CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215014Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;

(B) The seriousness of the disease or condition that is to be treated with the drug;

(C) The expected benefit of the drug with respect to such disease or condition;

(D) The expected or actual duration of treatment with the drug;

(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Empaveli (pegcetacoplan) to ensure that the benefits of the drug outweigh the risks of serious and life threatening infections caused by encapsulated bacteria. In reaching this determination, we considered the following:
A. The estimated number of patients in the United States with paroxysmal nocturnal hemoglobinuria (PNH) is 15.9 per million. This estimate is based on Hill A, et al. Blood. 2006; 108(11)L 290a.

B. PNH is a rare, progressive, and life-threatening disease characterized by uncontrolled complement activation leading to hemolytic anemia (both intravascular and extravascular), peripheral cytopenias, increased susceptibility to thrombosis, and bone marrow dysfunction (Brodsky 2014). PNH leads to significant morbidity and mortality with ongoing hemolysis and the disease is considered life-threatening. Morbidities for patients with PNH include thromboembolism, pulmonary hypertension, renal and cardiac failure, infection, myelodysplastic syndrome, and aplastic anemia. The reported median survival prior to available therapies was 10 to 22 years.

C. The effectiveness of pegcetacoplan was evaluated in APL2-302, an adequate and well controlled trial. Study APL2-302 demonstrated the beneficial effect of pegcetacoplan compared to eculizumab in improving Hb levels in adult patients with PNH receiving eculizumab with continued Hb levels <10.5 g/dL.

D. There is a continued unmet medical need for alternative treatment options for PNH that control hemolysis in both the intravascular and extravascular compartments. Patient’s benefiting from treatment may be continued on pegcetacoplan twice weekly, indefinitely.

E. Pegcetacoplan is a complement protein (C) 3 inhibitor. An important risk associated with C3 inhibition is increased susceptibility to serious infections caused by encapsulated bacteria including Streptococcus pneumoniae, Hemophilus influenzae, and Neisseria meningitidis. These infections are serious, life-threatening, and often require hospitalization and significant medical management. Use of eculizumab has been associated with a 1000-fold to 2000-fold increased incidence of meningococcal disease (Applegate et al. 2015), It is unknown whether pegcetacoplan will follow the established meningococcal infection risk profile of the C5 inhibitors. There were no reports of meningococcal infection or other serious infections with encapsulated bacteria through 161.7 person-years of systemic pegcetacoplan exposure in the clinical trials submitted in support of efficacy and/or safety determinations for pegcetacoplan (Studies APL-302, APL2-202, APL2-CP-PNH-204, CP0514, APL2-307 and APL2-308).

In Study APL2-302, the most commonly reported treatment emergent adverse events (>5%) associated with pegcetacoplan monotherapy were injection site reactions, infections, diarrhea, and abdominal pain. Additional risks include systemic hypersensitivity reactions (e.g., facial swelling, rash, urticaria).

F. Empaveli is a new molecular entity.
The elements of the REMS will be prescriber certification, pharmacy certification, an implementation system and a timetable for submission of assessments of the REMS.

The elements of the REMS will be elements to assure safe use, including that healthcare providers who prescribe Empaveli (pegcetacoplan) are specially certified, pharmacies and healthcare settings that dispense pegcetacoplan are specially certified, the drug is dispensed to patients with evidence or other documentation of safe use (vaccination history including antibiotic prophylaxis will be assessed and documented by pharmacies that dispense Empaveli (pegcetacoplan)), an implementation system and a timetable for submission of assessments of the REMS.

References


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/s/

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type: NDA
Application Number: 215014
PDUFA Goal Date: May 14, 2021
OSE RCM #: 2020-1932

Reviewer Name(s):
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Deputy Division Director: Doris Auth, Pharm.D.
Review Completion Date: May 13, 2021
Subject: Evaluation of Need for a REMS

Established Name: Pegcetacoplan
Trade Name: Empaveli
Name of Applicant: Apellis Pharmaceuticals, Inc.
Therapeutic Class: Complement inhibitor
Formulation(s): 1080 mg vial
Dosing Regimen: Pegcetacoplan 1080 mg subcutaneous infusion twice-weekly via a commercially available infusion pump.

Dosage for patients switching to pegcetacoplan from C5 inhibitors:
- For patients switching from eculizumab, initiate pegcetacoplan while continuing eculizumab at its current dose. After 4 weeks, discontinue eculizumab before continuing on monotherapy with pegcetacoplan.
- For patients switching from ravulizumab, initiate pegcetacoplan no more than 4 weeks after the last dose of ravulizumab.
## Table of Contents

EXECUTIVE SUMMARY ................................................................................................................................. 4

1 Introduction .................................................................................................................................................. 4

2 Background .................................................................................................................................................. 5
   2.1 Product Information ................................................................................................................................. 5
   2.2 Regulatory History ................................................................................................................................. 5

3 Therapeutic Context and Treatment Options ............................................................................................ 6
   3.1 Description of the Medical Condition ..................................................................................................... 6
   3.2 Description of Current Treatment Options ............................................................................................. 7

4 Benefit Assessment .................................................................................................................................... 7

5 Risk Assessment & Safe-Use Conditions .................................................................................................... 8
   5.1 Serious Infections Caused by Encapsulated Bacteria .............................................................................. 8
   5.2 Infusion-Related Reactions ..................................................................................................................... 9
   5.3 Monitoring PNH Manifestations after Discontinuation of EMPAVELI ................................................. 9
   5.4 Interference with Laboratory Tests ......................................................................................................... 9

6 Expected Postmarket Use .......................................................................................................................... 10

7 Risk Management Activities Proposed by the Applicant ............................................................................ 10
   7.1 Review of Applicant’s Proposed REMS ................................................................................................. 10
      7.1.1 REMS Goals ...................................................................................................................................... 10
      7.1.2 REMS Requirements ......................................................................................................................... 11
      7.1.3 Implementation System ..................................................................................................................... 13
      7.1.4 Timetable for Submission of Assessments of the REMS ................................................................ 13
      7.1.5 REMS Materials & Key Risk Messages .......................................................................................... 13
      7.1.6 REMS Assessment Plan ..................................................................................................................... 14
      7.1.7 REMS Supporting Document ........................................................................................................... 14
   7.2 Other Proposed Risk Management Activities ......................................................................................... 14

Reference ID: 4795364
EXECUTIVE SUMMARY

This review evaluates the proposed risk evaluation and mitigation strategy (REMS) for Empaveli (pegcetacoplan) to mitigate the risks of serious infections caused by encapsulated bacteria (*Streptococcus pneumoniae, Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B). Apellis Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 215014 for pegcetacoplan with the proposed indication for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). The serious risks associated with pegcetacoplan include serious infections caused by encapsulated bacteria, infusion-related reactions, monitoring PNH manifestations after discontinuation of Empaveli, and interference with laboratory tests. The applicant submitted a proposed REMS with elements to assure safe use (ETASU) to mitigate the risk of serious infections caused by encapsulated bacteria that consists of prescriber certification, pharmacy certification, an implementation system, and a timetable for submission of assessments.

The Division of Risk Management (DRM) and the Division of Non-Malignant Hematology (DNH) agree that a REMS with ETASU is needed to ensure the benefits of pegcetacoplan outweigh its risks. The risk of infections caused by encapsulated bacteria (*Streptococcus pneumoniae, Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B) with pegcetacoplan is serious and severe. It is necessary for prescribers to understand the risk of serious infections caused by encapsulated bacteria, the need for vaccination and antibiotic prophylaxis if required, the need to counsel patients, and the importance of monitoring for these risks. Based on the magnitude and severity of the risk, we agree that requiring a REMS with ETASU consisting of ETASU A (healthcare providers who prescribe pegcetacoplan are specially certified), ETASU B (pharmacies and healthcare settings that dispense pegcetacoplan are specially certified), and ETASU D (vaccination history including antibiotic prophylaxis will be assessed and documented by pharmacies that dispense pegcetacoplan), is necessary to ensure that the benefits outweigh the risk of serious infections caused by encapsulated bacteria.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)* Empaveli (pegcetacoplan) is necessary to ensure the benefits outweigh its risks. Apellis Pharmaceuticals, Inc. submitted a NDA 215014 for pegcetacoplan with the proposed indication for treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). This application is under review in the Division of Non-Malignant Hematology (DNH). The applicant submitted a REMS with elements to assure safe use (ETASU) for this application that consists of prescriber certification, pharmacy certification, an implementation system, and a timetable for submission of assessments to mitigate the risk of serious infections caused by encapsulated bacteria.

This review is written by the Division of Risk Management (DRM), in consultation with the Office of Prescription Drug Promotion (OPDP).

