CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218276Orig1s000

OTHER REVIEW(S)

Office of Prescription Drug Promotion

Internal Consult

****Pre-decisional Agency Information****

Please Note: The following review is for DRM only and should not be used to provide comments to the sponsor.

To: Ana Tavakoli, Health Communications Analyst
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Louiza Bako, Regulatory Review Officer, OPDP

CC: Jina Kwak, Team Leader, OPDP
Linda Wu, Safety Regulatory Project Manager, OSE
Jacqueline Sheppard, Team Leader, DRM
Lindsey Crist, Risk Management Analyst, DRM
Michael Wade, OPDP
CDER-OPDP-RPM

Date: 11/29/2023

Re: NDA 218276
FABHALTA® (iptacopan)
Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Materials

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Materials Reviewed

OPDP has reviewed the following proposed REMS materials for Fabhalta:

- Healthcare Provider (HCP) REMS Materials:
  - FABHALTA Prescriber Enrollment Form
  - FABHALTA Outpatient Pharmacy Enrollment Form
  - FABHALTA Inpatient Pharmacy Enrollment Form
  - FABHALTA Healthcare Provider Safety Brochure

- Direct-to-Consumer (Patient) REMS Materials:
  - FABHALTA Patient Guide
  - FABHALTA Patient Safety Card

- FABHALTA REMS Website

The version of the draft REMS materials used in this review were sent from DRM (Lindsey Crist) via email on November 17, 2023. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Fabhalta.

General Comment

Please remind Novartis Pharmaceuticals Corporation that REMS materials are not appropriate for use in a promotional manner.

OPDP notes links such as www.FABHALTA-REMS.com and toll-free numbers such as 1-833-99FABHA (1-833-993-2242). OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Novartis Pharmaceuticals Corporation that the REMS specific website should not be the sole source of approved REMS materials.

Comments are provided using the draft product labeling (PI) for Fabhalta dated November 17, 2023, and Medication Guide (MG) dated November 20, 2023.

OPDP notes that the current Fabhalta PI and MG are still being reviewed by DNH. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved label for Fabhalta.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see “Specific Comment[s]” below):

- Healthcare Provider (HCP) REMS Materials:

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

- Direct-to-Consumer (Patient) REMS Materials:
  - FABHALTA Patient Guide
  - FABHALTA Patient Safety Card

- FABHALTA REMS Website

Specific Comment[s]

OPDP considers the following statements promotional in tone and recommends revising them in the REMS pieces:

- FABHALTA Prescriber Enrollment Form

  - Page two of the FABHALTA Prescriber Enrollment Form includes the following statement under the header **"Before treatment initiation, I must:"** "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" (emphasis original).

    - **Risk**
      - This statement omits material information from the draft Fabhalta Prescribing Information (PI) necessary for the safe use of Fabhalta. Specifically, the WARNINGS AND PRECAUTIONS, "*FABHALTA REMS*" section of the draft Fabhalta PI states (emphasis added):

        "Prescribers must assess patient vaccination status for vaccines against encapsulated bacteria and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of FABHALTA."

        We recommend revising this statement to include this material information from the draft Fabhalta PI.

  - Page two of the FABHALTA Prescriber Enrollment Form includes the following statement under the header **"Before treatment initiation, I must:"** **"**Counsel the patient on the need to carry the **Patient Safety Card** at all times during treatment and for 2 weeks following the last dose of FABHALTA" (emphasis original).

- **Risk**
  - This statement omits material information from the draft Fabhalta PI necessary for the safe use of Fabhalta. Specifically, the PATIENT COUNSELING INFORMATION section of the draft PI states (emphasis added):

    "Inform patients that they will be given a Patient Safety Card for FABHALTA that they should carry with them at all times during and for 2 weeks following treatment with FABHALTA. This card describes symptoms which, if experienced, should prompt the patient to seek immediate medical evaluation."

    We recommend revising this statement to include this material information from the draft Fabhalta PI.

