CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218276Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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	218276
PDUFA Goal Date	December 5, 2023
Nexus TTT #	2023-4375
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Review Completion Date	December 4, 2023
Subject	Evaluation of Need for a REMS
Established Name	Iptacopan
Trade Name	Fabhalta
Name of Applicant	Novartis Pharmaceuticals Corporation
Therapeutic Class	Complement Factor B inhibitor
Formulation(s)	200 mg oral capsules
Dosing Regimen	200 mg orally twice daily

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EXECUTIVE SUMMARY

This review provides the Division of Risk Management (DRM) evaluation of whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Fabhalta (iptacopan) is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corporation (the Applicant) submitted a New Drug Application (NDA) 218276 for iptacopan with the proposed indication for the treatment of (b) (4) paroxysmal nocturnal hemoglobinuria. During the course of the review, the Agency revised the indication to: for the treatment of adults with paroxysmal nocturnal hemoglobinuria. The risk associated with iptacopan is serious infections caused by encapsulated bacteria. The Applicant's proposed FABHALTA REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of iptacopan outweigh the risk of serious infections caused by encapsulated bacteria. This review also provides the DRM and Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) evaluation of the proposed REMS and assessment plan (last amended on December 4, 2023, which is the focus of this review).

The benefits of iptacopan for the treatment of paroxysmal nocturnal hemoglobinuria were demonstrated in two phase 3 studies, APPLY-PNH (treatment-experienced population) and APPOINT-PNH (treatment-naïve population). In APPLY-PNH, there was a statistically significant greater number of subjects in the iptacopan-treated group who met the primary endpoints (sustained increase of ≥2 g/dL in hemoglobin from baseline and hemoglobin ≥12 g/dL in the absence of RBC transfusions) compared to the active comparator, complement C5 inhibitor therapy. APPOINT-PNH demonstrated consistent results on sustained increases in hemoglobin levels from baseline.

Serious infections including a death related to an infection by an encapsulated organism were reported in iptacopan-treated subjects. In the clinical trials, risk mitigation measures were in place to prevent infections caused by encapsulated bacteria (e.g., vaccination against *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type B). The risk of serious infections caused by encapsulated bacteria is a known risk of complement inhibitors that act proximally on the complement system and other approved complement inhibitors are subject to REMS for the risk of serious infections. Given the risk of serious infections caused by encapsulated bacteria, this risk will be communicated in labeling as a Boxed Warning, included in Section 5 – Warnings and Precautions in the Prescribing Information and summarized in the Medication Guide for patients.

DRM and DNH agree that a REMS is necessary to ensure the benefits of iptacopan outweigh the risk of serious infections caused by encapsulated bacteria. The proposed REMS, last amended on December 4, 2023, ensures all prescribers receive training about the risk of serious infections caused by encapsulated bacteria, the need to complete or update patients' vaccination against encapsulated bacteria at least 2 weeks prior to initiating iptacopan, the need to provide antibacterial drug prophylaxis if urgent iptacopan therapy is needed in patients that are not up to date on vaccinations, the need to counsel the patient on the life-threatening and fatal nature of these infections and to carry the *Patient Safety Card* detailing this risk. The REMS also ensures that prescribers and patients are aware of the signs and

symptoms of serious bacterial infections to monitor. DNH recommends approval of iptacopan, with a REMS, for the treatment of adults with paroxysmal nocturnal hemoglobinuria.

The goal of the FABHALTA REMS is to mitigate the risk of serious infections caused by encapsulated bacteria.

1. Patients are vaccinated against infections caused by encapsulated bacteria (Neisseria meningitidis serogroups A, C, W, Y, and B; Streptococcus pneumoniae; and Haemophilus influenzae type B) prior to starting therapy according to current Advisory Committee on Immunization Practices (ACIP) recommendations and receive antibacterial drug prophylaxis if needed.
2. Patients are aware of early signs and symptoms of serious encapsulated bacterial infections and the need for immediate medical evaluation.
3. Prescribers are aware of early signs and symptoms of serious encapsulated bacterial infections and the need for immediate medical evaluation.

The FABHALTA REMS includes the following REMS elements: ETASU A (healthcare providers who prescribe iptacopan are specially certified), ETASU B (pharmacies that dispense iptacopan are specially certified), ETASU D (dispensing of iptacopan may be done only with the documentation of safe-use conditions), an implementation system, and a timetable for submission of assessments. Prescriber certification ensures that prescribers are knowledgeable about the risk of serious infections caused by encapsulated bacteria associated with iptacopan, the need to provide the appropriate vaccines against encapsulated bacteria prior to iptacopan initiation, and the need for antibacterial drug prophylaxis if iptacopan is initiated prior to the patient being up to date on vaccines. As part of the prescriber certification, they must certify, attest to comply with the requirements of the REMS, and counsel patients about the risk of serious bacterial infections, the need for vaccination and antibacterial drug prophylaxis if needed, the signs and symptoms of serious bacterial infection, and the need to seek immediate medical evaluation if these symptoms occur. Pharmacies must certify to ensure awareness of the risk, obtain authorization from the REMS prior to each prescription to verify prescribers are certified, and attest to complying with the requirements of the REMS by establishing processes and procedures to assess and document the patients' vaccination status including antibacterial drug prophylaxis prior to dispensing iptacopan.

Based on the severity of the risk of serious infections caused by encapsulated bacteria, DRM and DNH agree that requiring a REMS consisting of prescriber certification, pharmacy certification, and documentation of safe use conditions (pharmacy assessment and documentation of vaccination against encapsulated bacteria and antibacterial drug prophylaxis prior to dispensing) is necessary to ensure that the benefits outweigh the risks of iptacopan. The REMS will also include an implementation system and timetable for submission of assessments.

DRM, in conjunction with DMAMES, evaluated the proposed REMS, including the Assessment Plan, Key Risk Messages, and Key Performance Indicators and find the REMS submitted on December 4, 2023 acceptable.

1. Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Fabhalta (iptacopan) is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corporation (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 218276 for iptacopan with the proposed indication for the treatment of (b) (4) paroxysmal nocturnal hemoglobinuria (PNH).[1] This application is under review in the Division of Nonmalignant Hematology (DNH). The Applicant's proposed REMS (last amended December 4, 2023) consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of iptacopan outweigh the risk of serious infections caused by encapsulated bacteria.[1,2] The Division of Risk Management (DRM), in conjunction with Division of Mitigation Assessment and Medication Error Surveillance (DMAMES), evaluated the proposed REMS, including the Assessment Plan, Key Risk Messages, and Key Performance Indicators.

2. Background

2.1. Product Information

Fabhalta (iptacopan), a new molecular entity,[a] is a complement Factor B inhibitor proposed for the treatment of (b) (4) PNH.[3] During the course of the review the Agency revised this indication to the following: for the treatment of adults with PNH.[3] Complement factor B is a key protease involved in activation of the complement alternative pathway and amplification of the complement classical pathway and lectin pathway. Iptacopan binds to Factor B and regulates the cleavage of C3, generation of downstream effectors of complement activation, and amplification of the terminal pathway.[3] Iptacopan acts proximally in the alternative pathway of the complement system to control both C3b mediated extravascular hemolysis and terminal complement mediated intravascular hemolysis.[3]

Iptacopan is proposed to be supplied as 200 mg hard capsules. The proposed dose is 200 mg orally twice daily.[3] PNH requires chronic treatment[b] and iptacopan is likely to be administered by patients in both the outpatient and inpatient setting. Abrupt treatment discontinuation is not recommended as there is a potential risk of hemolysis. Iptacopan is not currently approved in any jurisdiction.

If approved, iptacopan would be the first complement Factor B inhibitor and product that targets the alternative pathway for PNH. There are additional complement inhibitors approved that are subject to a REMS. Soliris (eculizumab), Ultomiris (ravulizumab), and Zilbrysq (zilucoplan) are complement C5 inhibitors that were approved with REMS to mitigate the risk of serious meningococcal infections. The approved Soliris REMS and Ultomiris REMS include ETASU (prescriber

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

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

certification [ETASU A]) and a timetable for submission of assessments; however, on May 16, 2023, the Applicant for Soliris and Ultomiris was issued a REMS Modification Notification Letter by the Agency stating they are required to modify their REMS to add pharmacy certification (ETASU B) and documentation of safe use (ETASU D).[4] The approved Zilbrysq REMS consists of ETASU (prescriber certification [ETASU A], pharmacy certification [ETASU B], and evidence of safe use conditions [ETASU D]), an implementation system, and a timetable for submission of assessments.[5] Empaveli (pegcetacoplan) is a complement C3 inhibitor that was approved with a REMS 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*). The Empaveli REMS consists of ETASU (prescriber certification [ETASU A], pharmacy certification [ETASU B], and evidence of safe use conditions [ETASU D]), an implementation system, and a timetable for submission of assessments.[6] The difference in the risks for these REMS is based on each drug's mechanism of action and target in complement system.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 218726 relevant to this review:

- **07/31/2020:** Orphan drug designation granted for IND 134655 for the treatment of PNH.
- **12/01/2020:** Breakthrough therapy designation granted for IND 134655 for the treatment of paroxysmal nocturnal hemoglobinuria.
- **04/05/2023:** NDA 218276 submission for the treatment of (b) (4) PNH paroxysmal nocturnal hemoglobinuria received. A REMS proposal was included in the submission. The Applicant submitted a Priority Review Voucher with this application.[1]
- **08/21/2023:** A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that a REMS for iptacopan is necessary to ensure that the benefits of the drug outweigh the risks of serious infections caused by encapsulated bacteria.
- **08/25/2023:** The Agency sent an information request (IR) to clarify questions on pharmacy requirements and processes, including the authorization process and more details on how iptacopan would be dispensed in the inpatient setting.[7]
- **08/31/2023:** The Applicant provided a response to the Agency's 8/25/2023 IR and included additional non-public website screenshots for the outpatient pharmacy authorization process.[8]
- **10/20/2023:** The Agency sent an IR with additional questions on pharmacy processes and requested the Applicant submit Key Risk Messages (KRMs).[9]
- **10/25/2023:** The Applicant provided a response to the Agency's 10/20/2023 IR and included an updated Supporting Document.[10]
- **10/26/2023:** The Agency sent the Applicant labeling revisions, including changes to the messaging for the risk of serious infections caused by encapsulated bacteria in the Boxed

Warning, Section 2.1 - Dosage and Administration, Section 5 - Warnings and Precautions, and Section 17 – Patient Counseling.