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*Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.*
2 Background

2.1 PRODUCT INFORMATION
Empaveli (pegcetacoplan), a NME, is a complement inhibitor proposed for treatment of adult patients with PNH. Pegcetacoplan binds to complement protein C3 and its activation fragment C3b, regulating the cleavage of C3 and the generation of downstream effectors of complement activation. It is supplied as a 1080 mg vial for subcutaneous injection. The proposed dosing regimen is pegcetacoplan 1080 mg subcutaneous infusion twice weekly via a commercially available infusion pump. For patients switching from eculizumab, initiate pegcetacoplan while continuing eculizumab at its current dose. After 4 weeks, discontinue eculizumab before continuing on monotherapy with pegcetacoplan. For patients switching from ravulizumab, initiate pegcetacoplan no more than 4 weeks after the last dose of ravulizumab. Pegcetacoplan was designated as an orphan product. Pegcetacoplan is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for pegcetacoplan NDA 215014 relevant to this review:

- 04/20/2014: Orphan drug designation granted
- 5/20/2020: Pre-NDA meeting with the sponsor where the FDA agreed with the applicant to submit a REMS for the risk of infections due to encapsulated bacteria
- 9/14/2020: NDA 215014 submission for treatment of adult patients with PNH received
- 01/21/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that their proposed REMS is currently under review
- 03/22/2021: Information Request (IR) sent to sponsor requesting a complete set of REMS website screenshots showing all content and functionality of the website, including screenshots showing online enrollment for prescribers, and a formatted version of REMS materials that incorporate any design elements and branding
- 03/26/2021: REMS Oversight Committee (ROC) meeting was held to discuss the proposed REMS with the goal of mitigating the risk of serious infections caused by encapsulated bacteria in patients who are to receive treatment with pegcetacoplan. The ROC agreed with the proposed REMS with ETASU for pegcetacoplan to mitigate the risk of serious infections caused

\[b\] Section 505-1 (a) of the FD&C Act: **FDAAA factor (D): The expected or actual duration of treatment with the drug.**

\[c\] As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.
by encapsulated bacteria. ROC members noted there needs to be reassurance that patients will be able to administer this product using proper aseptic technique.

- 03/29/2021: Apellis Pharmaceuticals, Inc. submitted PDF files of the REMS materials. The REMS document and REMS supporting document were submitted to replace the placeholder “BRAND” with “EMPAVELI”.
- 04/21/2021: The Agency sent comments to Apellis Pharmaceuticals, Inc. on the REMS materials.
- 04/30/2021: Apellis Pharmaceuticals, Inc. submitted the REMS materials.
- 05/04/2021: The Agency sent comments to Apellis Pharmaceuticals, Inc. on the REMS, REMS assessment plan, and REMS materials.
- 05/06/2021: A meeting was held between the Agency and the Applicant via teleconference to discuss questions on the collection of vaccination information by certified pharmacies in the Empaveli REMS. The Agency also discussed with the applicant identification of a key performance indicator for the Empaveli REMS.
- 05/06/2021: The Agency sent comments to Apellis Pharmaceuticals, Inc. on the REMS materials. The Agency also sent comments to Apellis Pharmaceuticals, Inc. on the key performance indicator and target for the Empaveli REMS.
- 05/07/2021: Apellis Pharmaceuticals, Inc. submitted the REMS document, REMS supporting document, and REMS materials.
- 05/10/2021: The Agency sent comments to Apellis Pharmaceuticals, Inc. on the REMS materials.
- 05/11/2021: The Agency sent comments to Apellis Pharmaceuticals, Inc. on the REMS supporting document.
- 05/11/2021: Apellis Pharmaceuticals, Inc. submitted the REMS supporting document and REMS materials.
- 05/12/2021: The Agency sent comments to Apellis Pharmaceuticals, Inc. on the REMS supporting document.
- 05/12/2021: Apellis Pharmaceuticals, Inc. submitted the REMS supporting document.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition
Paroxysmal nocturnal hemoglobinuria is a rare, chronic, life-threatening disorder characterized by complement-mediated hemolytic anemia, bone marrow failure, and increased risk of thrombosis. Hemolysis can result in symptoms including fatigue, chest pain, transfusion dependence, and abdominal
pain. Paroxysmal nocturnal hemoglobinuria has significant morbidities which lead to a reduced quality of life.\textsuperscript{d} The incidence of PNH is estimated at 0.1-0.2/100,000 persons per year.\textsuperscript{8,e}

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Two C5 complement inhibitors including eculizumab (Soliris) and ravulizumab (Ultomiris) have been approved by the FDA for the treatment of patients with PNH. Eculizumab was approved by the FDA for the treatment of patients with PNH to reduce hemolysis, the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy, the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive, and the treatment of neuromyelitis optica spectrum disorder in adult patients who are anti-aquaporin-4 antibody positive.\textsuperscript{9} Ravulizumab was approved by the FDA for the treatment of adult patients with PNH and the treatment of adults and pediatric patients one month of age and older with aHUS to inhibit complement-mediated thrombotic microangiopathy.\textsuperscript{10} These two C5 complement inhibitors have a boxed warning and REMS with ETASU to mitigate the risk of serious meningococcal infections.

Eculizumab and ravulizumab primarily act to reduce intravascular hemolysis. Despite C5 inhibitor therapy, there is a proportion of patients who continue to have evidence of anemia and need for packed red blood cell transfusions, which is due to ongoing extravascular hemolysis not controlled by this therapy.

4 Benefit Assessment

The pivotal trial NCT 03500549 (Study APL2-302) supporting this application for efficacy and safety consisted of a Phase 3, randomized, open label, active controlled study which evaluated pegcetacoplan in patients with PNH who had been treated with a stable dose of eculizumab for at least the previous 3 months and with hemoglobin (Hb) levels less than 10.5 g/dL.\textsuperscript{1,5,11} Patients entered a 4 week run in period in which they received pegcetacoplan 1080 mg subcutaneously twice weekly in addition to their current dose of eculizumab. Patients (N=80) were then randomized to pegcetacoplan 1080 mg twice weekly (N=41) or their current dose of eculizumab (N=39). The primary endpoint was change from baseline to Week 16 in Hb level. The adjusted mean change from baseline in Hb level was 2.37 g/dL in the pegcetacoplan group and -1.47 g/dL in the eculizumab group, adjusted mean difference 3.84 g/dL with pegcetacoplan compared to eculizumab at Week 16 (95% CI 2.33 to 5.34, p < 0.0001). The FDA

\textsuperscript{d} Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

\textsuperscript{e} Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.
clinical reviewer concluded Study APL2-302 indicated that pegcetacoplan was effective in improving Hb levels in patients with PNH compared with eculizumab.  

5 Risk Assessment & Safe-Use Conditions

The safety of pegcetacoplan was evaluated in NCT 03500549 (Study APL2-302). In the safety population from APL2-302, 41 patients received pegcetacoplan and 39 patients received eculizumab. Common adverse reactions reported with pegcetacoplan included injection-site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, viral infection, and fatigue.

The serious risks associated with pegcetacoplan, which include serious infections caused by encapsulated bacteria, infusion-related reactions, monitoring PNH manifestations after discontinuation of Empaveli, and interference with laboratory tests, are summarized in the sections below. If approved, labeling will include a boxed warning to communicate the serious risk of serious infections caused by encapsulated bacteria. In addition to labeling, pegcetacoplan will require an ETASU REMS to ensure the benefits outweigh the risks of these serious infections. The other serious risks including infusion-related reactions, monitoring PNH manifestations after discontinuation of Empaveli, and interference with laboratory tests will be communicated in the warnings and precautions section of the label.

5.1 Serious Infections Caused by Encapsulated Bacteria

Section 5 and a boxed warning in the draft labeling indicates that pegcetacoplan may predispose patients to serious, life-threatening, or fatal infections caused by encapsulated bacteria including Streptococcus pneumoniae, Neisseria meningitidis types A, C, W, Y, and B, and Haemophilus influenzae type B (Hib). To date, there have been no reported cases of serious infections caused by encapsulated bacteria in the pivotal trial, Study APL2-302, or in the three supportive trials for this application (APL-2-204, APL2-202, APL2-CP0514). In the clinical trial program, patients received vaccinations if required (if not previously vaccinated) against S. pneumoniae, N. meningitidis A, C, W, Y, and B, and H. influenzae. In addition, prophylactic antibiotics were administered under the direction of the investigator to minimize potential infection risk. Antibiotics were given in accordance with local regulations.