- FABHALTA Healthcare Provider Safety Brochure

  - Page three of the FABHALTA Healthcare Provider Safety Brochure includes the following statement under the header **"Before initiating a patient's FABHALTA treatment, prescribers must:"** "Counsel the patient using the **Patient Guide** and **Patient Safety Card**. Provide a copy of the materials to the patient" (emphasis original).

    - **Risk**
      - This statement omits material information from the draft Fabhalta PI necessary for the safe use of Fabhalta. Specifically, the PATIENT COUNSELING INFORMATION section of the draft PI states (emphasis added):

        "This card describes symptoms which, if experienced, should prompt the patient to seek immediate medical evaluation."

        We recommend including this material information from the draft Fabhalta PI.

  - Page four of the FABHALTA Healthcare Provider Safety Brochure includes the following statement (b) (4)

    - **Risk**
      - (b) (4)

(b) (4)

We recommend revising this statement to include this material information from the draft Fabhalta PI.

- FABHALTA Patient Guide
  - Page two of the FABHALTA Patient Guide includes the following statement under the header **"What is the serious risk of FABHALTA?"**: (b) (4)
    - **Risk**
      - (b) (4)

        (b) (4)

        (b) (4) We recommend revising the Fabhalta Patient Guide to include this material information.
  - Page four of the FABHALTA Patient Guide includes the following header **"Getting your vaccines."**
    - **Risk**
      - This header omits material information from the **"What is the most important information I should know about FABHALTA?"** section of the draft Fabhalta MG. Specifically, the draft MG states:

        "If you have been vaccinated against these bacteria in the past, you might need additional vaccinations before starting FABHALTA. Your healthcare provider will decide if you need additional vaccinations."

        We recommend revising this header to include this material information from the draft Fabhalta MG.

- Page four of the FABHALTA Patient Guide includes the following statement under the header **"Patient Safety Card"**: [redacted]

  - **Risk**
    - [redacted]

      [redacted]

      [redacted] We recommend revising the Fabhalta Patient Guide to include this material information from the draft Fabhalta MG.

- Page four of the FABHALTA Patient Guide includes the following statement under the header **"Patient Safety Card"** (in pertinent part): [redacted]

  - **Risk**
    - [redacted]

      "Your risk of serious infections may continue for a few weeks after your last dose of FABHALTA."

      We recommend revising this statement to include this material information from the draft Fabhalta MG.

- FABHALTA Patient Safety Card

  - Page one of the FABHALTA Patient Safety Card includes the following statement (in pertinent part): [redacted]

    - **Risk**
      - [redacted]

        "Your risk of serious infections may continue for a few weeks after your last dose of FABHALTA."

We recommend revising this statement to include this material information from the draft Fabhalta MG.

- Page two of the FABHALTA Patient Safety Card includes the following statement under the header **"INFORMATION FOR THE TREATING PHYSICIAN":** (b) (4)

  - **Risk**
    - (b) (4)

      (b) (4)

      We recommend revising this statement to include this material information from the draft Fabhalta PI.

- FABHALTA REMS Website

  - Page three of the FABHALTA REMS Website includes a section titled (b) (4) The second bullet in this section states:
    - (b) (4)

  - **Risk**
    - (b) (4)

      (b) (4)

      - The fifth bullet in this section includes the statement:
        - "Counsel the patient using the Patient Guide [link to Patient Guide] and Patient Safety Card [Link to Patient Safety Card]. Provide a copy of the materials to the patient."

- **Risk**
  - This statement omits REMS important material facts from the draft Fabhalta PI necessary for the safe use of Fabhalta. Specifically, the PATIENT COUNSELING INFORMATION section of the draft PI states (emphasis added):

    "Inform patients that they will be given a Patient Safety Card for FABHALTA that they should carry with them at all times during and for 2 weeks following treatment with FABHALTA. This card describes symptoms which, if experienced, should prompt the patient to seek immediate medical evaluation."

    We recommend revising these statements to include this material information from the draft Fabhalta PI.