- **11/01/2023:** A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant the REMS review was ongoing.
- **11/03/2023:** The Agency sent interim comments to the Applicant on the REMS proposal. The Agency revised the REMS Document and requested revisions to the REMS materials to align with the Agency's revisions to labeling and the REMS Document.[11]
- **11/06/2023:** The Applicant submitted a revised label and proposed additional changes.[12]
- **11/09/2023:** The Applicant submitted a REMS amendment in response to the Agency's comments.[13] The Applicant aligned the language with their proposed revisions to the Prescribing Information and Medication Guide as outlined in the 11/06/2023 submission.
- **11/17/2023:** The Agency sent draft Prescribing Information and Medication Guide with additional revisions.
- **11/20/2023:** The Applicant submitted revised labeling and proposed additional changes to the Boxed Warning and Section 5.1.
- **11/21/2023:** The Agency sent interim comments on the REMS to the Applicant to align materials with labeling, provide formatting and design changes to improve readability, and revisions to clarify the pharmacy vaccination assessment process.[14] In addition, the Agency raised concerns about the proposal to deactivate inpatient pharmacies after each patient specific shipment as it could result in excess burden and delays in treatment access.
- **11/22/2023:** The Applicant sent a correspondence describing the inpatient pharmacy certification process in more detail and responded to Agency concerns about the proposal to deactivate inpatient pharmacies and its impact on burden and access.[15]
- **11/27/2023:** The Applicant submitted a REMS Amendment and updated language throughout the REMS to align with their 11/20/2023 labeling revisions.[16] The Applicant agreed to update the process for inpatient pharmacy certification to avoid excess burden and treatment delays.
- **11/28/2023:** The Agency sent interim comments on the REMS to the Applicant with comments on the Supporting Document, including the Key Performance Indicators (KPI), KRMs, and the Assessment Plan.[17] In addition, the draft Prescribing Information and Medication Guide were sent with additional Agency revisions related to the risk of serious infections caused by encapsulated bacteria.
- **11/29/2023:** A teleconference was held between the Agency and the Applicant to discuss labeling. The Applicant agreed with labeling changes related to the risk of serious infections caused by encapsulated bacteria.
- **11/30/2023:** The Applicant submitted updated labeling and a REMS Supporting Document that incorporated the Agency's comments on KPIs, KRMs, and the Assessment Plan.[18,19] The

Applicant also provided additional clarity on the process for inpatient pharmacy certification related to notification of certification and ability to dispense. The Agency sent interim comments on the REMS to the Applicant with revisions to align with labeling and changes to the formatting and design of materials for readability.[20] The Applicant emailed the Agency and requested Agency feedback on proposed changes to the *Patient Safety Card* formatting and submitted an updated PDF file with changes to minimize the fold over key safety messages.

- **12/01/2023**: The Agency confirmed that changes to the *Patient Safety Card* were acceptable.
- **12/04/2023:** The Applicant sent draft Prescribing Information and Medication Guide with additional revisions.[21] The Applicant submitted a REMS Amendment in response to the Agency's 11/30/2023 interim comments.[2]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

PNH is a rare, chronic, life-threatening hematologic disorder characterized by uncontrolled activation of the terminal complement pathway leading to hemolytic anemia, bone marrow failure, and increased risk of thrombosis.[22,23,c] Hemolysis can result in symptoms including fatigue, chest pain, transfusion dependence, and organ damage.[23,24] If untreated, PNH is associated with risk of hospitalization, poor health-related quality of life, and increased risk of mortality, with thrombotic events accounting for approximately two-thirds of PNH-related deaths.[22] PNH primarily impacts adults with a median age of onset in the 30s, however cases in children have been reported.[23] There is no difference in PNH incidence by sex, geographic location, race, or ethnicity.[23] The incidence of PNH is estimated at 0.1-1/100,000 persons per year.[23,25,d]

3.2. Description of Current Treatment Options

There are three FDA-approved products for treatment of PNH: Soliris (eculizumab)[26], Ultomiris (ravulizumab)[27], and Empaveli (pegcetacoplan)[28] and as mentioned in section 2.1, each of these products are approved with a REMS. The complement C5 inhibitors (eculizumab and ravulizumab) are the current standard of care for the treatment of PNH, with ravulizumab providing greater convenience than eculizumab due to less frequent intravenous dosing and the option for a subcutaneous route of administration.[29] Eculizumab and ravulizumab reduce intravascular hemolysis (IVH) through inhibition of complement C5; however, some patients receiving complement C5 inhibitor therapy continue to experience symptomatic anemia and require transfusions due to extravascular hemolysis (EVH), or hemolysis occurring outside of the circulation in the spleen or liver.[30] Extravascular hemolysis occurs in patients taking complement C5 inhibitors due to accumulation of complement C3 fragments on red blood cells that are not hemolyzed due to

[c] 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.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

terminal complement inhibition.[31] Pegcetacoplan, a complement C3 inhibitor, acts proximally in the complement system controlling both C3b-mediated extravascular hemolysis and terminal complement-mediated intravascular hemolysis.[28] None of the available treatment options are available in an oral formulation. There is an unmet need for more convenient and effective options that fully inhibit complement mediated hemolysis (intravascular and extravascular hemolysis).[31] See Appendix 10.2 for a summary of the FDA-approved therapies for the treatment of PNH.

4. Benefit Assessment

The efficacy of iptacopan for the treatment of PNH was demonstrated in a phase 3 study (CLNP023C12302, National Clinical Trial [NCT] 04558918; hereafter referred to as APPLY-PNH) and a phase 3, open-label, single-arm study (NCT 04820530; hereafter referred to as APPOINT-PNH).

APPLY-PNH was a multicenter, randomized, active-comparator-controlled open-label study that evaluated 97 adults with PNH and residual anemia (defined as hemoglobin <10 g/dL) despite previous treatment with a complement C5 inhibitor (eculizumab or ravulizumab) for at least 6 months prior to randomization. Subjects were randomized in 8:5 ratio either to switch to iptacopan 200 mg orally twice daily (n=62) or to continue complement C5 inhibitor treatment (eculizumab n=23 or ravulizumab n=12) throughout the 24-week randomized controlled period. Randomization was stratified based on prior complement C5 inhibitor treatment and transfusion history within the last 6 months. Following the randomization period, subjects were eligible to enroll in a 24-week extension period and receive iptacopan monotherapy. After the extension period, subjects were eligible to enter a separate long-term extension study.

The two primary efficacy endpoints included 1) sustained increase of ≥ 2 g/dL in hemoglobin levels from baseline (hemoglobin improvement) and 2) sustained hemoglobin levels ≥ 12 g/dL.

The study population had a mean age of 51 years and was predominantly female (69.1%) and White (76.3%). The mean baseline hemoglobin level was 8.9 g/dL and the majority (57.7%) had received transfusions in the last 6 months prior to randomization. At 24 weeks of therapy, switching to iptacopan was superior to continuing on a complement C5 inhibitor in achieving hematologic response (sustained increase of ≥ 2 g/dL in hemoglobin levels from baseline and sustained hemoglobin levels ≥ 12 g/dL), along with transfusion avoidance and other markers of hemolysis. Table 1 below summarizes the primary endpoint results[e].

[e] The Agency did not agree with the Applicant's original prespecified statistical analysis plan for the primary endpoint. During review of the application, as per the Agency's recommendation, the Applicant reconducted the primary endpoint analyses. The label will reflect the Agency's recommended analysis.

Table 1. Primary Endpoints Results from APPLY-PNH[32]

Endpoints	Iptacopan (N=62)	Complement C5 inhibitor (N=35)	Difference (%) (95% CI)	p-value
Number (%) of subjects with sustained increase of ≥ 2 g/dL in Hb from baseline in the absence of RBC transfusions	51 (82.3%)	0 (0.0%)	81.5[a] (71.6, 91.4)	<0.0001
Number (%) of subjects Hb ≥ 12 g/dL in the absence of RBC transfusions	42 (67.7%)	0 (0.0%)	66.6[a] (54.6, 78.6)	<0.0001

Source: Adapted from Integrated Review and Full Prescribing Information (DRAFT as of December 4, 2023
Abbreviations: CI, confidence interval; Hb, hemoglobin; RBC, red blood cell
[a] Adjusted difference in proportion.

APPOINT-PNH was a phase 3, open-label, single-arm study that enrolled 40 adults with PNH, anemia (hemoglobin < 10 g/dL), and LDH > 1.5 times upper limit of normal. All subjects were treatment naïve (i.e., no previous treatment for PNH). All subjects received iptacopan 200 mg orally twice daily during the 24-week open-label core treatment period. Similar to the APPLY-PNH, after the core treatment period, subjects were eligible to enroll in a 24-week treatment extension period and continue iptacopan therapy followed by a separate long-term extension study. The majority of subjects (31/40; 77.5%) achieved a sustained increase in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBC transfusions. The review team concluded "such an effect would not be expected to occur spontaneously without treatment."[32]

The review team concluded that the Applicant provided substantial evidence of effectiveness based on two adequate and well-controlled trials: 1) APPLY-PNH that demonstrated improvement in hemoglobin and transfusion avoidance in adults previously treated with a complement C5 inhibitor and 2) APPOINT-PNH that demonstrated improvement in hemoglobin in treatment-naïve adults.[32,f]

5. Risk Assessment & Safe-Use Conditions

The primary safety population for iptacopan consisted of data from subjects in the active-comparator-controlled phase 3 study, APPLY-PNH which included treatment-experienced PNH subjects with residual anemia (N=62 subjects treated with iptacopan and N=35 subjects treated with a complement C5 inhibitor) and data from the phase 3 study, APPOINT-PNH in treatment-naïve PNH subjects (40 subjects treated with iptacopan).[32] Supportive data included data from a roll-over open-label long term extension program, phase 2 studies, and from studies for renal indications. A total of 223 subjects have been exposed to at least one dose of iptacopan 200 mg twice daily. Of these, 170 subjects with PNH received at least one dose of iptacopan and 154 of these subjects received iptacopan as a monotherapy.[32] The median duration of exposure to study treatment in APPLY-PNH was 24.1 weeks in the iptacopan group. The median duration for subjects who entered the roll-over extension was 47.9 weeks (range: 36.2 to

[f] 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.*

48.3), with 31 subjects having at least 48 weeks of exposure. Duration of exposure was similar in the APPOINT-PNH core treatment period (24.1 weeks) and extension (45.5 weeks).

In APPLY-PNH, a similar proportion of subjects in the iptacopan arm experienced a treatment-emergent adverse event compared to complement C5 inhibitor therapy, 82% vs 80%, respectively. The most common adverse reactions (>10%) in PNH subjects were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea, and rash.[3]

The clinical reviewer commented that the safety database is reasonable to support approval in the context of this rare, serious disease.[32]

5.1. Deaths

No deaths were reported in APPLY-PNH or APPOINT-PNH.[33] In the safety update, a death was reported in a 69 year old female who received iptacopan in the rollover extension study for APPLY-PNH who died from sepsis and cardiopulmonary compromise due to a serious infection caused by an encapsulated organism (identified as *Streptococcus gallolyticus).*[34] The clinical reviewer commented that serious infections caused by encapsulated bacteria is a risk that will be described as a Boxed Warning. See Section 5.3.1 for further discussion on the risk of serious infections caused by encapsulated bacteria.

5.2. Serious Adverse Events

In APPLY-PNH, the frequency of serious adverse events (SAEs)[g] was lower in the iptacopan group compared to the complement C5 inhibitor group (9.7% versus 14.3%, respectively). The reported SAEs in the iptacopan group included sinus node dysfunction, pyelonephritis, urinary tract dysfunction, COVID-19, increased creatinine phosphokinase, basal cell carcinoma, myelodysplastic syndrome, and transient ischemic attack. The reported SAEs in the complement C5 inhibitor group included breakthrough hemolysis, extravascular hemolysis, jaundice, arthritis bacterial, intervertebral discitis, pseudomonas infection, sepsis, staphylococcal infection, COVID-19, influenzae A virus test positive, acute kidney injury, and bilirubinuria. The clinical reviewer concluded that the infection SAEs were considered related to iptacopan as it interferes with the immune system.[32] The proportion of subjects experiencing SAEs in the extension period was similar to the randomized treatment period. The clinical reviewer concluded that the serious events in this period related to iptacopan included cellulitis and septic shock due to its impact on the immune system.[32] The rates of SAEs were similar in the APPOINT-PNH study (10%) and SAEs related to iptacopan included COVID-19 and bacterial pneumonia.