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<sup>†</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

<sup>§</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

<sup>h</sup> Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
treatment guidelines for patients with PNH who are receiving treatment with a complement inhibitor. However, pegcetacoplan inhibits C3 complement. Systemic complement inhibition leads to the predisposition to infections caused by serious encapsulated organisms, including S. pneumoniae, N. meningitidis, and H. influenzae. Based on the literature of patients with C3 deficiency, there is an increased risk of serious infection with encapsulated bacteria. Infections reported in patients with C3 deficiency involve the respiratory system, meninges, and blood stream and these infections are serious and potentially life-threatening.

The proposed label recommends that, to reduce the risk of infection, all patients must be vaccinated against encapsulated bacteria including S. pneumoniae, N. meningitidis, and H. influenzae type B according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with altered immunocompetence associated with complement deficiencies and to revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with pegcetacoplan. The proposed label recommends to vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of pegcetacoplan unless the risks of delaying pegcetacoplan therapy outweigh the risk of developing a serious infection. If immediate therapy with pegcetacoplan is indicated, administer required vaccine as soon as possible and provide patients with 2 weeks of antibacterial drug prophylaxis. The proposed label also recommends to monitor patients for early signs of serious infections and evaluate immediately if infection is suspected.

To mitigate the risk of serious infections caused by encapsulated bacteria with pegcetacoplan therapy, the sponsor proposed a REMS program, that requires pegcetacoplan only be available through this restricted program, and that prescribers and pharmacies must enroll in the program. In the Sponsor’s proposal, prescribers must counsel patients about the risk of serious infection, provide the patients with the REMS educational materials, and assess the patient’s vaccination status and immunize if needed against encapsulated bacteria.

5.2 Infusion-Related Reactions
Section 5 of the draft labeling indicates that systemic hypersensitivity reactions, including facial swelling, rash, and urticaria, have been reported with pegcetacoplan. The proposed label recommends to discontinue pegcetacoplan infusion immediately for severe hypersensitivity reactions and to institute appropriate treatment and monitor until signs and symptoms are resolved.

5.3 Monitoring PNH Manifestations after Discontinuation of Empaveli
Section 5 of the draft labeling recommends to closely monitor patients for signs and symptoms of hemolysis after discontinuation of pegcetacoplan. The proposed label recommends to monitor any patient who discontinues pegcetacoplan for at least 8 weeks to detect hemolysis and other reactions. If hemolysis, including elevated LDH, occurs after discontinuation of pegcetacoplan, to consider restarting treatment with pegcetacoplan.

5.4 Interference with Laboratory Tests
Section 5 of the draft labeling indicates that there may be interference between silica reagents in coagulation panels and pegcetacoplan, resulting in artificially prolonged activated partial thromboplastin time (aPTT). The proposed label recommends to avoid the use of silica reagents in coagulation panels.
6 Expected Postmarket Use

If approved, pegcetacoplan will primarily be used in outpatient settings such as outpatient infusion centers or in home settings. It may be self administered by the patient or administered by the patient’s caregiver, if the healthcare provider determines that it is appropriate.

Similar to Soliris and Ultomiris, the likely prescribers of pegcetacoplan for the proposed indication are hematologists and oncologists. However, there are ongoing clinical trials with pegcetacoplan in patients with geographic atrophy, amyotrophic lateral sclerosis, C3 glomerulopathy, immune complex membranoproliferative glomerulonephritis and cold agglutinin disease.3

7 Risk Management Activities Proposed by the Applicant

7.1 REVIEW OF APPLICANT’S PROPOSED REMS

To mitigate the risk of serious infections caused by encapsulated bacteria, the Applicant submitted prescribing information that contained a boxed warning, a Medication Guide as part of labeling, and a REMS.

The Applicant submitted a REMS proposal that included a REMS document, REMS materials and REMS Supporting Document. The proposed REMS submitted on September 14, 2020, included elements to assure safe use (ETASU) that included prescriber certification (A), pharmacy certification (B), an implementation system, and a timetable for submission of the assessment of the REMS.

Section 7.1.1 and 7.1.2 reflects the Applicant’s initial submission on September 14, 2020 and on March 29, 2021. During the review of this application the Applicant has amended their proposal based on feedback from the review team. Section 8.1 and the REMS document in the appendix of this review reflects the final agreed upon REMS.

7.1.1 REMS Goals

The Applicant’s proposed the following:
Reviewer's Comments: See section 8 for FDA changes to the REMS goals.

7.1.2 REMS Requirements
The Sponsor initially proposed the following ETASU as part of the REMS requirements: prescriber and pharmacy certification.
Reviewer’s Comments: We agree with the Applicant’s proposal to require prescriber certification as part of the REMS. A REMS with ETASU A would ensure that prescribers are educated on the risk of serious infections caused by encapsulated bacteria with pegcetacoplan and the need to counsel patients. The prescriber would need to certify in the REMS prior to prescribing pegcetacoplan and agree to monitor patients as described in labeling. The prescriber would need to assess the patient’s vaccination status prior to starting pegcetacoplan and vaccinate patients against encapsulated bacteria (S. pneumoniae, N. meningitidis types A, C, W, Y, and B, and H. influenzae type B) if needed at least 2 weeks prior to the first dose of pegcetacoplan. If immediate therapy with pegcetacoplan is indicated prior to vaccination, vaccination should occur as soon as possible, and patients should be provided with 2 weeks of antibiotic prophylaxis.
We also agree with the Applicant’s proposal for pharmacy certification to ensure that prescribers are certified in the REMS program prior to dispensing. The Pharmacy Enrollment Form is used to support this ETASU. To further inform if education and certification of prescribers results in appropriate vaccination of patients, we recommend the collection of a vaccination history for each patient at the initiation of treatment to assess compliance with vaccination and prophylactic antibiotics in patients prior to starting treatment with pegcetcoplan. Pharmacist documentation of vaccination history and antibiotic prophylaxis requires that the REMS include ETASU D (The drug be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results). See section 8 for FDA changes to the pharmacy certification (ETASU B) and a discussion on ETASU D.

The REMS Document that was submitted by the applicant has been amended on May 7, 2021, the REMS submitted on May 7, 2021 has addressed out comments and is attached in the appendix of this review.

7.1.3 Implementation System
The Applicant’s proposed implementation system includes:

- REMS Program Website
- REMS Call Center
- Secure data base
- Establish plans to detect and address noncompliance
- Take reasonable steps to improve implementation and compliance

Reviewer’s Comments: The proposed implementation system is appropriate for the REMS and we have no comments.

7.1.4 Timetable for Submission of Assessments of the REMS
The applicant proposed to submit REMS Assessments at 6 months, 12 months, and annually from the date of initial approval of the REMS.

Reviewer’s Comments: This is acceptable.

7.1.5 REMS Materials & Key Risk Messages
The Applicant included the following materials as part of the original submission of the REMS:

- Healthcare Provider Brochure
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Patient Safety Guide
- Patient Wallet Card
- REMS website

Reviewer’s Comments: We agree with the Applicant’s proposed REMS materials, but also communicated on March 22, 2021, April 21, 2021, May 4, 2021, May 6, 2021, and May 10, 2021 that changes were needed to the proposed materials.
The Applicant did not include key risk messages with their submissions of the REMS materials. See section 8 of this review for our proposed key risk messages.

7.1.6 REMS Assessment Plan
The Applicant included a REMS assessment plan for the proposed REMS in their REMS Supporting Document submitted on September 14, 2020, March 29, 2021 and May 7, 2021.

_Reviewer’s Comments:_ We provided a revised REMS assessment plan to the Applicant on May 4, 2021, which reflects current assessment plan categories for REMS assessments, and includes metrics for vaccine and antibiotic prophylaxis that the certified pharmacies will collect. In a teleconference with Apellis on May 6, 2021, the Agency discussed the recommended key performance indicator (KPI) of prescriber enrollment, and the recommended performance target for this KPI of 98%. On May 7, 2021 the Applicant provided an updated assessment plan that was acceptable. The final and agreed upon REMS Assessment Plan is included in the Appendix 10.2 of this review.

7.1.7 REMS Supporting Document
_Reviewer’s Comments:_ During the review of the application the Applicant revised their REMS Supporting Document to align with the changes to the amended REMS and REMS materials.

7.2 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES
The applicant did not propose other risk management activities.

8 Discussion of Need for a REMS
The FDA clinical reviewer recommends approval of pegcetacoplan on the basis of the efficacy and safety information currently available. Pegcetacoplan is a complement inhibitor and is an additional treatment option for adult patients with PNH. The efficacy of pegcetacoplan was supported by Study APL2-302, in which pegcetacoplan was effective in improving Hb levels in patients with PNH compared with eculizumab.

