diagnosis of myasthenia gravis in an adult patient who is ACh Receptor (AChR) antibody-positive?</p>	<p><b>Yes:</b> Go to # 8</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>

Approval Criteria		
<p>8. Has the patient tried:</p> <ul style="list-style-type: none"> <li>at least 2 or more immunosuppressant therapies (e.g., glucocorticoids in combination with azathioprine or mycophenolate mofetil or cyclosporine or tacrolimus or methotrexate or rituximab) for 12 months without symptom control OR</li> <li>at least 1 or more nonsteroidal immunosuppressant with maintenance intravenous immunoglobulin once monthly or plasma exchange therapy (PLEX) over 12 months without symptom control?</li> </ul>	<b>Yes:</b> Go to #9	<b>No:</b> Pass to RPh. Deny; medical appropriateness
<p>9. Is the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score <math>\geq 6</math>?</p>	<b>Yes:</b> Approve for 12 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
<p>1. Is there objective documentation of treatment benefit from baseline?</p> <p>Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom control or improvement, functional improvement, etc.).</p>	<p><b>Yes:</b> Approve for 12 months</p> <p>Document baseline assessment and physician attestation received.</p>	<b>No:</b> Pass to RPh. Deny; medical appropriateness

**Table 1. FDA-Approved Indications and Dosing for Eculizumab<sup>1</sup>**

	Eculizumab (Soliris <sup>®</sup> )
<b>FDA-approved Indications</b>	<ul style="list-style-type: none"> <li>Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody</li> <li>Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)</li> <li>Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)</li> <li>Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive</li> </ul>

<b>Recommended NMOSD dose in patients 18 yo and older</b>	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
<b>Recommended PNH dose in patients 18 yo and older</b>	600 mg IV every week x 4 weeks, followed by 900 mg IV for the fifth dose 1 week later, then 900 mg IV every 2 weeks thereafter		
<b>Recommended aHUS dose in patients less than 18 yo</b>	<b>Body Weight</b>	<b>Induction Dose</b>	<b>Maintenance Dose</b>
	5 kg to 9 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300mg every 3 weeks
	10 kg to 19 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300mg every 2 weeks
	20 kg to 29 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600mg every 2 weeks
	30 kg to 39 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
	≥ 40 kg	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
<b>Recommended aHUS dose in patients 18 yo and older</b>	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
<b>Recommended generalized MG dose</b>	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
<b>Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion</b>	Dependent on most recent eculizumab dose: refer to prescribing information for appropriate dosing (300 mg to 600 mg)		

1. Soliris (eculizumab) Solution for Injection Prescribing Information. Boston, MA: Alexion Pharmaceuticals, Inc. 11/2020.

P&T/DUR Review: 12/21; 4/21 (DM)  
Implementation: 5/1/21

## Ravulizumab (Ultomiris®)

### **Goal(s):**

- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Ravulizumab is approved by the FDA for the following indications:
  - The treatment of adults and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH)
  - Inhibiting complement-mediated thrombotic microangiopathy in adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS)

### **Length of Authorization:**

Up to 12 months

### **Requires PA:**

- Ultomiris® (Ravulizumab) pharmacy and physician administered claims

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is this request for continuation of therapy?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to # 4
4. Has the patient been vaccinated against <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> type B, and <i>Neisseria meningitidis</i> serogroups A, C, W, and Y and serogroup B according to current Advisory Committee on Immunization Practice (ACIP) recommendations for vaccination in patients with complement deficiencies?  Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2 week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness
5. Is the diagnosis for a patient at least 1 month of age or older and weighs at least 5 kg with atypical Hemolytic Uremic Syndrome (aHUS) or Paroxysmal Nocturnal Hemoglobinuria (PNH) ?  Note: Ravulizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).	<b>Yes:</b> Go to #6	<b>No:</b> Pass to RPh. Deny; medical appropriateness

## Approval Criteria

6. Does the requested dosing align with the FDA- approved dosing ( <b>Table 1</b> )?	<b>Yes:</b> Approve for 12 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness
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## Renewal Criteria

<p>1. Is there objective documentation of treatment benefit from baseline?</p> <p>Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).</p>	<p><b>Yes:</b> Approve for 12 months</p> <p>Document baseline assessment and physician attestation received.</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>
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**Table 1. FDA-Approved Intravenous Infusion Dosing for Ravulizumab<sup>1</sup>**

Body Weight	Loading Dose	Maintenance Dose (begins 2 weeks after loading dose)
5 to 9 kg	600 mg	300 mg every 4 weeks
10 to 19 kg	600 mg	600 mg every 4 weeks
20 to 29 kg	900 mg	2,100 mg every 8 weeks
30 to 39 kg	1,200 mg	2,700 mg every 8 weeks
40 to 59 kg	2,400 mg	3,000 mg every 8 weeks
60 to 99 kg	2,700 mg	3,300 mg every 8 weeks
100 kg or greater	3,000 mg	3,600 mg every 8 weeks

1. Ultomiris™ (Ravulizumab-cwvz) Solution for Intravenous Infusion Prescribing Information. Boston, MA: Alexion Pharmaceuticals Inc. 6/2021.

P&T/DUR Review: 12/21 (DM); 4/21 (DM)  
Implementation: 1/1/22; 5/1/21

## Pegcetacoplan (Empaveli™)

### Goal(s):

- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Pegcetacoplan is approved by the FDA for the following indication:
  - Treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH)

### Length of Authorization:

Up to 12 months

### Requires PA:

- Empaveli™ (pegcetacoplan) pharmacy and physician administered claims

### Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is this request for continuation of therapy?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to # 4

Approval Criteria		
<p>4. Has the patient been vaccinated against <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i> type B, and <i>Neisseria meningitidis</i> serogroups A, C, W, and Y and serogroup B according to current Advisory Committee on Immunization Practice (ACIP) recommendations for vaccination in patients with complement deficiencies?</p> <p>Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2 week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.</p>	<p><b>Yes:</b> Go to #5</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>
<p>5. Is the diagnosis for an adult (age 18 years or older) with Paroxysmal Nocturnal Hemoglobinuria (PNH)?</p>	<p><b>Yes:</b> Approve for 12 months</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>

Renewal Criteria		
<p>1. Is there objective documentation of treatment benefit from baseline?</p> <p>Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).</p>	<p><b>Yes:</b> Approve for 12 months</p> <p>Document baseline assessment and physician attestation received.</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>

P&T/DUR Review: 12/21 (DM)  
Implementation: 1/1/22