[g] 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.

5.3. Adverse Events of Special Interest

5.3.1. Serious infections caused by encapsulated bacteria

Complement inhibitors, including iptacopan, increase a patient's susceptibility to serious, life-threatening, or fatal infections caused by encapsulated bacteria including *Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae*. These infections may become rapidly life-threatening and fatal if not treated immediately. Life-threatening and fatal meningococcal infections have occurred in patients receiving the complement C5 inhibitors, Soliris and Ultomiris.[26,27] If approved, iptacopan would be the first complement Factor B inhibitor that targets the alternative pathway for PNH. Iptacopan binds to Factor B and regulates the cleavage of complement C3 and impacts downstream complement activation. Case reports in patients with hereditary Factor B deficiency report infections caused by encapsulated bacteria, including pneumococcal and meningococcal infections.[35,36]

Subjects in the APPLY-PNH and APPOINT-PNH studies were required to be vaccinated against *Neisseria meningitidis* and recommended to be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B. If treatment was started prior to 2 weeks post vaccination, prophylactic antibiotic therapy was prescribed. In the pooled PNH studies safety population for subjects receiving iptacopan (N=170) all subjects were vaccinated against meningococcal serogroups A, C, and W and *Streptococcus pneumoniae*; 169 subjects (99.4%) against meningococcal serogroup Y; 117 subjects (68.8%) against serogroup B; and 135 (79.4%) against *Haemophilus influenzae* type B.[h,33] In the APPLY-PNH study, all subjects received vaccination against meningococcal serogroups A, C, W, and Y and *Streptococcus pneumoniae* prior to or during the study. Approximately 87% of subjects received vaccination against meningococcal serogroup B and 90.5% received vaccination against *Haemophilus influenzae* type B. Subjects in the study also received a patient safety card and were counseled to monitor for signs and symptoms of infections.[1]

In the randomized treatment period of APPLY-PNH, serious infections occurred in 3.2% of subjects in the iptacopan treated group compared to 8.6% in the complement C5 inhibitor arm compared to the iptacopan arm.[33,i] There was an event of bronchitis caused by *Haemophilus influenzae* in the iptacopan arm in a subject who was previously vaccinated against *Haemophilus influenzae* type B. The subject received antibiotics and no changes were made to the study drug. In the core treatment period of APPOINT-PNH, serious infections were reported in 5% of subjects. In the pooled PNH studies, 11 (6.5%) subjects had a serious TEAE of infection while receiving iptacopan. The most common serious infection was COVID-19, but bacterial infections

[h] The Applicant notes that vaccination was lower against meningococcal serogroup B and *Haemophilus influenzae* type B due to nonavailability of the vaccine in certain countries or due to local practices.

[i] 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.*

including pneumonia, urinary tract infection, cellulitis, pyelonephritis also occurred. There were 7 cases of infections caused by or potentially caused by encapsulated organisms. Additional events reported in the safety update in the pooled PNH studies included bacterial pneumonia (causative organisms reported as *Streptococcus vestibularis* and *Streptococcus salivarius*) and the death (described above) due to sepsis from an infection caused by an encapsulated organism (*Streptococcus gallolyticus)*.[34] To date, there have been no reported cases of serious meningococcal infections in the clinical development program for iptacopan.[33] The clinical reviewer commented that iptacopan is expected to increase the risk of serious infections, particularly infections caused by encapsulated bacteria due to its mechanism of action and impact on the immune system.[32]

The Advisory Committee on Immunization Practices (ACIP) recommends vaccinating persons receiving a complement inhibitor with meningococcal vaccines for serogroups A, B, C, W, and Y due to the substantially increased risk for meningococcal infections in this population.[37] ACIP does not have specific pneumococcal vaccination recommendations for persons receiving complement inhibitors. However, ACIP recommends that unvaccinated individuals with primary immunodeficiency including complement deficiency should receive pneumococcal vaccination with either a single dose of PCV20 or PCV15 followed by PPSV23 at least 8 weeks later.[38] Additional recommendations are available for people with a history of vaccination with a previous pneumococcal vaccine.[38] Similar to pneumococcal vaccination, there are no specific recommendations for vaccination against *Haemophilus influenzae* type B for persons receiving a complement inhibitor. Vaccination against *Haemophilus influenzae* type B is recommended for all infants; however, a portion of the anticipated patient population may not have received this series as a child based on when these vaccines were first approved.[39] Early complement deficiency is a risk factor for invasive *Haemophilus influenzae* disease. ACIP provides recommendations for children ages 12-59 months at high risk of invasive infection.[39] In light of the increased risk of infection due to *Haemophilus influenzae* type B, prescribers should assess whether vaccination is necessary in an adult when iptacopan therapy is planned. Vaccinated patients may be still at risk for infections caused by encapsulated bacteria, despite development of antibodies due to iptacopan's effect on the complement system and because there are strains for which the vaccines do not target.[3]

During the course of this review, there were several multidisciplinary meetings to discuss labeling for the risk of serious infections for the complement inhibitor class. The Division of Anti-Infectives (DAI) and the Center for Biologics Evaluation and Research (CBER) were consulted for recommendations for communicating this risk in labeling.[40,41] Changes were made to clarify the required vaccinations and timing of vaccinations prior to treatment initiation as well as the optimal use of antibacterial drug prophylaxis. Additional changes were made to the label to clearly communicate that serious infections may occur in both vaccinated and unvaccinated patients and emphasize the importance of early identification and prompt treatment of serious infections.

Given the risk of serious infections caused by encapsulated bacteria, this risk will be communicated in labeling as a Boxed Warning, included in Section 5 – Warnings and Precautions in the Prescribing Information[3] and summarized in the Medication Guide[42] for patients. The recommended vaccination and prophylaxis for encapsulated bacterial infections is summarized in Section 2.1 and patient counseling information is summarized in Section 17. In addition, similar to other approved complement inhibitors, a REMS is necessary to ensure the benefits outweigh the risk of serious infections caused by encapsulated bacteria. As iptacopan inhibits Factor B and impacts the complement system higher in the system, the risk of iptacopan includes serious infections from encapsulated bacteria similar to Empaveli (pegcetacoplan).

6. Expected Postmarket Use

If approved, iptacopan will be a chronic oral therapy option for patients with PNH. Iptacopan is likely to be primarily used in the outpatient setting; however, treatment initiation and continuation of therapy may be required in the inpatient setting.

The likely prescribing population for iptacopan for the proposed indication are hematologists and oncologists. This prescribing population is similar to other complement inhibitors approved for this indication. These prescribers may be familiar with the approved REMS for Soliris, Ultomiris, and Empaveli and the associated risk of infection with complement inhibitors. However, as the different complement inhibitors target different parts of the complement system, prescribers may not be aware of the differences in risks and vaccine requirements across this class. Given the broader risk of serious infections caused by encapsulated bacteria, healthcare providers who prescribe and pharmacies that dispense iptacopan need to be aware of the risk, the vaccine requirements, and appropriate management should an infection occur. Given the severe risk of serious infections caused by encapsulated bacteria, it is important that patients are aware of the early signs and symptoms of infections, the need for vaccination, and the need to seek immediate medical attention when symptoms occur.

7. Risk Management Activities Proposed by the Applicant

7.1. Review of Applicant's Proposed REMS

The Applicant submitted a complete REMS proposal on April 5, 2023 and was last amended on December 4, 2023. The December 4, 2023 amendment is the subject of this review. The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of iptacopan outweigh the risk of serious infections caused by encapsulated bacteria. The ETASU included prescriber certification (ETASU A), pharmacy certification (ETASU B), and documentation of safe use conditions (ETASU D).

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7.1.1. REMS Goals

The Applicant proposed the following:

The goal of the FABHALTA REMS is to mitigate the risk of serious infections caused by encapsulated bacteria.

1. Patients are vaccinated against infections caused by encapsulated bacteria (Neisseria meningitidis serogroups A, C, W, Y, and B; Streptococcus pneumoniae; and Haemophilus influenzae type B) prior to starting therapy according to current Advisory Committee on Immunization Practices (ACIP) recommendations and receive antibacterial drug prophylaxis if needed.

2. Patients are aware of early signs and symptoms of serious encapsulated bacterial infections and the need for immediate medical evaluation.

3. Prescribers are aware of early signs and symptoms of serious encapsulated bacterial infections and the need for immediate medical evaluation.

Reviewer's Comments: *The Applicant's proposed goals and objectives submitted on April 5, 2023 required revisions* (b) (4) *When determining how to revise the goals and objectives for this REMS, we considered the overall aim of the REMS which is to prevent serious infections caused by encapsulated bacteria to the extent possible. We also considered the medication use process for iptacopan, potential care gaps, and the intended focus on primary prevention (vaccination and antibacterial prophylaxis if needed) and secondary prevention (awareness and early identification of infections). The Applicant revised the goals based on Agency feedback. The proposed goals and objectives as submitted on December 4, 2023 are acceptable.*

7.1.2. REMS Elements

The Applicant proposed the following ETASU as part of the REMS requirements: prescriber certification (ETASU A), pharmacy certification (ETASU B), and documentation of safe use conditions (ETASU D).

ETASU A: Prescriber certification

The Applicant proposed that a prescriber must certify in the Fabhalta REMS prior to prescribing iptacopan. To become certified, prescribers must review the prescribing information (PI), the *Healthcare Provider Safety Brochure*, *Patient Guide*, and *Patient Safety Card*. The prescriber must complete and submit the *Prescriber Enrollment Form* to the REMS.

Prior to initiating treatment with iptacopan, prescribers must: 1) assess the patient for unresolved serious infections caused by encapsulated bacteria, 2) assess the patient's vaccination status for *Neisseria meningitidis* serogroups A, C, W, Y, and B; *Streptococcus*

pneumoniae; and *Haemophilus influenzae* type B and vaccinate, as needed, according to the current Advisory Committee on Immunization Practices (ACIP) recommendations, 3) provide the patient with a prescription for antibacterial drug prophylaxis if the patient is not up to date with vaccines against encapsulated bacteria and must start iptacopan right away, and 4) counsel the patient using the *Patient Guide* and *Patient Safety Card*.

During treatment prescribers must: 1) assess the patient for early signs and symptoms of serious bacterial infection and evaluate immediately if infection is suspected and 2) revaccinate patients as needed according to current ACIP recommendations.

At all times prescribers must report adverse events suggestive of serious bacterial infections, including the patient's clinical outcomes, to the Applicant.

Reviewer's Comments: *We agree with the requirement for prescriber certification (ETASU A). The prescriber certification requirement is similar to the other complement inhibitors subject to a REMS. A REMS with ETASU A would ensure that prescribers are educated on the risk of serious infections caused by encapsulated bacteria associated with iptacopan and the need to counsel patients on this risk which supports the goal and objectives of the REMS. We agree with the inclusion of the Prescriber Enrollment Form, Healthcare Provider Safety Brochure, Patient Safety Card, and Patient Guide to support prescriber education and patient counseling; and find these materials acceptable.*

ETASU B: Pharmacy Certification

The Applicant proposes iptacopan be dispensed by certified pharmacies with separate requirements for outpatient and inpatient pharmacies to accommodate flexibility and to avoid treatment interruption in the inpatient setting. Outpatient and inpatient pharmacies must become certified by designating an authorized representative on the respective *Pharmacy Enrollment Forms.* This authorized representative will be responsible for coordinating REMS activities on behalf of the pharmacy, reviewing training materials, enrolling in the REMS, and ensuring all relevant staff are trained in the REMS and are responsible for establishing processes and procedures to meet the REMS requirements. If the authorized representative changes, the new authorized representative must re-enroll in the REMS in order to maintain certification.