DNH and DRM agree that, should pegcetacoplan be approved, a REMS with ETASU will be needed to ensure that the benefits of pegcetacoplan outweigh its risks. The risk associated with pegcetacoplan of serious infections caused by encapsulated bacteria are serious and severe. Pegcetacoplan inhibits C3 complement; systemic complement inhibition leads to the predisposition to infections caused by serious encapsulated organisms, including _S. pneumoniae, N. meningitidis, and H. influenzae_. Patients with C3 deficiency have an increased risk of serious infection with encapsulated bacteria. Infections reported in patients with C3 deficiency involve the respiratory system, meninges, and blood stream and these infections are serious and potentially life-threatening. There have been no reported cases of serious infections caused by encapsulated bacteria with pegcetacoplan in the clinical development program. However, in the clinical trial program, patients received vaccinations if required against _S. pneumoniae, N. meningitidis A, C, W, Y, and B, and H. influenzae_ and prophylactic antibiotics were administered under the direction of the investigator to minimize potential infection risk. Pegcetacoplan
was also studied only in 80 patients, and infections may occur in the postmarketing setting. In addition, there are two approved complement inhibitors (Soliris, Ultomiris) that are approved with a REMS with ETASU for similar risks (i.e., serious meningococcal infections). Furthermore, the proposed risk mitigations measures that include vaccination and prophylactic antibiotics can mitigate the risk and severity of infections due to encapsulated bacteria; however, vaccination reduces but does not eliminate the risk of serious infections.

A REMS with ETASU would ensure that prescribers are educated on the risk of serious infections caused by encapsulated bacteria with pegcetacoplan and the need to counsel patients. For this REMS, the prescriber would need to certify in the REMS prior to prescribing pegcetacoplan and agree to monitor patients as described in labeling. As described in the Prescriber Enrollment form, before treatment initiation (at least 2 weeks before the first dose) the prescriber would need to assess the patient’s vaccination status and immunize if needed according to the current Advisory Committee on Immunization Practices for the following: S. pneumoniae, N. meningitidis types A, C, W, Y, and B, and H. influenzae type B. The prescriber would provide the patient with a prescription for a 2-week course of antibiotic prophylaxis if pegcetacoplan must be started less than 2 weeks after the patient was immunized. Pharmacy certification will ensure that prescribers are certified in the REMS program prior to dispensing.

The REMS for pegcetacoplan was discussed at the REMS Oversight Committee (ROC) on March 26, 2021. The ROC agreed with the proposed REMS with ETASU for pegcetacoplan to mitigate the risk of serious infections caused by encapsulated bacteria. However, ROC members noted there needs to be reassurance that patients will be able to administer this product using proper aseptic technique. The DNH has indicated that the proposed pegcetacoplan IFU addresses the ROCs concern about proper aseptic technique by patients. The DMEPA reviewer for this application stated that the product IFU and the various pump IFUs should appropriately instruct users how to use the product safely – including from an aseptic technique standpoint.15

The other serious risks associated with pegcetacoplan of infusion-related reactions, monitoring PNH manifestations after discontinuation of Empaveli, and interference with laboratory tests will be communicated in the warnings and precautions section of the label.

8.1 REMS REQUIREMENTS AND DESIGN
The proposed intervention in this REMS is educating health care providers who prescribe pegcetacoplan. A REMS with ETASU is needed to ensure that prescribers are educated on the risk of serious infections caused by encapsulated bacteria with pegcetacoplan, the need for vaccination and antibiotic prophylaxis if required, the need to counsel patients, and agree to monitor patients as described in labeling. Pharmacy certification will ensure that prescribers are certified in the REMS program prior to dispensing. To further inform if education and certification of prescribers in the REMS results in appropriate vaccination of patients, we recommend that pharmacists obtain a vaccination history for each patient at the initiation of treatment to assess compliance with vaccination and prophylactic antibiotics in patients prior to starting treatment with pegcetacoplan.
The following sections 8.1.1. and 8.1.2 describe the final REMS submission provided by the Applicant on May 7, 2021.

8.1.1 REMS Goals
The REMS goals should be as follows:

The REMS goals are to mitigate the occurrence and morbidity associated with encapsulated bacteria infections (Streptococcus pneumoniae, Neisseria meningitidis types A, C, W, Y, and B, and Haemophilus influenzae type B) by educating healthcare providers and patients about:

1. the potential risk of infections caused by encapsulated bacteria with Empaveli
2. the need for vaccination and antibiotic prophylaxis, if required,
3. the early signs of invasive encapsulated bacteria infections, and
4. the need for immediate medical evaluation of signs and symptoms consistent with possible encapsulated bacteria infections

The modifications to the REMS goals are clearer and can provide a better framework for the assessment. Furthermore, the modifications to the REMS goals will align with the other complement inhibitors for the same indication as pegcetacoplan. We provided the revised REMS goals to the Applicant on May 4, 2021. The applicant agreed with the changes to the REMS goals but aligned the sequence of encapsulated bacteria with the proposed label. The DRM agrees with these proposed changes.

8.1.2 REMS Requirements
The following REMS requirements have been added under pharmacy certification (ETASU B).

To become certified to dispense

- Establish processes and procedures to contact the prescriber to assess the patient’s vaccination history including antibiotic prophylaxis and document the findings.

Before dispensing

- Assess the patient’s vaccination history including antibiotic prophylaxis by contacting the prescriber and document the findings through the processes and procedures established as a requirement of the REMS Program.

Pharmacists will be required to obtain a vaccination history for each patient at the initiation of treatment to assess compliance with vaccination and prophylactic antibiotics in patients prior to starting treatment with pegcetacoplan to further inform whether the educational intervention of the REMS results in appropriate vaccination of patients. The applicant agreed with the changes to pharmacy certification. Assessment of adherence to vaccine and antibiotic prophylaxis recommendations are also discussed in section 8.1.4 below.

Requiring pharmacists to document vaccination history and antibiotic prophylaxis requires the inclusion of ETASU D (The drug be dispensed to patients with evidence or other documentation of safe use
conditions, such as laboratory test results) in this REMS. However, this requirement is not linked to a condition associated with dispensing but is necessary for assessment of the REMS.

8.1.3 REMS Materials & Key Risk Messages
The key risk messages for healthcare providers are:

1. Meningococcal infections may occur in patients treated with Empaveli and may become rapidly life-threatening or fatal if not recognized and treated early.
2. 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 (Hib).
3. Vaccinate patients against encapsulated bacteria, at least 2 weeks prior to administering first dose unless delaying Empaveli therapy outweighs the risk of developing a serious infection.
4. Provide 2 weeks of antibacterial drug prophylaxis to patients if Empaveli must be initiated immediately and vaccines are administered less than 2 weeks before starting therapy.
5. Assess patients for early signs of serious infections and treat immediately if infection is suspected.
6. Counsel patients using the Patient Safety Brochure and Patient Wallet Card on:
   - the requirement to vaccinate patients against encapsulated bacteria.
   - recognizing and responding to signs and symptoms of serious bacterial infection, using the Patient Safety Guide and Patient Wallet Card.
7. Instruct patient to carry the Patient Wallet Card at all times during treatment and for 2 months after the last Empaveli dose. Tell patients to show the wallet card to any healthcare professional that provides treatment.

The key risk messages for patients/caregivers are:

1. Empaveli may increases the risk of getting serious infections.
2. Serious infections may quickly become life threatening and cause death if not recognized and treated early.
3. These serious infections are caused by certain bacteria. You must be vaccinated against certain bacteria at least 2 weeks before your first dose of EMPAVALI unless you have already had the vaccines.
4. Call your doctor or get emergency medical care right away if you get any signs or symptoms of a serious infection.
   a. Signs and symptoms may include: fever with or without shivers or the chills, fever and a rash, shortness of breath, extreme pain or discomfort, headache with nausea or vomiting, high heart rate, headache and a fever, headache with a stiff neck or stiff back, confusion, muscle aches with flu-like symptoms, clammy skin, eyes sensitive to light.
5. Carry the Empaveli Patient Wallet Card at all times during treatment and for 2 months after your last Empaveli dose. Show the card to any healthcare provider that treats you.

8.1.4 REMS Assessment Plan
The REMS Assessment Plan is included in the Appendix 10.2 of this review.
The goal of the REMS is to mitigate the occurrence and morbidity associated with encapsulated bacteria infections (*Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B) by educating healthcare providers and patients about:

1. the potential risk of infections caused by encapsulated bacteria with Empaveli
2. the need for vaccination and antibiotic prophylaxis, if required,
3. the early signs of invasive encapsulated bacteria infections, and
4. the need for immediate medical evaluation of signs and symptoms consistent with possible encapsulated bacteria infections

The Empaveli REMS must include an assessment of the extent to which the REMS is meeting its risk mitigation goals. The Empaveli REMS Assessment Plan includes metrics to inform this goal as well as to provide information about the implementation and overall functioning of the REMS.