- Page four of the FABHALTA REMS Website includes the following statement under the header **"Program Requirements for Outpatient Pharmacies"** (b) (4)

  - Risk
    - (b) (4)
      :

      "FABHALTA is available only through a restricted program under a REMS called FABHALTA REMS, because of the risk of serious infections caused by encapsulated bacteria."

      By omitting this material information, the statement may minimize the severity of the REMS risk. We recommend revising the FABHALTA REMS Website to include the material information that the REMS program is to ensure prescribers and patients are informed of the serious infections caused by encapsulated bacteria.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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/s/

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Division of Epidemiology I (DEPI-I)

Date:	November 16th, 2023
Reviewer / Team Leader:	CDR Steven Bird, PhD, PharmD, MS, USPHS Division of Epidemiology 1
Associate Director for Oncology and RWE:	Kira Leishear White, PhD, MS Division of Epidemiology 1
OPE Deputy Director (acting):	CAPT David Moeny, R.Ph., MPH, USPHS Office of Pharmacovigilance and Epidemiology (OPE)
OSE Sentinel:	José J. Hernández-Muñoz, RPh, MPH, MSc, PhD Regulatory Science Staff
Subject:	ARIA Sufficiency Memo for iptacopan and serious infections
Drug Name:	iptacopan (Fabhalta®)
Application Type/Number:	NDA 218276
Applicant/Sponsor:	Novartis Pharmaceuticals Corp.
Nexus TTT:	2023-6763

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

The Applicant submitted New Drug Application (NDA) 218276 for iptacopan with the proposed indication for the treatment of (b) (4) paroxysmal nocturnal hemoglobinuria (PNH). PNH is a rare, life-threatening disease of the blood characterized by uncontrolled complement activation, leading to destruction of red blood cells and platelets in addition to impairment in bone marrow function [1]. It has been estimated that PNH may affect up to 15.9 persons per million [2]. Iptacopan is a first in class oral targeted factor B inhibitor of the alternative complement pathway, dosed as a 200 mg capsule taken twice daily. Other complement inhibitors have been approved for the treatment of PNH, but they target different pathways. Eculizumab and ravulizumab target complement protein C5 while pegcetacoplan targets complement protein C3.

Draft labeling for iptacopan contains a boxed warning for serious infections caused by encapsulated bacteria. Contraindications include hypersensitivity to iptacopan or any of the excipients and patients with unresolved serious infections caused by encapsulated bacteria [highlights of prescribing in draft labeling]. The most common adverse reactions in adult patients with PNH (incidence >10%) were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea, and rash [section 6.1 in draft labeling].

1.2. Describe the Safety Concern

The draft label has a boxed warning and a REMS to communicate risk for serious infections caused by encapsulated bacteria. The mechanism of action of iptacopan provides proximal inhibition of the complement system, which creates a higher risk of serious infections caused by encapsulated bacteria, including *Streptococcus pneumonia, Haemophilus influenza* and *Neisseria meningitidis*. All approved complement inhibitors for treatment of PNH (eculizumab, ravulizumab, pegcetacoplan) increase risk for serious infections from encapsulated bacteria and contain a boxed warning to communicate this risk.

Among 170 patients with PNH from 6 clinical studies with iptacopan, there were 7 patients (4.1%) with serious infections from encapsulated bacteria. An additional 2 patients (3.8%) had serious infections from encapsulated bacteria among 53 patients treated with iptacopan for complement-mediated kidney disease [3].

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The purpose of this analysis is to characterize the safety of iptacopan in treatment naïve patients and to study the long-term risk of serious infections from encapsulated bacteria.

1.5. Effect Size of Interest or Estimated Sample Size Desired

This is a real-world observational study. PNH is a very rare disease and thus no sample size has been specified.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The desired population consists of patients with paroxysmal nocturnal hemoglobinuria (PNH).

2.2 Is ARIA sufficient to assess the intended population?

PNH can be identified through diagnosis codes in claims data. ARIA is sufficient to identify the intended population.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure is interest is iptacopan.