Reviewer's Comments: *We agree with the proposal to have pharmacy certification as pharmacies are responsible for documentation of safe use conditions prior to dispensing (see more below in ETASU D). We agree with the inclusion of the Outpatient Enrollment Form, Inpatient Enrollment Form; and find these materials acceptable.*

ETASU D: Documentation of Safe Use Conditions

The Applicant proposed documentation of safe use conditions prior to dispensing iptacopan. The safe use requirements for pharmacies differ depending on whether the patient is receiving iptacopan therapy as an outpatient or in an inpatient setting.

Outpatient Pharmacy - Safe Use Conditions

Prior to dispensing the first dose of iptacopan, the outpatient pharmacy must obtain authorization to dispense each prescription by contacting the REMS to verify the prescriber is certified and contacting the prescriber to assess and document the patient's vaccination status and/or need for antibacterial drug prophylaxis. For patients who are not up to date with vaccines when starting treatment, the outpatient pharmacy must assess and document the patient's vaccination status for up to 6 months after the first dose of iptacopan. Beyond the first 6 months, the outpatient pharmacy is required to obtain authorization prior to each dispense to verify the prescriber is certified.

Inpatient Pharmacy - Safe Use Conditions

Prior to dispensing the first dose of iptacopan, the inpatient pharmacy[j] must verify if the patient is initiating or continuing treatment through the processes and procedures established as a requirement of the REMS. For patients already receiving treatment with iptacopan and continuing treatment, there are no additional safe use conditions required before dispensing. In this scenario, the inpatient pharmacy is not required to confirm that the prescriber is certified (a noncertified prescriber can prescribe). For patients initiating treatment (i.e., no previous outpatient dispenses), the inpatient pharmacy requirements are similar to those described for outpatient pharmacies prior to the first dose. Prior to the first dose, the inpatient pharmacy must obtain authorization to dispense by contacting the REMS to verify prescriber certification. The inpatient pharmacy must also contact the prescriber to assess and document the patient's vaccination status and/or need for antibacterial drug prophylaxis. At discharge, the pharmacy must dispense no more than a 30 days' supply.

Reviewer's Comments: *We agree with the requirements for documentation of safe use conditions. During the course of this review, changes were made to the pharmacy requirements to align with the changes to labeling. Prior to every dispense, outpatient pharmacies must verify the prescriber is certified. The pharmacist must also contact the prescriber prior to the first dispense to assess and document the patient's vaccination and antibacterial drug prophylaxis status. If the information cannot be obtained, pharmacies may dispense iptacopan and continue to follow up with the prescriber to collect these data to avoid treatment delays.*

The contact with prescribers will serve as a reminder to vaccinate if needed and documentation of vaccination and antibacterial drug prophylaxis will further inform if education and certification of prescribers results in appropriate vaccination of patients and therefore achieves the overall goal of the REMS. If patients are not up to date at the time of the initial dispense, the patients may require additional vaccines to complete the series or may be eligible for boosters or

[j] The *Inpatient Pharmacy Enrollment Form* includes the following location options for the authorized representative to select from: hospital, nursing home, hospice, mental health facility, assisted living, prison, rehabilitation facility, and other.

additional vaccines as recommended by ACIP. The vaccine series for some of the required vaccines (e.g., meningococcal) can take up to 6 months to complete; therefore, pharmacies are required to continue to assess the patient's vaccination status for up to 6 months if patients are not up to date at the time of the first dispense.

We agree with the different requirements for documentation of safe use conditions for inpatient pharmacies depending on whether the patient is initiating treatment or continuing treatment. For patients initiating treatment, the inpatient pharmacy will verify the prescriber is certified and assess the patient's vaccination status prior to the first dose similar to the outpatient pharmacy requirements. For patients continuing therapy, these patients would have been prescribed iptacopan by a certified prescriber and would have had an initial vaccination assessment completed prior to the first dose. For patients continuing treatment, iptacopan treatment may be continued in the inpatient setting without confirming the prescriber is certified. The inpatient pharmacy is also not required to assess vaccination status via the REMS, although we would expect this to be part of good clinical practice to provide or update vaccines as needed. Assessments can be resumed by the outpatient pharmacy when the patient is discharged if applicable. This approach is reasonable given the half-life of iptacopan and the risk of hemolysis associated with abrupt discontinuation.

We agree with the inclusion of the Healthcare Provider Safety Brochure and find it acceptable.

7.1.3. Implementation System

Elements of the implementation system proposed by the Applicant to support REMS operations are listed in the REMS Supporting Document and include:

- **REMS Website:** The Applicant proposes to maintain a *REMS website* to support prescriber and pharmacy ability to interface with the REMS and provide the option to complete prescriber certification online. REMS materials will be made available electronically by the Applicant through the website.

- **REMS Coordinating Center:** The Applicant proposes a REMS Coordinating Center to provide REMS support to stakeholders. The staff will receive inbound calls from stakeholders and provide support for questions regarding the REMS requirements; provide educational materials to stakeholders upon request; receive and process enrollment forms for prescribers and pharmacies; maintain the REMS database of certified prescribers, certified pharmacies, and contracted wholesaler-distributors; verify prescriber certification for certified pharmacies prior to dispensing based on requirements; triage calls regarding adverse events, medical information requests, and complaints per the processes and procedures; receive product dispensing data electronically from each certified outpatient pharmacy to confirm REMS requirements are met; and receive distribution data electronically from each wholesaler-distributor to confirm REMS requirements are met.

- **REMS Database:** The Applicant proposes to maintain a validated, secure database of all REMS participants who are certified in the REMS.

Reviewer's Comments*: The proposed implementation system is consistent with other complement inhibitor REMS. We agree with the Applicant's proposal for an implementation system and find it acceptable.*

7.1.4. Timetable for Submission of Assessments

The Applicant proposes to submit REMS Assessments at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS.

Reviewer's Comments: *The proposed timetable for submission of assessments is acceptable.*

7.1.5. REMS Materials & Key Risk Messages

Key Risk Messages:

The Applicant proposed the following Key Risk Messages (KRMs) for the Fabhalta REMS:

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(b) (4)

Reviewer's Comments*: The Applicant initially proposed KRM's in response to the Agency's information request on October 20, 2023 and added a section to the Supporting Document. The Applicant revised the KRMs to separate the messages by stakeholder (healthcare provider and patient) and to align with labeling. The KRMs as submitted on December 4, 2023 are acceptable.*

REMS Materials:

The Applicant included the following materials as part of the REMS submission:

- Prescriber Enrollment Form: serves to enroll prescribers in the REMS and for prescribers to attest they understand the requirements of the REMS as part of the process to become certified to prescribe iptacopan.

- Outpatient Pharmacy Enrollment Form: completed by the outpatient pharmacy's authorized representative on behalf of the outpatient pharmacy to enroll in the REMS. The authorized representative attests they understand the requirements of the REMS as part of the process to become certified to dispense, will train staff on the REMS requirements, and will develop processes and procedures to meet the REMS requirements.

- Inpatient Pharmacy Enrollment Form: completed by the inpatient pharmacy's authorized representative on behalf of the inpatient pharmacy to enroll in the REMS. The authorized representative attests they understand the requirements of the REMS as part of the process to become certified to dispense, will train staff on the REMS requirements, and will develop processes and procedures to meet the REMS requirements.

- Healthcare Provider Safety Brochure: serves to inform prescribers and pharmacy staff of the risks of serious infections caused by encapsulated bacteria with iptacopan, REMS requirements, and the responsibilities of the prescriber and pharmacies.

- Patient Guide: serves to inform patients of the risk of serious infections caused by encapsulated bacteria associated with iptacopan, the need for vaccinations against encapsulated bacteria, the need to take antibiotics as directed by the prescriber, the early signs and symptoms of serious infection, when to seek immediate medical

attention, and the need to carry the *Patient Safety Card* at all times during treatment and for 2 weeks after the last dose of iptacopan.

- Patient Safety Card: Prescribers provide this card to the patient and counsel the patient to carry the card with them at all times for the duration of treatment and for 2 weeks after the last dose of iptacopan. The patient should present the card to treating healthcare provider if the patient experiences any signs or symptoms of a serious infection. The card serves to inform any healthcare provider treating the patient that the patient is receiving a complement inhibitor. It also includes the risk of serious infections, signs and symptoms of serious infections, and recommends treatment healthcare providers to contact the patient's prescriber.

- REMS Website: serves as a source of information for stakeholders and part of the implementation system for the Applicant. It allows prescribers to enroll in the REMS online. Outpatient pharmacists will have the option to use the website to obtain authorization for each dispense. The REMS materials will be available on the website and downloadable in an electronic format.

Reviewer's Comments*: During the review of the application, we provided comments on the proposed materials and made several changes to improve messaging and overall design.[14,17] The Applicant has addressed our comments and we agree with the Applicant's proposed REMS materials and find them to be acceptable.*

7.1.6. REMS Supporting Document

The proposed REMS Supporting Document (last amended December 4, 2023) includes the Applicant's rationale for the REMS, how the REMS will be implemented (e.g., proposed distribution model, process for how outpatient pharmacies (and inpatient pharmacies, when applicable) confirm that prescribers are certified in the REMS , process for pharmacy assessment and documentation of patient vaccination status including antibacterial drug prophylaxis prior to dispensing), and Key Risk Messages for the various stakeholders. The Supporting Document also includes the REMS Assessment Plan, screenshots of the website (b) (4)

Reviewer's Comments: *In response to the Agency's information request on October 20, 2023, the Applicant submitted nonpublic screenshots for outpatient pharmacies as requested to demonstrate how the outpatient pharmacy obtains authorization. In addition, the website screenshots included additional operational screenshots for adding staff and completing the Pharmacy Audit Questionnaire. The Agency did not provide comments on the submitted screenshots* (b) (4) *The full audit and non-*

compliance plan methodologies should be submitted as a REMS Assessment Methodology within 60 days of product approval for Agency review.

Patients or their caregivers were not initially included as a stakeholder to be surveyed in the Applicant's overview of their plans for the KAB surveys or in their proposed REMS Assessment Plan. A patient KAB survey is needed to inform on the objective if patients are aware of the early signs and symptoms of serious encapsulated bacterial infections and the need for immediate medical evaluation. During review of the application, we provided comments on November 28, 2023, which included our recommendation to include patients/caregivers as a stakeholder to be surveyed to which the Applicant agreed. The Applicant should submit their KAB survey protocols as a REMS Assessment Methodology within 90 days of approval for Agency review.

7.1.7. REMS Assessment Plan

The proposed REMS Assessment Plan is included in the REMS Supporting Document (last amended December 4, 2023). The proposed REMS Assessment Plan includes metrics on Program Implementation and Operations, Safe Use Behaviors, Health Outcomes and/or Surrogates of Health Outcomes, Knowledge, and an Overall Assessment of REMS Effectiveness. The REMS Assessment Plan includes metrics to inform the outcome and process Key Performance Indicators (see section 8), that if met would demonstrate if the REMS is meeting its goal.