The primary intervention of the Empaveli REMS is education of healthcare providers who prescribe Empaveli. It is expected that education on the risks of encapsulated bacteria infections and the need for vaccination and antibiotic prophylaxis, therefore, will result in appropriate vaccination and antibiotic prophylaxis. Healthcare providers who prescribe will also be educated on the early signs of invasive encapsulated bacteria infections and the need for immediate medical evaluation of signs and symptoms consistent with possible encapsulated bacteria infections. As a condition of enrollment, prescribers attest that they understand these risks, agree to immunize their patients prior to treatment, prescribe antibiotic prophylaxis if necessary, and counsel patients on the risks, the signs and symptoms of invasive encapsulated bacteria infections and when they should seek medical evaluation for symptoms consistent with encapsulated bacteria infections. Only pharmacies that are certified in the Empaveli REMS can receive Empaveli and as a condition of the REMS must ensure that prescriptions are only dispensed to patients if the prescriber is enrolled in the Empaveli REMS.

The key performance indicator, or the metric that will be used to evaluate the success of the Empaveli REMS, therefore, is enrollment of prescribers of Empaveli. The target for this key performance indicator, is that 98% of dispensed prescriptions for Empaveli, will have been prescribed by enrolled prescribers during each REMS assessment period. Other REMS programs designed to address a similar risk, but that lack a requirement for pharmacy enrollment, have achieved this level of compliance or higher with prescriber education. Although less frequent, there are clinical circumstances that occur when a patient will need urgent treatment and prescribers may not have not had time to enroll in the REMS program.

Other metrics that will support our understanding of whether the REMS is meeting its goal of educating healthcare providers and patients will be surveys to assess healthcare provider and patient knowledge, vaccination and prophylactic antibiotic use, and adverse event data.

**Healthcare provider and patient knowledge**
Knowledge of the risks of Empaveli, the need for vaccination or antibiotic prophylaxis, the signs and symptoms of invasive bacteria infections and the need for immediate medical evaluation of the signs and symptoms consistent with possible encapsulated bacteria infections will be evaluated by periodic surveys of HCPs enrolled in the REMS and patients receiving Empaveli. The sponsor should submit protocols used to evaluate healthcare provider and patient knowledge, including thresholds for
knowledge for each stakeholder survey, at least 90 days prior to conducting the surveys in order to allow FDA time to review and comment.

**Vaccination and antibiotic prophylaxis**
The Empaveli REMS will require that pharmacists obtain vaccination and antibiotic prophylaxis history for patients receiving Empaveli to assist in determining if the intervention of educating prescribers results in patients being vaccinated or receiving prophylactic antibiotics. No benchmark for complete vaccination history or antibiotic prophylaxis has been predetermined for this metric. It may be helpful to compare the rate of vaccination of individuals with complement deficiencies to help in establishing a benchmark for vaccination of patients taking Empaveli.

**Adverse events**
Lastly, information from adverse event reports of serious bacterial infections will inform our understanding of the occurrence of these events in patients receiving Empaveli, and whether these events are occurring in vaccinated as well as unvaccinated patients or those who have received prophylactic antibiotics.

### 9 Conclusion & Recommendations,

The risk of serious infections caused by encapsulated bacteria (*S. pneumoniae*, *N. meningitidis* types A, C, W, Y, and B, and *H. influenzae* type B) with pegcetacoplan is serious and severe and it is necessary for prescribers to understand this risk, the need for vaccination and antibiotic prophylaxis if required, the need to counsel patients, and the importance of monitoring for them. Based on the magnitude and severity of the risk, we agree that requiring a REMS with ETASU consisting of ETASU A (healthcare providers who prescribe pegcetacoplan are specially certified), ETASU B (pharmacies and healthcare settings that dispense pegcetacoplan are specially certified), and ETASU D (vaccination history including antibiotic prophylaxis will be assessed and documented by pharmacies that dispense pegcetacoplan) is necessary to ensure that the benefits outweigh the risk of serious infections caused by encapsulated bacteria.

### 10 Appendices

#### 10.1 REFERENCES


2. OPDP REMS Consult Review; signed in DARRTS on April 13, 2021 by Rebecca Falter.


10.2 REMS ASSESSMENT PLAN

The Empaveli REMS assessment plan must include, but is not limited to, the following:

**Program Implementation and Operations:**

1. REMS Program Implementation (6-month and 1-year assessments only)
   a. Date of first commercial distribution of Empaveli
   b. Date of Empaveli REMS program launch
   c. Date when the Empaveli REMS website became live and fully operational
   d. Date when healthcare providers who can prescribe could become certified in the Empaveli REMS
   e. Date when pharmacies could become certified in the Empaveli REMS
   f. Date when distributors/wholesalers were authorized to dispense and distribute the drug (i.e., first order placed)
   g. Date when the REMS Coordinating Center was established and fully operational

2. REMS Certification and Enrollment Statistics (provide for each reporting period and cumulatively)
   a. Healthcare provider (HCP) certification
      i. Numbers certified: total, newly certified, and active (prescribed Empaveli at least once during the reporting period), stratified by credentials (e.g., MD, DO, NP, PA, other), medical specialty, and geographic region (as defined by US Census)
      ii. Method of certification
      iii. Number of healthcare providers who were unable to become certified, accompanied by a summary of the reasons they were unable to be certified
      iv. A key performance indicator is enrollment of prescribers of Empaveli. The target for this key performance indicator, is that 98% of Empaveli prescriptions that are dispensed will be written by enrolled prescribers during each REMS assessment period.
   b. Pharmacy certification
      i. Identity and numbers of each pharmacy certified: total and newly enrolled and active (dispensed Empaveli at least once during the reporting period stratified by pharmacy type), (e.g., hospital, specialty)
      ii. Method of certification
      iii. Number of pharmacies that were unable to become certified, accompanied by a summary of the reasons they were unable to be certified
c. Wholesaler/Distributors
   i. Numbers contracted: total and newly contracted, and active (distributed Empaveli at least once during the reporting period)

3. Empaveli Utilization Data (provide for each reporting period and cumulatively)
   a. For certified network specialty pharmacies, Number of prescriptions dispensed by stratified by
      i. Prescriber specialty, degree/credentials, and geographic region.
      ii. Patient demographics (e.g., age, gender), and geographic region [as defined by US Census])
   b. For wholesaler /distributors, Number of vials sold

4. REMS Compliance (beginning with the 1-year assessment report and provide for each reporting period thereafter)
   a. A summary report of non-compliance identified, associated corrective and preventive action (CAPA) plans, and the status of CAPA plans including, but not limited to:
      i. A copy of the non-compliance plan, including the criteria for non-compliance for prescribers facilitated by certified network specialty pharmacies, actions taken to address non-compliance for each case, and which events will lead to suspension or decertification from the REMS
      ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, report the following information:
         1)The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
         2)The source of the noncompliance data
         3)The results of root cause analysis
         4) action(s) taken in response
      iii. Number and percent of prescribers who prescribed Empaveli but were not certified as identified by the certified network specialty pharmacy
      iv. Specific reasons that prescribers were not certified at the time of prescribing (i.e., emergency use, etc.), and whether these prescribers subsequently became certified.
   b. Audits: Summary of audit activities including but not limited to:
      i. A copy of the audit plan used for each audited stakeholder
      ii. The number of audits expected, and the number of audits performed for each stakeholder
      iii. The number and types of deficiencies noted
iv. **a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.**

v. **Documentation of completion of training for relevant staff**

vi. **A summary report of documented processes and procedures for complying with the REMS requirements including how certified network specialty pharmacies obtain patient vaccination status from HCPs**

vii. **Verification that at each audited stakeholder’s site the designated authorized representative is up to date. If, include the number of new authorized representatives and verification of the site’s recertification.**

viii. **Describe any corrective actions taken for any non-compliance identified during the audits as well as preventative measures that were developed from uncovering these non-compliance events**

1) **For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of the audit**

2) **For any that did not complete the CAPA within one month of the audit, describe additional actions taken**

5. **REMS Infrastructure and Performance (provide for each reporting period and cumulatively)**

   a. **REMS Website**
      i. Number of visits and unique visits to the REMS website
      ii. Number of REMS materials downloaded or printed for each material

   b. **REMS Coordinating Center Report**
      i. Number of contacts by stakeholder type (patient/caregiver, healthcare provider, etc.
      ii. A table summarizing the reasons for calls (e.g., enrollment question) by stakeholder type
      iii. If the summary reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
      iv. A summary report of corrective actions resulting from issues identified