3.2 Comparator Exposure(s)

The objective of this PMR is to better characterize the safety profile of iptacopan in the real-world, with emphasis on serious infections from encapsulated bacteria. This objective can be completed with descriptive statistics and does not require calculation of risk in reference to a comparator exposure. Thus, no comparator exposure will be used in this study.

3.3 Is ARIA sufficient to identify the exposure of interest?

Iptacopan is expected to be identifiable through national drug codes (NDC) post approval. ARIA is sufficient for the exposure.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcome of interest is serious infections from encapsulated bacteria, including *Streptococcus pneumonia, Haemophilus influenza* and *Neisseria meningitidis*.

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA has an algorithm to identify serious infections with an overall positive predictive value (PPV) of 80.2% and the following breakdown of PPV by infection type: bacteremia 84.1%, pneumonia 83.3%, skin/soft tissue infection 79.0%, gastrointestinal infection 69.4%, acute osteomyelitis 68.6%,

acute osteomyelitis 68.6%, acute pyelonephritis 81.1%, acute meningitis 69.2% [4]. However, this algorithm does not have the capacity to characterize infections due to encapsulated bacteria or to identify the specific bacterial strain leading to infection.

Some data partners within ARIA have access to laboratory data. However, given the limited laboratory data available within ARIA and that PNH is a very rare disease, ARIA is not sufficient to identify whether the pathogens leading to infection are from encapsulated bacteria.

5 COVARIATES

5.1 Covariates of Interest

A complete vaccination history with meningococcal, pneumococcal, and H. influenza vaccination status is required for this study.

5.2 Is ARIA sufficient to assess the covariates of interest?

No. Vaccination history cannot be obtained with sufficient completeness in a 1-year lookback typically used within claims-based studies. A longer lookback would hinder sample size. Therefore, ARIA is not sufficient for this covariate.

Sentinel can capture other covariates of interest. Use of prophylactic antibiotics is of interest because this would modify infection risk. A patient's age, the presence of multiple chronic diseases (e.g. diabetes, hypertension), cognitive disorders, and institutionalization (e.g. nursing home) may affect infection risk. Other drugs that compromise the immune system (e.g. corticosteroids) are also of interest for this study.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The intended study design is an observational study with descriptive data analysis.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

This will be a descriptive study. The analytic tools within Sentinel are sufficient.

7 NEXT STEPS

As of November 15th, 2023, the proposed PMR language is:

(b) (4)

[redacted]

8 REFERENCES

[1] Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014;124(18):2804-11.

[2] Roth A, Maciejewski J, Nishimura J, Jain D, Weitz JI. Screening and diagnostic clinical algorithm for paroxysmal nocturnal hemoglobinuria: expert consensus. Eur J Haematol. 2018;101(1):3-11.

[3] US Food and Drug Administration. NDA 218276 multi-disciplinary review and evaluation [draft]. Accessed 3 November 2023.

[4] Lo Re V, Carbonari DM, Jacob J, et al. Validity of ICD-10-CM diagnoses to identify hospitalizations for serious infections among patients treated with biologic therapies. Pharmacoepidemiol Drug Saf. 2021;30(7):899-909.

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/s/

STEVEN BIRD
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KIRA N LEISHEAR WHITE
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DAVID G MOENY
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JOSE J HERNANDEZ
11/20/2023 03:14:20 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 09, 2023
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 218276
Product Name, Dosage Form, and Strength:	Fabhalta (iptacopan) capsule, 200 mg
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation (Novartis)
TTT ID #:	2023-4374-1
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on October 12, 2023 and November 6, 2023 for Fabhalta. We reviewed the revised container labels for Fabhalta (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented most of our recommendations. However, the Applicant did not agree to include the following statements on the container labels for the following reasons:

- "Store and dispense in the original container." as it is overly restrictive and not supported by data in the NDA. In addition, the Applicant proposes to revise the storage statement in the MG to remove (b) (4)
- "Swallow the capsules whole. Do not open, break, or chew capsules." on the principal display panel as not supported by data in the NDA.