Reviewer's Comments: *The REMS Assessment Plan was designed to evaluate whether the REMS is meeting its goal of mitigating the risk of serious infections caused by encapsulated bacteria, to evaluate if the REMS is being implemented and functioning as intended, to determine if stakeholders are compliant with REMS requirements, and to assess any unintended burden on the healthcare system or issues with patient access. During the review of the application, the Agency provided comments and edits on November 28, 2023.[17] The Applicant has addressed all of our comments regarding the metrics in the REMS Assessment Plan last amended on December 4, 2023, and it is acceptable. The final and agreed upon REMS Assessment Plan is included in the Appendix of this review and will be included in the Fabhalta Approval Letter.*

7.1.8. Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on November 1, 2023 to provide feedback on the content of the *Prescriber Enrollment Form, Outpatient Pharmacy Enrollment Form, Inpatient Pharmacy Enrollment Form, Healthcare Provider Safety Brochure, Patient Guide, Patient Safety Card*, and *REMS Website*. The OPDP review was completed by Louiza Bako, Regulatory Review Officer, OPDP on November 29, 2023.[43]

OPDP provided comments on the materials based on draft prescribing information dated November 17, 2023 and Medication Guide dated November 20, 2023. Labeling discussions were

ongoing; therefore, OPDP recommended to revise REMS materials, as appropriate, to reflect all changes in the final approved label. Labeling has been revised since the completion of the consult; consequently, a number of the OPDP recommendations are no longer applicable for DRM to address.

OPDP recommendations are summarized below:

- Revise the prescriber attestation regarding the assessment of vaccination status to include the timing of "two weeks prior to the first dose of Fabhalta".

  Reviewer Comment: *Although the prescriber attestation above does not include the 2-week timing, the following attestation provides requirements to provide antibacterial prophylaxis for patients who are not up to date with the required vaccines at least 2 weeks prior to initiation of treatment and who must start FABHALTA urgently. Therefore, we have determined that no changes are necessary as the key message is already included, just split across two attestations. This approach is consistent with how this message is conveyed for other complement inhibitors.*

- Revise the prescriber attestation for counseling the patient on the Patient Safety Card to add the following statement "This card describes symptoms which, if experienced, should prompt the patient to seek immediate medical evaluation".

  Reviewer Comment: *The statement was not added to the prescriber attestations as this information is a description of the Patient Safety Card rather than essential information for the requirement. DRM added this statement to the Healthcare Provider Safety Brochure as this is an appropriate place for additional clarification on the material's purpose. This approach is consistent with information included for other complement inhibitors.*

Unless noted above, DRM agrees with OPDP's remaining recommendations and updated the REMS materials accordingly.

8. Discussion

Discussion of Need for a REMS

The benefits of iptacopan for the treatment of PNH were demonstrated in two phase 3 studies, APPLY-PNH (treatment-experienced population) and APPOINT-PNH (treatment-naïve population). In APPLY-PNH, there was a statistically significant greater number of subjects in the iptacopan-treated group who met the primary endpoints (sustained increase of ≥2 g/dL in hemoglobin from baseline and hemoglobin ≥12 g/dL in the absence of RBC transfusions) compared to the active comparator, complement C5 inhibitor therapy. APPOINT-PNH demonstrated consistent results on sustained increases in hemoglobin levels from baseline.

Serious infections including a death related to an infection by an encapsulated organism were reported in iptacopan-treated subjects. During the clinical trials, risk mitigation measures were in place to prevent infections caused by encapsulated bacteria (e.g., vaccination against *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type B). The risk of serious infections caused by encapsulated bacteria is a known risk for the complement inhibitor class. Other complement inhibitors indicated for PNH are subject to a REMS to mitigate the risk of serious infections. The specific risk (serious infections caused by encapsulated bacteria or serious meningococcal infections) is based on the product's mechanism of action and target within the complement system. Iptacopan inhibits Factor B and impacts the complement system proximally (prior to C3 activation) resulting in a broad risk of serious infections caused by encapsulated bacteria. Given the risk of serious infections caused by encapsulated bacteria, this risk will be communicated in labeling as a Boxed Warning, included in Section 5 – Warnings and Precautions in the Prescribing Information and summarized in the Medication Guide for patients. The recommended vaccination and prophylaxis for encapsulated bacterial infections is summarized in Section 2.1 and patient counseling information is summarized in Section 17.

The review team determined that a REMS is necessary to ensure the benefits of treatment with iptacopan outweigh the risk of serious infections caused by encapsulated bacteria. The REMS is comprised of ETASU, an implementation system and a timetable for submission of assessments. The ETASU include prescriber certification, pharmacy certification, and documentation of safe-use condition [verification of prescriber certification and assessment of vaccination status and need for or antibacterial drug prophylaxis]) which are necessary in combination to form a program that will mitigate the risks of serious infection caused by encapsulated bacteria and provide data to assist in determining if the goals of the program are being met. The design of this REMS is similar to other approved complement inhibitors (e.g., Empaveli REMS and Zilbrysq REMS) and aligns with the Agency's current thinking on the ETASU that are necessary to ensure safe use for these products.

Prescriber certification ensures that prescribers receive training about the risk of serious infections caused by encapsulated bacteria associated with iptacopan, the need to complete or update patients' vaccination against encapsulated bacteria prior to initiation of iptacopan treatment, and the need for antibacterial prophylaxis if treatment must be started urgently and the patient is not up to date on vaccinations. Prescribers also attest to counsel patients on the early signs and symptoms of serious infections and the need to seek medical attention if symptoms are present. In addition, prescribers attest to providing the patient a *Patient Safety Card* and informing the patient of the need to carry the card with them at all times and show to any healthcare provider treating them.

Outpatient pharmacy certification ensures that dispensing pharmacy staff are trained about the risk of serious infections, the need to obtain authorization prior to each dispense, and to assess patient vaccination status and document the findings prior to dispensing and for up to six months after the first dose of iptacopan. Inpatient pharmacy certification ensures that pharmacy staff are trained about the risk, the need to verify whether the patient is initiating therapy or continuing therapy, and the requirements for when a patient is initiating therapy inpatient. The requirements to assess vaccination status and document the findings will assist in assessing if the REMS goals are being accomplished.

While we would like all patients to be vaccinated, we recognize that some patients will decline or be unable to be vaccinated; therefore, 100% compliance with vaccination is not reasonable for this drug.

The proposed REMS for iptacopan as well as other complement inhibitor products were shared with the REMS Oversight Committee (ROC)[k] on August 15, 2023. The ROC members did not raise any concerns regarding the planned strategy.

Assessment of the REMS and Key Performance Indicators

Key Performance Indicators (KPIs) are measures that are used to determine whether the REMS is achieving its goal of mitigating the risk of serious meningococcal infection. The KPIs have been established by developing a minimum target threshold for specific assessment metrics that indicate if the REMS is functioning as designed and may help determine if modifications to the REMS are necessary. A KPI at or below the established minimum threshold indicates that the REMS is not functioning as expected and may require a modification to meet the goals of the REMS. The Applicant may also need to conduct a root cause analysis (RCA) or deploy corrective and preventative actions (CAPAs) if the KPI is below the target threshold.

Although mitigation of serious infections is an overall goal of the REMS, life-threatening and fatal serious infections caused by encapsulated bacteria have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors; therefore, it may not be possible to prevent all cases of serious infection. While the number of cases of serious infections will be measured and assessed, this will not be a KPI to assess the success of the REMS. The REMS provides training to prescribers and is intended to affect safe use behavior so prescribers do not start treatment in patients with an unresolved serious infection caused by encapsulated bacteria, patient vaccination status is assessed and patients receive required vaccines prior to initiating treatment with iptacopan, and patients receive antibacterial drug prophylaxis if the patient must start therapy urgently before the vaccinations are up to date. To align the KPIs with the objectives of the REMS, the KPIs are related to vaccination rates against encapsulated bacteria and education of prescribers (achieved through prescriber certification).

The KPIs and minimum target thresholds for iptacopan are described below.

- Percentage (%) of patients dispensed Fabhalta who received at least one dose of Advisory Committee on Immunization Practices (ACIP) recommended meningococcal vaccines (against all of the following serogroups: A, B, C, W, Y) and antibacterial drug prophylaxis if needed before the first dispense
    - Numerator: Number of patients who received at least one dose of ACIP recommended meningococcal vaccines before the first Fabhalta dispense and

[k] 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.

antibacterial drug prophylaxis if the patient has not received a complete series or vaccination occurred <2 weeks before first dispense of Fabhalta
    - Denominator: Number of patients who received a first dispense of Fabhalta
    - Minimum target threshold: 80%

- Percentage (%) of patients dispensed Fabhalta who received at least one ACIP recommended pneumococcal vaccine and antibacterial drug prophylaxis if needed before the first dispense
    - Numerator: Number of patients who received at least one ACIP recommended pneumococcal vaccine before the first Fabhalta dispense and antibacterial drug prophylaxis if vaccination occurred <2 weeks before dispense
    - Denominator: Number of patients who received a first dispense of Fabhalta
    - Minimum target threshold: 80%

- Percentage (%) of patients dispensed Fabhalta who have a history of childhood vaccination for Haemophilus influenzae type B or received at least one adult dose of a Haemophilus influenzae type B vaccine and antibacterial drug prophylaxis if needed before the first dispense
    - Numerator: Number of patients who received Haemophilus influenzae type B vaccination (childhood series or a dose as an adult) before the first Fabhalta dispense and antibacterial drug prophylaxis if vaccination occurred <2 weeks before dispense
    - Denominator: Number of patients who received a first dispense of Fabhalta
    - Minimum target threshold: 75%

- Percentage (%) of outpatient Fabhalta dispenses corresponding to prescriptions written by REMS certified Healthcare Providers
    - Numerator: Number of Fabhalta dispenses corresponding to prescriptions written by REMS certified Healthcare Providers
    - Denominator: Number of Fabhalta outpatient dispenses
    - Minimum target threshold: 99%

These KPIs align with our approach for related products with approved REMS in this therapeutic class and include both outcome and process measures for REMS program evaluation.

The KPI and minimum target thresholds for the meningococcal and pneumococcal vaccination were derived based on the following considerations: design of the REMS not requiring vaccination as a hard stop for dispensing, how the data will be collected by the pharmacy and the potential for missing data at the time of the first dispense, the Agency's experience with related products with approved REMS in this therapeutic class, and national rates of compliance for other vaccine schedules. The KPI and minimum target threshold for *Haemophilus influenzae* type B vaccination differs from those for meningococcal and pneumococcal vaccination due to a few considerations. Childhood vaccination for *Haemophilus*

influenzae type B is currently routine; however, a portion of the anticipated patient population may not have received this series as a child based on when the vaccines were first approved. In light of the increased risk of infection due to *Haemophilus influenzae* type B, prescribers should assess whether vaccination is necessary in an adult when iptacopan therapy is planned. Vaccination rates for *Haemophilus influenzae* type B in the clinical development program for iptacopan were lower than the rates for meningococcal and pneumococcal vaccination, and we anticipate vaccination rates in real world practice may be lower than in the clinical trials.

The KPI on prescriber certification was modified to only include outpatient dispenses. Data on inpatient dispenses will be collected as outlined in the Assessment Plan; however, it will not be captured as a KPI. The KPI threshold (99%) for the prescriber certification KPI is based on the pharmacy verification of prescriber certification being a closed system and compliance rates with closed systems in other REMS. Although the REMS is a closed system, there is still opportunity for human error as these actions are not integrated into the pharmacy system and pharmacists must step outside their typical workflow to obtain authorization to verify prescriber certification and to assess/document patient vaccination status and antibacterial prophylaxis. Therefore, the proposed REMS relies on the pharmacy authorized representative to ensure that training and processes and procedures are developed and there is good compliance. As described in a the "Improving the Reliability of Health Care" white paper from the Institute of Healthcare Improvements (IHI) the expected failure rate in a system that has process in place, which includes an identification trigger to help identify and mitigate failure such as a pharmacy identifying patients that are not vaccinated per ACIP recommendations, will help move the reliability of the care process to 10^{-2}.[44] Therefore, the expected failure rate is very low and a high threshold of 99% is achievable, appropriate, and in line with the expected reliability of 10^{-2}. Therefore, we consider 99% a reasonable minimum target threshold for this KPI.