Safe Use Behaviors

6. **Safe Use Behaviors (provide for each reporting period and cumulatively)**

   a. Information captured by pharmacies regarding the number and percent of patients who were vaccinated against encapsulated bacteria *(Streptococcus pneumoniae, Neisseria meningitidis* types A, C, W, Y and B and *Haemophilus influenzae* Type B). This information is to include, regarding each vaccination type:
i. The serotype (if applicable)

ii. The timing of the vaccination in relation to the dosing of Empaveli (if available)

iii. The dates when vaccine administration occurred (i.e., Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis) (if available)

iv. The dosing (if a vaccination requires a second dose and whether the second dose occurred or is pending)

v. Whether the patient was vaccinated as per the Advisory Committee on Immunization Practices (ACIP) recommendations

vi. Whether the patient received prophylactic antibiotics, and timing of antibiotics in relation to the dosing of Empaveli (if available)

vii. If any of the above information is missing, the reasons why this information is missing;

Health Outcomes and/or Surrogates of Health Outcomes

7. Summary of cases of meningococcal, streptococcal, or haemophilus infections in patients receiving Empaveli (provide for each reporting period and cumulatively)

   a. For US cases, (b)(4):

      i. In the most recent Periodic Safety Update Report (PSUR) submitted to the Empaveli NDA with a link to that PSUR identified

      ii. Cumulative listing of all cases of encapsulated bacteria infections from approval to include cases identified during the current reporting period

b. For each US case, provide the following information:

   i. MedWatch or other case report number

   ii. Date of report and date of report to FDA

   iii. Patient age and gender

   iv. Indication for Empaveli treatment

   v. Encapsulated bacteria vaccination status, to include the specific vaccines; the dates they were administered; your conclusions as to whether the vaccinations complied with the ACIP guidelines; and references to the specific versions of the ACIP guidelines that were in effect at the time the infections occurred

   vi. Whether the patient was administered any prophylactic antibiotics and if so:
1. The specific antibiotics, antibiotic regimen (dose/frequency), and routes of administration

2. The duration of the antibiotic treatment

3. The timing of the course of the antibiotics in relation to Empaveli treatment

vii. Summary of clinical course and the outcome; specifically report whether the patient:

viii. Was admitted to an intensive care unit

ix. Experienced any organ system failure, such as (but not limited to) requiring mechanical ventilation or medication (vasopressors) to support blood pressure

x. Died

xi. Causative encapsulated bacteria organism and serotype

xii. Whether the Patient Card was presented during the process of the patient seeking treatment

c. For each non-US case, provide the following information:

i. Case report number

ii. Patient age and gender

iii. Indication for Empaveli treatment

iv. Encapsulated bacteria vaccination status if known

v. Outcome

8. Encapsulated Bacteria Infections Rate (provide for each reporting period and cumulatively)

a. Among patients who received Empaveli in the US and worldwide, the number of reported cases of encapsulated bacteria infection per 100,000 patient-years of post-marketing exposure to Empaveli; by year and age subgroup (≤18 years, 19-55 years, and >55 years).

Knowledge

9. Stakeholder surveys (beginning with the 1-year assessment report and for each reporting period thereafter)

a. An assessment of healthcare provider (HCP) and patient understanding regarding:

i. the potential risk of infections caused by encapsulated bacteria with Empaveli

ii. the early signs of invasive encapsulated bacteria infections
iii. the need for immediate medical evaluation of signs and symptoms consistent with possible encapsulated bacteria infections

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRAD T MORIYAMA
05/13/2021 03:57:18 PM

KATE H OSWELL
05/13/2021 04:09:47 PM

SHELLY L HARRIS on behalf of WAMBUI G KIRUTHI
05/13/2021 04:21:33 PM
as proxy for Wambui Kiruthi

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DORIS A AUTH
05/13/2021 04:44:13 PM
Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type: NDA
Application Number: 215014
PDUFA Goal Date: May 14, 2021
OSE RCM #: 2020-1932

Reviewer Name(s):
- Brad Moriyama, Pharm.D., BCCCP
- Kate Oswell, M.A.
- Wambui Kiruthi, Pharm.D., MPH

Team Leader: Naomi Boston, Pharm.D.
Division Director: Doris Auth, Pharm.D.
Review Completion Date: May 3, 2021
Subject: Evaluation of the REMS and REMS materials

Established Name: Pegcetacoplan
Trade Name: Empaveli
Name of Applicant: Apellis Pharmaceuticals, Inc.
Therapeutic Class: Complement inhibitor
Formulation(s): 1080 mg vial
Dosing Regimen: Pegcetacoplan 1080 mg subcutaneous infusion twice-weekly via a commercially available infusion pump.

Dosage for patients switching to pegcetacoplan from C5 inhibitors:
- For patients switching from eculizumab, initiate pegcetacoplan while continuing eculizumab at its current dose. After 4 weeks, discontinue eculizumab before continuing on monotherapy with pegcetacoplan.
- For patients switching from ravulizumab, initiate pegcetacoplan no more than 4 weeks after the last dose of ravulizumab

Reference ID: 4789757
1 Introduction

This review provides comments and changes to the proposed risk evaluation and mitigation strategy (REMS) and the REMS materials for the new molecular entity (NME) Empaveli (pegcetacoplan). On September 14, 2020, Apellis Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 215014 for pegcetacoplan with the proposed indication for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). This application is under review in the Division of Non-Malignant Hematology (DNH).

The Applicant submitted proposed REMS on September 14, 2020 and on March 29, 2021, which are the subject of this review. General comments on the Applicant’s REMS materials were provided on April 21, 2021. On April 30, 2021, the Applicant provided responses to the Agency’s comments. The risk of pegcetacoplan to be mitigated by the REMS is serious infections caused by encapsulated bacteria. Apellis Pharmaceuticals, Inc. submitted a proposed REMS with elements to assure safe use (ETASU) for this application that consists of prescriber certification, pharmacy certification, an implementation system, and a timetable for submission of assessments to mitigate the risk of serious infections caused by encapsulated bacteria. Additional review of the REMS for this application by DRM will be provided in the final review.

2 Materials Reviewed

General comments on the Applicant’s REMS materials were provided on April 21, 2021. On April 30, 2021, the Applicant provided responses to the Agency’s comments. In addition to the review by the Division of Risk Management, the REMS document and attestations for the prescriber and pharmacy enrollment forms have been reviewed by the Office of Chief Counsel (OCC). The revisions to these materials include OCC’s comments.

The following materials have been reviewed and comments on these materials are appended to this review:

REMS Document
REMS assessment plan
Attestations for the prescriber and pharmacy enrollment forms
Healthcare Provider Brochure
Prescriber Enrollment Form
Pharmacy Enrollment Form
Patient Safety Guide
Patient Wallet Card
REMS website

3 Comments for the Applicant
DRM recommends DNH send the following comments to the Applicant on the proposed REMS and REMS materials.

**General comments for the applicant:**

The Agency has reviewed your proposed Empaveli REMS document submitted on September 14, 2020 and March 29, 2021 and have provided changes to the REMS Document which is appended to this communication.

The Agency has reviewed your proposed Empaveli REMS assessment plan submitted on September 14, 2020 and March 29, 2021. We have the following comments below.

The REMS materials submitted on April 30, 2021 have additional changes. We have the following comments below.

Please note that the REMS Supporting Document must be updated to include changes in the aforementioned materials.

Provide a copy of the Empaveli REMS noncompliance plan and audit plan.

We request that you respond to these comments on the REMS document, REMS assessment plan, and REMS materials by close of business, Friday May 7th, 2021. In your resubmission, please resubmit the REMS document, all appended materials and the REMS Supporting Document, submitted as separate documents in the same submission; include a Word tracked changes version, a Word clean version, and a .pdf version of the REMS Document, REMS supporting document, all appended materials.