We reached out to the Office of Pharmaceutical Quality (OPQ) to determine if exclusion of these statements on the container labels is acceptable. OPQ determined the removal (b) (4)

[a] Black, S. Label and Labeling Review for Fabhalta (NDA 218276). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 OCT 2. TTT ID No.: 2023-4374.

(b) (4) is acceptable and agreed the statement "Store and dispense in the original container" on the container labels is not needed. However, as OPQ did not locate information in the NDA to support opening the capsules prior to administration, they continued to recommend to the Applicant including the statement "Swallow the capsules whole. Do not open, break, or chew capsules." in the PI, MG and container labels. In response, on November 6, 2023, the Applicant accepted the inclusion of this statement in the PI, MG and container labels and provided revised container labels. In addition, the Applicant already printed container labels submitted on October 12, 2023 and plans to launch their product with those container labels to allow Novartis to have the product available for patients at the time of action date or shortly thereafter. The revised container labels received on November 6, 2023 will begin to be utilized after the 4 months production run. The difference between the two sets of container labels is the addition of the statement "Swallow the capsules whole. Do not open, break, or chew capsules." on the PDP. As there was no change to any other content on the container labels and as this information can be found in the Prescribing Information and Medication Guide, we find this proposal acceptable.

Lastly, we note the revised dosage statement, the decreased prominence of the manufacturer information and location of the product identifier (including the lot number and expiration date) on the container labels and the format of the expiration date as YYYY-MMM-DD. From a medication error perspective, we find these revisions acceptable. We have no further recommendations at this time.

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CLINICAL INSPECTION SUMMARY

Date	October 27, 2023
From	Anthony Orencia, M.D., Ph.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., F.A.A.P., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Donna Whyte-Stewart, M.D., Physician Carrie Diamond, M.D., Medical Team Leader Ann Farrell, M.D., Division Director Courtney Hamilton, Pharm.D., Regulatory Project Manager Division of Nonmalignant Hematology (DNH) Office of Cardiovascular, Hematology, Endocrinology and Nephrology Drugs (OCHEN)
NDA	NDA 218276
Applicant	Novartis Pharmaceutical Corp
Drug	LNP023 (iptacopan)
NME	Yes
Therapeutic Classification	Factor B inhibitor of the complement alternative pathway
Proposed Indications	The treatment of paroxysmal nocturnal hemoglobinuria
Review Type	Priority Review
Consultation Request Date	May 2, 2023
Summary Goal Date	August 31, 2023. Extension: November 6, 2023.
Action Goal Date	December 1, 2023
PDUFA Date	December 5, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study CLNP023C12302 were submitted to the Agency in support of a new drug application (NDA) for the drug iptacopan, proposed for the treatment of paroxysmal nocturnal hemoglobinuria. Two foreign clinical investigators, Alexander Roeth, M.D. and Regis P. de Latour, M.D., as well as the sponsor were inspected for Study CLNP023C12302.

Based on the inspection results, the study appears to have been conducted adequately and the study data derived from the above clinical investigator sites are considered reliable. The data from Study CLNP023C12302 submitted by the sponsor to the Agency for assessment appear acceptable in support of the proposed indication.

II. BACKGROUND

Iptacopan is a small molecular weight, factor B inhibitor of the alternative pathway of the complement system. Iptacopan binds to complement factor B, thereby blocking alternative pathway activation as well as amplification of the classical and lectin complement pathways via the amplification loop. Inhibition of complement factor B therefore leads to inhibition of both C3 cleavage, which is responsible for opsonization and subsequent clearance of cells, and membrane attack complex (MAC, C5b-9) formation.