9. Conclusion & Recommendations

The risk of serious infections caused by encapsulated bacteria is significant and can be life-threatening and fatal. Therefore, it is necessary for prescribers, pharmacists, and patients to understand this risk, the need to assess patients' vaccination status and complete or update vaccination against encapsulated bacteria at least 2 weeks prior to treatment initiation, the need for antibacterial drug prophylaxis if urgent therapy is indicated and the risk of delaying treatment outweighs the risk of serious infection caused by encapsulated bacteria, and how to recognize and manage infections should they occur. Based on the severity of the risk, DRM and DNH agree that requiring a REMS consisting of prescriber certification, pharmacy certification, and documentation of safe use conditions (pharmacy assessment and documentation of vaccination and antibacterial drug prophylaxis prior to dispensing) is necessary to ensure that the benefits outweigh the risks. The REMS will also include an implementation system and timetable for submission of assessments. Collectively these elements in conjunction with the assessment metrics form a REMS program that are intended to mitigate the serious infections caused by encapsulated bacteria and assess if the program is meeting its intended to goals.

DRM and DMAMES finds the Applicant's Fabhalta REMS last amended on December 4, 2023, to be acceptable and it is appended to this review.

10. Appendices

10.1. References

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10.2. Summary of FDA-Approved Therapies for PNH

Drug (Approval Date)	**Indication**	**Dosing and Administration**	**Important Safety and Tolerability Issues**	**Risk Management Approaches**
Soliris-eculizumab (2007)	PNH to reduce hemolysis	IV infusion: 600 mg weekly for first 4 weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter	Meningococcal infection, other infections, infusion-related reactions	REMS-ETASU Labeling- Boxed Warning, Warnings and Precautions
Ultomiris-ravulizumab (2018)	Adult and pediatric patients one month of age and older with PNH	IV infusion: weight based, maintenance dose every 4 or 8 weeks, starting 2 weeks after loading dose Maintenance subcutaneous	Meningococcal infections, other infections, infusion-related reactions	REMS-ETASU Labeling- Boxed Warning, Warnings and Precautions

		injection (on-body delivery system, adults only): 490 mg once weekly		
Empaveli-pegcetacoplan (2021)	Adult patients with PNH	Subcutaneous infusion: 1,080 mg twice weekly	Serious infections caused by encapsulated bacteria, infusion-related reactions	REMS-ETASU Labeling- Boxed Warning, Warnings and Precautions

10.3. Assessment Plan

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

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.

Program Implementation and Operations

1. REMS Implementation (for the first REMS Assessment only)
   a. Date of first commercial distribution of FABHALTA
   b. Date of FABHALTA REMS launch
   c. Date when the **REMS Website** became live and fully operational
   d. Date when healthcare providers who can prescribe could become certified in the FABHALTA REMS
   e. Date when pharmacies could become certified in the FABHALTA 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
   a. Healthcare Provider Certification
      i. Numbers certified: total, newly certified, and active (prescribed FABHALTA at least once during the reporting period), stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Advanced Practice Registered Nurse, Physician Assistant, Other), medical specialty, and geographic region (as defined by the United States (US) Census)
      ii. Method of certification
      iii. Number of healthcare providers who have prescribed but were unable to become certified, accompanied by a summary of the reasons they were unable to be certified
   b. Pharmacy Certification (stratify by inpatient and outpatient)
      i. Identity and number of pharmacies certified: total and newly certified and active (dispensed FABHALTA at least once during the reporting period), stratified by geographic region (as defined by US Census)

ii. 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 FABHALTA at least once during the reporting period)

3. FABHALTA Utilization Data (stratify by inpatient and outpatient pharmacies)
   a. The number of FABHALTA shipments sent to pharmacies, overall, and stratified by quantity per shipment
   b. For certified pharmacies, number of prescriptions dispensed 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]
      iii. Whether the prescription was new or a refill
   c. For wholesaler-distributors, number of orders distributed
   d. The number of unique patients who received FABHALTA stratified by age, gender, and geographic regions (as defined by US Census)
   e. Percentage (%) of FABHALTA dispenses corresponding to prescriptions written by REMS certified healthcare providers
   f. The number of prescriptions not dispensed, accompanied by a listing and summary of all reasons for not dispensing the prescription (e.g., healthcare providers not certified, REMS related issue)

4. REMS Compliance
   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 and certified 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:
         a) The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
         b) The source of the noncompliance data
         c) The results of root cause analysis
         d) What action(s) were taken in response
      iii. Number and percent of FABHALTA outpatient prescriptions that were dispensed that were submitted by non-certified prescribers:
         a) Specific reasons that prescribers were not certified at the time of prescribing (e.g., emergency use), and whether these prescribers subsequently became certified

iv. The number and percentage of drug distributions to inpatient and outpatient pharmacies that are not certified

v. The specific reasons for the drug distributions to inpatient and outpatient pharmacies that are not certified

vi. The number of inpatient and outpatient pharmacies who became decertified, accompanied by a summary of reasons for decertification

b. Audits: Summary of audit activities including but not limited to:

i. A copy of the audit plan used for each audited stakeholder type (pharmacies, REMS Coordinating Center, and wholesalers-distributors)

ii. The number of audits expected, and the number of audits performed for each stakeholder type

iii. The number and category of observations noted, stratified by category

iv. A unique ID for each stakeholder that had observations to track observations by stakeholder over time

v. Documentation of completion of training for relevant staff (those involved in the distribution or dispensing of FABHALTA)

vi. A summary report of documented processes and procedures for complying with the REMS requirements including how certified inpatient and outpatient pharmacies obtain patient vaccination status

vii. Verification that at each audited stakeholder's site the designated Authorized Representative is up to date. If different, include the number of new Authorized Representatives and verification of each 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

a) For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan by the due date

b) For any that did not complete the CAPA by the due date, describe additional actions taken

5. REMS Infrastructure and Performance

a. REMS Website

i. Number of visits and unique visits to the **REMS Website**

ii. Number of REMS materials downloaded for each material

b. REMS Coordinating Center Report

i. Number of contacts by stakeholder type (i.e., patient/caregiver, healthcare provider, pharmacy)

ii. A table summarizing the reasons for calls (e.g., enrollment question) by stakeholder type

iii. If the reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether it indicates a potential REMS burden or patient access issue

iv. A summary report of corrective actions resulting from issues identified

Safe Use Behaviors

6. Safe Use Behaviors
    a. Information captured by inpatient and outpatient pharmacies regarding the number and percent of patients who were vaccinated against encapsulated bacteria (*Neisseria meningitidis* serogroups A, C, W, Y and B, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B). This information is to include, regarding each vaccination type:
        i. The date of first vaccine administration (to include for each serogroup when applicable)
        ii. The number of days between vaccination and initiation of therapy with FABHALTA (if available)
        iii. Status and date of second vaccine doses and booster doses for MenACWY and MenB serogroup vaccines (if available)
        iv. The date when FABHALTA was first dispensed
        v. Whether the patient received antibacterial drug prophylaxis, and timing of antibacterial drug prophylaxis in relation to the dosing of FABHALTA (if available)
        vi. If any of the above information is missing, the reasons why this information is missing such as:
            a) Healthcare provider records do not include this information
            b) Healthcare provider declined to provide information
            c) Pharmacy unable to get healthcare provider to respond to queries
    b. The number and percentage of new patients treated with FABHALTA who completed or were up to date with vaccination against encapsulated bacteria (*Neisseria meningitidis* serogroups A, C, W, Y and B, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B) as per the most current Advisory Committee on Immunization Practices (ACIP) recommendations
    c. The number and percentage of patients who did not receive vaccination against encapsulated bacteria (*Neisseria meningitidis* serogroups A, C, W, Y and B, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B) in accordance with the current ACIP recommendations or given antibacterial drug prophylaxis if needed, prior to initiating treatment with FABHALTA

Include a narrative describing the vaccines that were not administered (i.e., *Neisseria meningitidis* serogroups A, C, W, Y and B serogroups, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B)

    d. Number and percentage (%) of patients dispensed FABHALTA who received at least one dose of ACIP recommended meningococcal vaccines (against all of the following serogroups: A, B, C, W, Y) and antibacterial drug prophylaxis if needed before the first dispense
    e. Number and percentage (%) of patients dispensed FABHALTA who received at least one ACIP recommended pneumococcal vaccine and antibacterial drug prophylaxis if needed before the first dispense
    f. Number and percentage (%) of patients dispensed FABHALTA who have a history of childhood vaccination for *Haemophilus influenzae* type B or received at least one ACIP recommended *Haemophilus influenzae* type B vaccine and antibacterial drug prophylaxis if needed before the first dispense

g. For patients who were not initially up to date with vaccines (stratify by meningococcal, pneumococcal, and *Haemophilus influenzae* type B vaccines) when starting treatment, report the number and percentage who, up to 6 months after the first dose:

   i. Completed vaccines
   ii. Did not complete vaccines but were receiving antibacterial drug prophylaxis
   iii. Vaccination status was unknown after completed follow-up attempts

Health Outcomes and/or Surrogates of Health Outcomes

7. Summary of cases of meningococcal, pneumococcal, and *Haemophilus influenzae* type B infections in patients receiving FABHALTA:
   a. For US cases include:
      i. A summary of all cases included in the most recent Periodic Safety Update Report (PSUR) submitted to the FABHALTA NDA with a link to that PSUR identified
      ii. A cumulative listing of all cases of meningococcal, pneumococcal, and *Haemophilus influenzae* type B infections from approval to include cases identified during the current reporting period
   b. For each US case, provide the following information (if available):
      i. MedWatch or other case report number
      ii. Date of report and date of report to FDA
      iii. Patient age, race and gender
      iv. Indication for FABHALTA treatment
      v. Meningococcal, pneumococcal, and *Haemophilus influenzae* type B bacteria vaccination status, to include the specific vaccines and the dates they were administered
         a) Date of vaccine(s) (i.e., all of the meningococcal (ACWY and MenB), pneumococcal, and *Haemophilus influenzae* type B vaccines doses that a patient received including the first vaccine dose, second vaccine dose, and booster doses)
         b) Name of vaccine(s)
         c) Timing in relation to FABHALTA (i.e., the dates or duration that a patient received FABHALTA in relation to the vaccine(s))
         d) ACIP compliance and antibacterial drug prophylaxis status
            1) Antibacterial drug prophylaxis regimen
            2) Timing (i.e., include the dates or duration that a patient received FABHALTA in relation to antibacterial drug prophylaxis)
         e) Clinical course
            1) Outcome and causative bacteria (include serogroup where applicable)
            2) Source of the vaccine information when available. For information that is not available (listed as “unk” or “unknown”) the number and type (patient, prescriber, etc.) of outreach attempts made to obtain the information for each case. Also, if the information is not available, a narrative is presented explaining why the information is unknown (“unk”) or unavailable for each reported case

vi. Whether or not the patient was administered any antibacterial drug prophylaxis and if so:
    a) The specific antibiotic(s), antibiotic regimen (dose/frequency), and route(s) of administration
    b) The duration of the antibiotic treatment
    c) The timing of the course of the antibiotics in relation to FABHALTA treatment
vii. Summary of clinical course and the outcome; specifically report whether the patient:
    a) Was admitted to an intensive care unit
    b) Experienced any organ system failure, such as (but not limited to) requiring mechanical ventilation or medication (vasopressors) to support blood pressure
    c) Died
viii. The length of time between onset of symptoms and when the patient presented for medical evaluation (if available)
ix. Causative encapsulated bacteria organism and serogroup
x. Whether the **Patient Safety Card** was presented during the process of the patient seeking treatment

c. For each non-US case, the following information, as available, will be provided:
    i. Case report number
    ii. Patient age and gender
    iii. Indication for FABHALTA treatment
    iv. Encapsulated bacteria vaccination status if known
    v. Outcome
    vi. If associated with any clinical trials