**REMS Assessment Plan**

The Empaveli REMS assessment plan must include, but is not limited to, the following:

**Program Implementation and Operations:**

1. REMS Program Implementation (6-month and 1-year assessments only)
   a. Date of first commercial distribution of Empaveli
   b. Date of Empaveli REMS program launch
   c. Date when the Empaveli REMS website became live and fully operational
   d. Date when healthcare providers who can prescribe could become certified in the Empaveli REMS
   e. Date when pharmacies could become certified in the Empaveli REMS
   f. Date when distributors/wholesalers
   g. Date when the REMS Coordinating Center was established and fully operational

2. REMS Certification and Enrollment Statistics (provide for each reporting period and cumulatively)
   a. Healthcare provider (HCP) certification

Reference ID: 4789757
i. Numbers certified: total, newly certified, and active (prescribed Empaveli at least once during the reporting period), stratified by credentials (e.g. MD, DO, NP, PA, other), medical specialty, and geographic region (as defined by US Census)

ii. Method of certification

iii. Number of healthcare providers who were unable to become certified, accompanied by a summary of the reasons they were unable to be certified

b. Pharmacy certification

i. Identity and numbers of each pharmacy certified: total and newly enrolled and active (dispensed Empaveli at least once during the reporting period stratified by pharmacy type), (e.g., hospital, specialty)

ii. Method of certification

iii. Number of pharmacies that were unable to become certified, accompanied by a summary of the reasons they were unable to be certified

c. Wholesaler/Distributors

i. Numbers contracted: total and newly contracted, and active (distributed Empaveli at least once during the reporting period)

3. Empaveli Utilization Data (provide for each reporting period and cumulatively)

a. Number of prescriptions dispensed stratified by

i. Prescriber specialty, degree/credentials, and geographic region.

ii. Pharmacy type

iii. Patient demographics (e.g., age, gender), and geographic region [as defined by US Census])

4. REMS Compliance (beginning with the 1-year assessment report and provide for each reporting period thereafter)

a. A summary report of non-compliance identified, associated corrective and preventive action (CAPA) plans, and the status of CAPA plans including, but not limited to:

i. a copy of the non-compliance plan, including the criteria for non-compliance for prescribers, actions taken to address non-compliance for each case, and which events will lead to suspension or decertification from the REMS

ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, report the following information:

1) The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time

2) The source of the noncompliance data

3) The results of root cause analysis

4) action(s) taken in response
iii. Number and percent of prescribers who prescribed Empaveli but were not certified
iv. Specific reasons that prescribers were not certified at the time of prescribing (i.e. emergency use, etc.), and whether these prescribers subsequently became certified.

b. Audits: Summary of audit activities including but not limited to:
   i. A copy of the audit plan used for each audited stakeholder
   ii. The number of audits expected, and the number of audits performed for each stakeholder
   iii. The number and types of deficiencies noted
   iv. A unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.
   v. Documentation of completion of training for relevant staff
   vi. A summary report of documented processes and procedures for complying with the REMS requirements including how pharmacies obtain patient vaccination status from HCPs
   vii. Verification that at each audited stakeholder’s site the designated authorized representative is up to date. If, include the number of new authorized representatives and verification of the site’s recertification.
   viii. Describe any corrective actions taken for any non-compliance identified during the audits as well as preventative measures that were developed from uncovering these non-compliance events
      1) For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of the audit
      2) For any that did not complete the CAPA within one month of the audit, describe additional actions taken

5. REMS Infrastructure and Performance (provide for each reporting period and cumulatively)
   a. REMS Website
      i. Number of visits and unique visits to the REMS website
      ii. Number of REMS materials downloaded or printed for each material

   b. REMS Coordinating Center Report
      i. Number of contacts by stakeholder type (patient/caregiver, healthcare provider, etc.
      ii. A table summarizing the reasons for calls (e.g., enrollment question) by stakeholder type
      iii. If the summary reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
      iv. A summary report of corrective actions resulting from issues identified

Safe Use Behaviors
6. Safe Use Behaviors (provide for each reporting period and cumulatively)
   a. Information captured by pharmacies regarding the number and percent of patients who were vaccinated against encapsulated bacteria (Neisseria meningitidis types A, C, W, Y, and B, Streptococcus pneumoniae, and Haemophilus influenzae Type B). This information is to include, regarding each vaccination type:
      i. The serotype (if applicable)
      ii. The timing of the vaccination in relation to the dosing of Empaveli (if available)
      iii. The dates when vaccine administration occurred (i.e. Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis) (if available)
      iv. The dosing (if a vaccination requires a second dose and whether the second dose occurred or is pending)
      v. Whether the patient was vaccinated as per the Advisory Committee on Immunization Practices (ACIP) recommendations
      vi. Whether the patient received prophylactic antibiotics, and timing of antibiotics in relation to the dosing of Empaveli (if available)
      vii. If any of the above information is missing, the reasons why this information is missing;

Health Outcomes and/or Surrogates of Health Outcomes

7. Summary of cases of meningococcal, streptococcal, or haemophilus infections in patients receiving Empaveli (provide for each reporting period and cumulatively)
   a. For US cases:
      i. In the most recent Periodic Safety Update Report (PSUR) submitted to the Empaveli BLA with a link to that PSUR identified
      ii. Cumulative listing of all cases of encapsulated bacteria infections from approval to include cases identified during the current reporting period
   b. For each US case, provide the following information:
      i. MedWatch or other case report number
      ii. Date of report and date of report to FDA
      iii. Patient age and gender
      iv. Indication for Empaveli treatment
v. Encapsulated bacteria vaccination status, to include the specific vaccines; the dates they were administered; your conclusions as to whether the vaccinations complied with the ACIP guidelines; and references to the specific versions of the ACIP guidelines that were in effect at the time the infections occurred.

vi. Whether the patient was administered any prophylactic antibiotics and if so:
   1. The specific antibiotics, antibiotic regimen (dose/frequency), and routes of administration
   2. The duration of the antibiotic treatment
   3. The timing of the course of the antibiotics in relation to Empaveli treatment

vii. Summary of clinical course and the outcome; specifically report whether the patient:
   1. Was admitted to an intensive care unit
   2. Experienced any organ system failure, such as (but not limited to) requiring mechanical ventilation or medication (vasopressors) to support blood pressure
   3. Died

viii. Causative encapsulated bacteria organism and serotype

ix. Whether the Patient Card was presented during the process of the patient seeking treatment

b. For each non-US case, provide the following information:
   i. Case report number
   ii. Patient age and gender
   iii. Indication for Empaveli treatment
   iv. Encapsulated bacteria vaccination status if known
   v. Outcome

8. Encapsulated Bacteria Infections Rate (provide for each reporting period and cumulatively)

   a. Among patients who received Empaveli in the US and worldwide, the number of reported cases of encapsulated bacteria infection per 100,000 patient-years of post-marketing exposure to Empaveli; by year and age subgroup (≤18 years, 19-55 years, and >55 years).

Knowledge

9. Stakeholder surveys (beginning with the 1-year assessment report and for each reporting period thereafter)

   a. An assessment of healthcare provider (HCP) and patient understanding regarding:
      i. the potential risk of infections caused by encapsulated bacteria with Empaveli
      ii. the early signs of invasive encapsulated bacteria infections
      iii. the need for immediate medical evaluation of signs and symptoms consistent with possible encapsulated bacteria infections
10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

**REMS Materials**

The requirements for prescribers to become certified includes reviewing the Prescribing Information, Healthcare Provider Brochure, Patient Safety Guide and Patient Wallet Card. Reviewing the patient materials is not currently included in the certification requirements when described in the materials.

- In the Healthcare Provider Brochure, update the prescriber certification requirements on page 2.
- On the Prescriber Enrollment Form, update the instructions.
- In the REMS website, update the prescriber certification requirements, and the instructions on the Prescriber Enrollment Form.

**Pharmacy Enrollment Form**

On the Pharmacy Enrollment Form, we note that are included and we recommend that you remove this data field from the form or provide rationale for why it should be included. For we have not seen this category as a requirement on pharmacy forms and request that that data field be made optional. We note that

**Attestations**

The changes made to the attestations are acceptable. However, we have one revision to the following attestation for prescribers:

**During treatment**

- Assess the patient for early signs and symptoms of serious bacterial infection and treat immediately, if infection is suspected.

Revise the Prescriber Enrollment Form to include this revision to the attestations.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRAD T MORIYAMA
05/03/2021 06:12:06 PM

KATE H OSWELL
05/03/2021 07:00:34 PM

SHELLY L HARRIS on behalf of WAMBUI G KIRUTHI
05/03/2021 07:33:44 PM
proxy for Wambui Kiruthi

DORIS A AUTH on behalf of NAOMI S BOSTON
05/03/2021 07:38:28 PM

DORIS A AUTH
05/03/2021 07:38:55 PM
Application Type: NDA
Application Number: 215014
PDUFA Goal Date: May 14, 2021
OSE RCM #: 2020-1932
Reviewer Name(s): Brad Moriyama, Pharm.D., BCCCP
Kate Oswell, M.A.
Team Leader: Naomi Boston, Pharm.D.
Division Director: Doris Auth, Pharm.D.
Review Completion Date: April 21, 2021
Subject: Evaluation of the REMS and REMS materials

Established Name: Pegcetacoplan
Trade Name: Empaveli
Name of Applicant: Apellis Pharmaceuticals, Inc.
Therapeutic Class: Complement inhibitor
Formulation(s): 1080 mg vial
Dosing Regimen: Pegcetacoplan 1080 mg subcutaneous infusion twice-weekly via a commercially available infusion pump.

Dosage for patients switching to pegcetacoplan from C5 inhibitors:

- For patients switching from eculizumab, initiate pegcetacoplan while continuing eculizumab at its current dose. After 4 weeks, discontinue eculizumab before continuing on monotherapy with pegcetacoplan.
- For patients switching from ravulizumab, initiate pegcetacoplan after the last dose of ravulizumab.
1 Introduction

This review provides comments and changes to the proposed risk evaluation and mitigation strategy (REMS) materials for the new molecular entity (NME) Empaveli (pegcetacoplan). On September 14, 2020, Apellis Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 215014 for pegcetacoplan with the proposed indication for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). This application is under review in the Division of Non-Malignant Hematology (DNH).

The Applicant submitted proposed REMS materials on September 14, 2020 and on March 29, 2021, which are the subject of this review. The risk of pegcetacoplan to be mitigated by the REMS is serious infections caused by encapsulated bacteria. Apellis Pharmaceuticals, Inc. submitted a proposed REMS with elements to assure safe use (ETASU) for this application that consists of prescriber certification, pharmacy certification, an implementation system, and a timetable for submission of assessments to mitigate the risk of serious infections caused by encapsulated bacteria. Additional review of the REMS for this application by DRM will be provided in the final review. Comments on the REMS assessment plan will be provided at a later date.

2 Materials Reviewed

REMS Materials

The Applicant included the following materials as part of the original submission of the REMS on September 14, 2020 and on March 29, 2021:

- Healthcare Provider Brochure
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Patient Safety Guide
- Patient Wallet Card
- REMS website

Reviewer’s Comments:

Healthcare Provider Brochure: Edits to better align the brochure with the REMS document and current label are attached in the appendix of this review.

Prescriber Enrollment Form: Align attestations on the form with those on the Attestation Document. If possible, increase font size of data field identifiers to size 8. The sponsor should explain the rationale behind collecting state license data as the NPI number is required.

Pharmacy Enrollment Form: Align attestations on the form with those on the Attestation Document. If possible, increase font size of data field identifiers to size 8.

Patient Safety Guide: Edits to simplify language and better align with the Medication Guide are attached in the appendix of this review.
**Patient Wallet Card:** Research on wallet cards shows that the colors red and yellow should be used to capture attention and reflect an emergency situation. In addition, providers are used to seeing graphics such as exclamation points on medical equipment and understand that a statement with an exclamation shows importance. Incorporate color or graphics on the card to help draw attention to the card. Additional edits on the card to simplify content are attached in the appendix of this review. Also, on the PDF version of the card, it appears that the panel that shows patient name and prescriber name and phone, are on the patient side of the card. Confirm if that is accurate.

**REMS website:** Incorporate any changes to the REMS Website as provided by the FDA on the other REMS materials.

The homepage is lengthy and requires a user to scroll far down the page, which is not user friendly. We recommend deleting (b)(4).

We suggest making a pharmacy landing page a separate page. Including “Pharmacy” as a link at the top of the page, is one option to get to that separate page. Or, on some REMS websites with multiple audiences, the home page has icons with a choice of audiences (Prescriber, Pharmacist, patient) and each audience has their own landing page. These revisions would make the home page concise, and let each audience find their specific information more easily. Another option would be to include a link that states, “Click here for Program Requirements for [insert audience]” or other similar language; the link would open a new page for this audience.

The (b)(4) heading at the top of the page can be removed as it is repeated at the bottom of the page.

On page 5, it is not clear (b)(4). Please describe what is acceptable for a signature.

In addition, edits and comments on the website screenshots are attached in the appendix of this review.

The Applicant did not include key risk messages with their submissions of the REMS materials. A detailed discussion of the proposed key risk messages will be included in a forthcoming review.

### 3 Comments for the Applicant

DRM recommends DNH send the following comments to the Applicant on the proposed REMS materials.

**General comments for the applicant:**

The Agency has reviewed your proposed Empaveli REMS materials submitted on September 14, 2020 and March 29, 2021. We have the following comments below. Please see additional comments on each document attached to this correspondence.

Please note that the REMS document and REMS assessment plan is still under review, and comments will be forthcoming. We request that you respond to these comments on the REMS materials by close of
business, Friday April 30th, 2021. In your resubmission, please resubmit all REMS materials, submitted as separate documents in the same submission; include a Word tracked changes version, a Word clean version, and a .pdf version of all REMS materials.

**REMS Materials**

We remind you that REMS materials must align with the Prescribing Information.

**Healthcare Provider Brochure**
We have made edits to better align the brochure with the REMS document and current label.

**Prescriber Enrollment Form**
Align attestations on form with those on Attestation Document. If possible, increase font size of data field identifiers to size 8. Please explain the rationale behind collecting state license data. Is this information needed since the NPI number is already required on the form?

**Pharmacy Enrollment Form**
Align the attestations on this form with those on the Attestation Document. If possible, increase font size of data field identifiers to size 8.

**Patient Safety Guide:** We have made edits to simplify language and better align with the Medication Guide.

**Patient Wallet Card**
Research on wallet cards that shows that the colors red and yellow should be used to capture attention and reflect an emergency situation. In addition, providers are used to seeing graphics such as exclamation points on medical equipment and understand that a statement with an exclamation shows importance. Incorporate color or graphics on the card to help draw attention to the card.

We have made additional edits on the card to simplify content. Also, on the PDF version of the card, it appears that the panel that shows patient name and prescriber name and phone, are on the patient side of the card. Please confirm if that is accurate.

**REMS website**
Incorporate any changes to the REMS Website as provided by the FDA on the other REMS materials. In addition, we have made edits and comments on the website screenshots.

The homepage is lengthy and requires a user to scroll far down the page, which is not user friendly. **We recommend deleting** (b) (4) **We suggest making a pharmacy landing page a separate page. Including “Pharmacy” as a link in the at the top of the page is one option to get to that separate page. Or, on some REMS websites with multiple audiences, the home page has icons with a choice of audiences (Prescriber, Pharmacist, Patient) and each audience has their own landing page. These revisions would make the home page concise and let each audience find their specific information more easily. Another option would be to include a link that states, “Click here for Program Requirements for [insert audience]” or other similar language; this link would open a new page for this audience.**
The heading at the top of the page can be removed as it is repeated at the bottom of the page.

On page 5, it is not clear Please describe what is acceptable for a signature.
EMPANELI Draft Attestation Document

Healthcare Providers

I have:

- Reviewed Empaveli’s Prescribing Information.

Before treatment initiation (at least 2 weeks before first dose), I must

- Assess the patient’s vaccine status and immunize if needed according to the current Advisory Committee on Immunization Practices for the following: Neisseria meningitidis types A, C, W, Y, and B, Streptococcus pneumoniae, and Haemophilus influenzae Type B.
- Provide the patient with prescription for a 2-week course of antibiotic prophylaxis if Empaveli must be started less than 2 weeks after the patient was immunized.
- Counsel the patient using the Patient Safety Guide and Patient Wallet Card. Provide a copy of the materials to the patient.

During treatment

- Assess the patient for early signs and symptoms of serious bacterial infection and evaluate immediately, if infection is suspected.
- Consider discontinuing Empaveli in patients who are being treated for serious bacterial infection
- Revaccinate patients according to the current Advisory Committee on Immunization Practices recommendations.

At all times

- Report cases of serious bacterial infection, including the patient’s clinical outcomes, to Apellis Pharmaceuticals, Inc.

Pharmacies

As the Authorized Representative, I must:

- Review the Healthcare Provider Brochure.
- Train all relevant staff involved in dispensing Empaveli using the Healthcare Provider Brochure
- Establish processes and procedures to contact the prescriber to assess the patient’s vaccination history including antibiotic prophylaxis.

Before dispensing, all pharmacy staff must:

- Obtain authorization to dispense each prescription by contacting the Empaveli REMS to verify the prescriber is certified.
- Assess the patient’s vaccination history including antibiotic prophylaxis by contacting the prescriber through the processes and procedures established as a requirement of the Empaveli REMS.

At all times

- Report adverse events suggestive of serious bacterial infections to Apellis Pharmaceuticals, Inc.
- Not distribute, transfer, loan, or sell Empaveli, except to certified dispensers.
• Maintain records of staff’s completion of Empaveli REMS training.
• Maintain records that all processes and procedures are in place and are being followed.
• Comply with audits carried out by Apellis Pharmaceuticals, Inc. or a third party acting on behalf of the applicant, to ensure that all processes and procedures are in place and are being followed.

To maintain certification to dispense, any new Authorized Representative must:

• Enroll in the Empaveli REMS by completing the Pharmacy Enrollment Form and submitting it to the Empaveli REMS.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRAD T MORIYAMA
04/21/2021 09:48:57 AM

KATE H OSWELL
04/21/2021 09:51:29 AM

NAOMI S BOSTON
04/21/2021 09:53:01 AM

DORIS A AUTH
04/21/2021 09:59:03 AM