8. Meningococcal, pneumococcal, and *Haemophilus influenzae* type B infection rate:
    a. Among patients who received FABHALTA in the US and worldwide, the number of reported cases of meningococcal, pneumococcal, and *Haemophilus influenzae* type B infections per 100,000 patient-years of post-marketing exposure to FABHALTA; reporting rate will be summarized cumulatively since the approval of FABHALTA and stratified by year and age subgroup (e.g., ≤ 18 years, 19-55 years, and > 55 years)

Knowledge

9. Knowledge
    a. Stakeholder Surveys for prescribing healthcare providers and patients (beginning with the 1-year assessment report and provide for each reporting period thereafter)
        i. An assessment of healthcare providers' and patients' awareness regarding:
            a) Patients are vaccinated against infections caused by encapsulated bacteria (*Neisseria meningitidis* serogroups A, C, W, Y and B, *Streptococcus pneumoniae,* and *Haemophilus influenzae* type B) prior to starting therapy according to current ACIP recommendations and receive antibacterial drug prophylaxis if needed
            b) The early signs and symptoms of encapsulated bacterial infections
            c) The need for immediate medical evaluation

Overall Assessment of REMS Effectiveness

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.

10.4. REMS

- REMS Document
- Prescriber Enrollment Form
- Outpatient Pharmacy Enrollment Form
- Inpatient Pharmacy Enrollment Form
- Healthcare Provider Safety Brochure
- Patient Guide
- Patient Safety Card
- REMS Website

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LINDSEY W CRIST
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12/04/2023 08:51:50 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	218276
PDUFA Goal Date	December 5, 2023
Nexus TTT#	2023-4375
Reviewer Names	Lindsey W. Crist, PharmD, BCPS (DRM) Anahita Tavakoli, MA (DRM)
Team Leader	Jacqueline Sheppard, PharmD (DRM)
Review Completion Date	November 30, 2023
Subject	Interim Review of proposed REMS
Established Name	Iptacopan
Trade Name	Fabhalta
Name of Applicant	Novartis Pharmaceuticals Corporation
Therapeutic Class	Complement Factor B inhibitor
Formulation(s)	200 mg oral capsules
Dosing Regimen	200 mg orally twice daily

TABLE OF CONTENTS

1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Fabhalta (iptacopan), New Drug Application (NDA) 218276, submitted by Novartis Pharmaceuticals Corporation (hereafter referred to as the Applicant) on April 5, 2023, and amended on November 9, 2023 and November 27, 2023.[1,2]

Fabhalta (iptacopan) is a complement Factor B inhibitor proposed for the treatment of (b) (4) (b) (4) paroxysmal nocturnal hemoglobinuria (PNH). This application is under review in the Division of Nonmalignant Hematology (DNH).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of iptacopan outweigh the risk of serious infections caused by encapsulated bacteria. The ETASU include prescriber certification (A), pharmacy certification (B), and documentation of safe use conditions (D).

This interim review provides comments on the REMS submitted on April 5, 2023, last amended on November 27, 2023 and provides revisions to align with labeling.

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- **11/28/2023:** The Agency sent interim comments on the REMS to the Applicant. In addition, the draft Prescribing Information and Medication Guide were sent with additional Agency revisions related to the risk of serious infections caused by encapsulated bacteria.
- **11/29/2023:** A teleconference was held between the Agency and the Applicant to discuss labeling. The Applicant agreed with labeling changes related to the risk of serious infections caused by encapsulated bacteria.
- **11/30/2023:** The Applicant submitted updated labeling and a REMS Supporting Document that incorporated the Agency's comments on key performance indicators, key risk messages, and the Assessment Plan.

3. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on April 5, 2023 and last amended on November 27, 2023. The revisions to the REMS are intended to align with the labeling sent to the Applicant on November 28, 2023 and discussed at the November 29, 2023 teleconference. We also have comments regarding design and formatting of your REMS materials. Review of the REMS is ongoing; these comments should not be considered final. For the REMS to be acceptable, the REMS Document and all appended materials must align with final FDA-approved labeling. Please note that additional substantial changes to the REMS could impact the action date.

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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	218276
PDUFA Goal Date	December 5, 2023
Nexus TTT#	2023-4375
Reviewer Names	Lindsey W. Crist, PharmD, BCPS (DRM) Anahita Tavakoli, MA (DRM) Mitkumar Patel, PharmD, Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
Team Leaders	Barbara Bergquist, PharmD (DMAMES) Jacqueline Sheppard, PharmD (DRM)
Review Completion Date	November 28, 2023
Subject	Interim Review of proposed REMS
Established Name	Iptacopan
Trade Name	Fabhalta
Name of Applicant	Novartis Pharmaceuticals Corporation
Therapeutic Class	Complement Factor B inhibitor
Formulation(s)	200 mg oral capsules
Dosing Regimen	200 mg orally twice daily

TABLE OF CONTENTS

1. Introduction

This review by the Division of Risk Management (DRM) and Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Fabhalta (iptacopan), New Drug Application (NDA) 218276, submitted by Novartis Pharmaceuticals Corporation.

Fabhalta (iptacopan) is a complement Factor B inhibitor proposed for the treatment of (b) (4) (b) (4) paroxysmal nocturnal hemoglobinuria (PNH). This application is under review in the Division of Nonmalignant Hematology (DNH).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of iptacopan outweigh the risk of serious infections caused by encapsulated bacteria.[1,2] The ETASU include prescriber certification (A), pharmacy certification (B), and documentation of safe use conditions (D).

This review focuses primarily on the Assessment Plan and Supporting Document submitted on April 5, 2023 and last amended on November 27, 2023.

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- **11/20/2023:** The Applicant submitted revised labeling and proposed additional changes to the Boxed Warning and Section 5.1.
- **11/21/2023:** The Agency sent interim comments on the REMS to the Applicant.
- **11/22/2023:** The Applicant sent a correspondence describing the inpatient pharmacy certification process in more detail and responded to Agency concerns regarding burden and access.[3]
- **11/27/2023:** The Applicant submitted a REMS Amendment and updated language throughout the REMS to align with their 11/20/2023 labeling revisions.[2]

3. Comments to the Applicant

We have the following comments on the proposed REMS submitted on April 5, 2023 and last amended on November 27, 2023. These comments primarily focus on the Assessment Plan and Supporting Document last submitted on November 27, 2023. Review of the REMS is ongoing; these comments should not be considered final. We acknowledge labeling discussions are ongoing that may impact the REMS materials. For the REMS to be acceptable, the REMS Document and all appended materials must align with final FDA-approved labeling.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Resubmission Instructions:

Submit your revised Supporting Document, which includes the REMS Assessment Plan (MS Word tracked change document, MS Word Clean Document, and PDF) no later than Thursday, November 30, 2023 at 10:00 AM Eastern Time that addresses these comments. Do not submit a REMS Amendment or make additional changes to the REMS Document or appended materials at this time. We will provide additional guidance on when to resubmit your next complete REMS Amendment following the labeling discussions with the Agency.

4. References

1. Novartis Pharmaceuticals Corporation. Original-1 Submission for iptacopan, NDA 218276 submitted on April 5, 2023. .
2. Novartis Pharmaceuticals Corporation. REMS Amendment for iptacopan, NDA 218276 (sequence 0058) submitted on November 27, 2023.
3. Novartis Pharmaceuticals Corporation. REMS Correspondence. Inpatient Pharmacy Certification. November 22, 2023.

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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	218276
PDUFA Goal Date	December 5, 2023
Nexus TTT#	2023-4375
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS Anahita Tavakoli, MA
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD (DRM)
Review Completion Date	November 21, 2023
Subject	Interim Review of proposed REMS
Established Name	Iptacopan
Trade Name	Fabhalta
Name of Applicant	Novartis Pharmaceuticals Corporation
Therapeutic Class	Complement Factor B inhibitor
Formulation(s)	200 mg oral capsules
Dosing Regimen	200 mg orally twice daily

TABLE OF CONTENTS

1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Fabhalta (iptacopan), New Drug Application (NDA) 218276, submitted by Novartis Pharmaceuticals Corporation (hereafter referred to as the Applicant) on April 5, 2023, and amended on November 9, 2023.[1,2]

Fabhalta (iptacopan) is a complement Factor B inhibitor proposed for the treatment of (b) (4) (b) (4) paroxysmal nocturnal hemoglobinuria (PNH). This application is under review in the Division of Nonmalignant Hematology (DNH).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of iptacopan outweigh the risk of serious infections caused by encapsulated bacteria. The ETASU include prescriber certification (A), pharmacy certification (B), and documentation of safe use conditions (D).

This interim review provides DRM's comments on the REMS amendment submitted on November 9, 2023.[2] In this amendment, the Applicant incorporated comments[3] from the Agency sent on November 3, 2023 and also proposed additional changes to the REMS Document, REMS materials, and REMS Supporting Document.

The proposed changes to the REMS include the following:

- Incorporated the conditionally acceptable proprietary name "FABHALTA"
- Submitted PDF materials with "creative treatment applied" (e.g., logos, coloring, shading, and other design features)
- Revised the REMS material names to **Healthcare Provider Safety Brochure**, **Patient Guide**, and **Patient Safety Card**
- Updated content to align with the Applicant's DRAFT Prescribing Information and Medication Guide submitted to the Agency on November 6, 2023.[4]
- REMS Document
    - Revised the prescriber requirement to not initiate therapy in a patient with an unresolved serious infection caused by encapsulated bacteria
    - Revised the prescriber requirement related to counseling the patient to carry the **Patient Safety Card** for clarity
    - Removed the requirement (b) (4)
    - Revised the patient requirement timing category for informing prescriber or seeking emergency medical care upon recognition of signs or symptoms of serious infection and for carrying the **Patient Safety Card**
    - Updated the audit language in the REMS Document for pharmacies and proposed to (b) (4)
- REMS materials
    - Updated materials to align with labeling and the REMS Document.

- REMS Supporting Document

(b) (4)

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- **11/09/2023:** The Applicant submitted a REMS amendment in response to the Agency's November 3, 2023 comments.[2] The Applicant aligned the language with their proposed revisions to the Prescribing Information and Medication Guide as outlined in the 11/06/2023 submission.[4]
- **11/17/2023:** The Agency sent draft Prescribing Information and Medication Guide with additional revisions.

3. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on April 5, 2023 and amended on November 9, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final. The revisions provided are based on the revisions to the draft Prescribing Information and Medication Guide sent by the Agency on November 17, 2023.

REMS Document

- Changes are required to your REMS Document to align with revisions to the draft Prescribing Information and Medication Guide sent by the Agency on November 17, 2023 and for consistency with the REMS Document Technical Conformance Guide.
  See the attached redlined document for details. Please note that substantial changes to the REMS document, including changes to the requirements could impact the action date.

REMS Materials

The following materials were revised to reflect the revisions to the REMS Document, draft Prescribing Information, and Medication Guide sent by the Agency on November 17, 2023. Additional comments and changes were made to improve the design, formatting, and messaging. See the attached redlined materials for details.

- Prescriber Enrollment Form
- Outpatient Pharmacy Enrollment Form
- Inpatient Pharmacy Enrollment Form
- Healthcare Provider Safety Brochure

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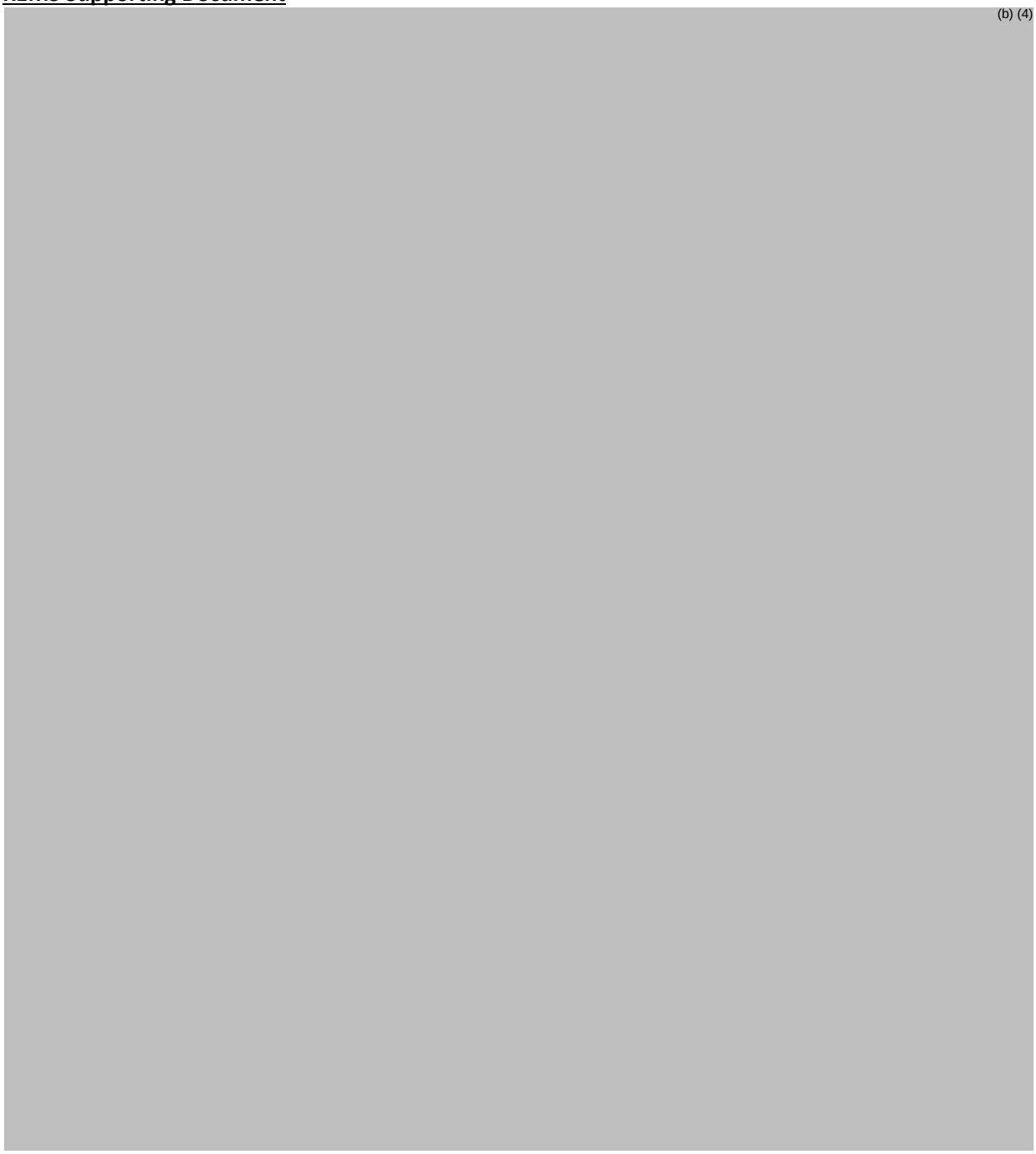
- Patient Guide
- Patient Safety Card
- REMS Website

REMS Supporting Document

(b) (4)



REMS Assessment Plan

- Your assessment plan is under review and comments will be sent out in a separate communication.

Resubmission Instructions:

Submit a REMS amendment by Monday, November 27, 2023 by noon Eastern Time that addresses these comments.

The following materials contain revisions, comments, or require updates. Update the materials with the revisions and resubmit these materials with the next complete submission. Indicate any new changes you propose as redlined changes in your next submission. Include all formatting when submitting REMS materials (MS Word and PDF) in your next submission, including any logos, coloring, shading, or other design features.

- REMS Document
- Prescriber Enrollment Form
- Outpatient Pharmacy Enrollment Form
- Inpatient Pharmacy Enrollment Form
- Healthcare Provider Safety Brochure
- Patient Guide
- Patient Safety Card
- REMS Website

Your complete REMS proposal should be submitted as separate documents in the same submission, should include a Word tracked changes version, a Word clean version, and a .pdf version of each of the documents and appended materials. See the chart below with a summary of required formats for document submission.

Material	Required Format
REMS Document	Tracked MS Word, Clean MS Word, Clean PDF version
REMS Supporting Document	Tracked MS Word, Clean MS Word, Clean PDF version
Prescriber Enrollment Form	Tracked MS Word, Clean MS Word, Clean PDF version
Outpatient Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, Clean PDF version

Inpatient Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, Clean PDF version
Healthcare Provider Safety Brochure	Tracked MS Word, Clean MS Word, Clean PDF version
Patient Guide	Tracked MS Word, Clean MS Word, Clean PDF version
Patient Safety Card	Tracked MS Word, Clean MS Word, Clean PDF version
REMS Website	Tracked PDF or MS Word with comments identifying key changes, Clean PDF version
Compiled PDF file that includes the REMS Document and all REMS materials in their final, clean format	PDF version

4. References

1. Novartis Pharmaceuticals Corporation. Original-1 Submission for iptacopan, NDA 218276 submitted on April 5, 2023. .
2. Novartis Pharmaceuticals Corporation. REMS Amendment for iptacopan, NDA 218276 (sequence 0052) submitted on November 9, 2023.
3. Hamilton C. REMS Interim Comments to Applicant for FABHALTA (iptacopan) REMS, NDA 218276 November 3, 2023.
4. Novartis Pharmaceuticals Corporation. Labeling/Package Insert Draft; Labeling/Container-Carton Draft; Labeling/MedGuide Draft for iptacopan, NDA 218276 (sequence 0044) submitted on November 6, 2023.

5. Appendix

- REMS Document
- Prescriber Enrollment Form
- Outpatient Pharmacy Enrollment Form
- Inpatient Pharmacy Enrollment Form
- Healthcare Provider Safety Brochure
- Patient Guide
- Patient Safety Card
- REMS Website

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JACQUELINE E SHEPPARD
11/21/2023 10:25:16 AM

CYNTHIA L LACIVITA
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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	218276
PDUFA Goal Date	December 5, 2023
Nexus TTT#	2023-4375
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS Anahita Tavakoli, MA
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD (DRM)
Review Completion Date	November 2, 2023
Subject	Interim Review of proposed REMS
Established Name	Iptacopan
Trade Name	Fabhalta
Name of Applicant	Novartis Pharmaceuticals Corporation
Therapeutic Class	Complement Factor B inhibitor
Formulation(s)	200 mg oral capsules
Dosing Regimen	200 mg orally twice daily

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This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Fabhalta (iptacopan), New Drug Application (NDA) 218276, submitted by Novartis Pharmaceuticals Corporation (hereafter referred to as the Applicant) on April 5, 2023.

Fabhalta (iptacopan) is a complement Factor B inhibitor proposed for the treatment of (b) (4) (b) (4) paroxysmal nocturnal hemoglobinuria (PNH). This application is under review in the Division of Nonmalignant Hematology (DNH).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of iptacopan outweigh the risk of serious infections caused by encapsulated bacteria. The ETASU include prescriber certification (A), pharmacy certification (B), and documentation of safe use conditions (D).

This interim review provides DRM's initial comments on the REMS proposal.

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- **07/31/2020:** Orphan drug designation granted for IND 134655 treatment of paroxysmal nocturnal hemoglobinuria.
- **12/01/2020:** Breakthrough therapy designation granted for IND 134655 for the treatment of paroxysmal nocturnal hemoglobinuria.
- **04/05/2023:** NDA 218276 submission for the treatment of (b) (4) PNH received. A REMS proposal was included in the submission. The Applicant submitted a Priority Review Voucher with this application.
- **08/21/2023:** A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that a REMS for iptacopan is necessary to ensure that the benefits of the drug outweigh the risks of serious infections caused by encapsulated bacteria.
- **08/25/2023:** The Agency sent an information request (IR) to clarify questions on pharmacy requirements and processes.
- **08/30/2023:** The Applicant provided a response to the Agency's 8/25/2023 IR and included additional non-public website screenshots for the outpatient pharmacy authorization process.
- **10/20/2023:** The Agency sent an IR with additional questions on pharmacy processes and requested the Applicant submit Key Risk Messages (KRMs).
- **10/25/2023:** The Applicant provided a response to the Agency's 10/20/2023 IR and included an updated Supporting Document.
- **10/26/2023:** The Agency sent the Applicant labeling revisions, including changes to the messaging for the risk of serious infections caused by encapsulated bacteria in the Boxed

Warning infections, Section 2.1 - Dosage and Administration, Section 5 - Warnings and Precautions, and Section 17 – Patient Counseling. These changes impact the proposed REMS.

- **11/01/2023:** A Late-cycle meeting was held between the Agency and the Applicant via teleconference.

3. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on April 5, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final. The revisions provided are based on the current proposed labeling sent by the Agency on October 26, 2023. However, for the REMS to be acceptable, all materials must be consistent with the final FDA-approved labeling.

(b) (4)

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REMS Assessment Plan

- Your assessment plan is under review and comments will be sent out in a separate communication.

Resubmission Instructions:

Submit a REMS amendment within 5 business days that addresses these comments. Reach out to the Agency if there are significant edits to labeling related to the risk of serious encapsulated bacterial infections to determine whether your REMS submission should be delayed until these labeling revisions are addressed.

The following materials contain revisions, comments, or require updates. If you find these acceptable, update the materials with the revisions and resubmit these materials with the next complete submission. Indicate any new changes you propose as redlined changes in your next submission. Include all formatting when submitting REMS materials in your next submission, including any logos, coloring, shading, or other design features.

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- Patient Guide
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Patient Guide	Tracked MS Word, Clean MS Word, Clean PDF version
Patient Safety Card	Tracked MS Word, Clean MS Word, Clean PDF version
REMS Website	Tracked PDF or MS Word with comments identifying key changes, Clean PDF version
Compiled PDF file that includes the REMS Document and all REMS materials in their final, clean format	PDF version

4. Appendix

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- Patient Safety Card
- REMS Website

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