Paroxysmal nocturnal hemoglobinuria is a rare acquired hemolytic disorder characterized by complement-mediated intravascular hemolysis, bone marrow failure, and severe thrombophilia. The biological process begins with the clonal expansion of a hematopoietic stem cell that has acquired a somatic mutation in the phosphatidylinositol N-acetylglucosaminyltransferase subunit A gene. Patients' blood cells lack the glycophosphatidylinositol anchor protein and are deficient in the membrane-bound complement inhibitory proteins CD55 and CD59. As a result, paroxysmal nocturnal hemoglobinuria type red blood cells are attacked by complement leading to complement mediated lysis. Signs and symptoms may include anemia, thrombosis, smooth muscle dystonia, fatigue, hemoglobinuria, chronic kidney disease and pulmonary hypertension. The clinical presentation is driven by uncontrolled complement activation on CD55 and CD59 deficient paroxysmal nocturnal hemoglobinuria type red blood cells, culminating with hemolysis and the release of free hemoglobin, and platelet activation. Thromboembolism is a major cause of mortality. Eculizumab and ravulizumab (engineered from eculizumab with prolonged dosing interval) are approved anti-C5 antibody therapies for the treatment of paroxysmal nocturnal hemoglobinuria and the current standard of care where available.

Iptacopan received Breakthrough Therapy Designation on December 1, 2020, for the treatment of paroxysmal nocturnal hemoglobinuria.

Study CLNP023C12302

Study CLNP023C12302 was a multi-center, randomized, open-label, active comparator-controlled, parallel group study, which was comprised of a screening period, a 24-week active controlled, parallel group treatment period and a 24-week LNP023 treatment extension period. Eligible patients were randomized (8:5) to receive either iptacopan monotherapy at a dose of 200 mg orally b.i.d. or intravenous anti-C5 antibody treatment (with the same regimen during the randomized treatment period as they were prior to randomization).

The primary objective was to demonstrate superiority of iptacopan compared to anti-C5 antibody treatment in the proportion of patients achieving hematological response.

The primary efficacy endpoints were two hematological response criteria defined as:

- Increase from baseline hemoglobin levels at least 2 g/dL (assessed between Day 126 and Day 168) in the absence of red blood cell transfusion between Day 14 and Day 168, and
- Hemoglobin levels at least 12 g/dL (assessed between Day 126 and Day 168) in the absence of red blood cell transfusion between Day 14 and Day 168.

Sustained hematological response was used for the above endpoints, defined as increase from baseline hemoglobin levels ≥2 g/dL and hemoglobin levels ≥ 12 g/dL for 3 out of 4 assessments between Day 126 and Day 168.

Absence of red blood cell transfusion was defined as patient did not receive a transfusion or met one of the following pre-defined criteria for transfusion:

- Hemoglobin level ≤ 9 g/dL with signs /and or symptoms of sufficient severity to warrant a transfusion
- Hemoglobin of ≤ 7 g/dL, regardless of presence of clinical signs and/or symptoms

There were 39 centers across 12 countries that enrolled subjects. The study initiation date was on (b) (4) (first patient first visit)). The submitted clinical study report (primary endpoint completion) consists of all the data collected up to the cut-off (September 26, 2022) which comprised all the efficacy data from the 24-week randomized treatment period, safety data up to the cut-off and pharmacokinetic data up to cut-off of July 31, 2022.

III. RESULTS (by site)

1. **Alexander Roeth, M.D./Site 3001**
   Universitaetsklinikum Essen
   Essen, North Rhinewestphalia
   45147 Germany

   Inspection dates: October 23-26, 2023

   There were 10 subjects who were screened. Eight subjects were enrolled. All enrolled patients were subsequently randomized and completed the treatment phase of the study.

   Regulatory and source documents were reviewed. The audit involved a review of records and procedures related to the clinical trial protocol and its amendments; subject selection criteria and consenting; test article controls, including accountability; source data evaluation, adverse event reporting, and laboratory testing.

   Source records for all enrolled study subjects were examined and verifiable. Records were noted to be complete, legible, and organized. Study activities were conducted in compliance with the protocol. The study primary efficacy endpoint (that is, hematological response criteria: hemoglobin levels in the absence of red blood cell transfusion) was verifiable and there was no evidence of under-reporting of adverse events. No lapses in approvals or failure to file required reports were noted. No discrepancies were noted.

   No significant objectionable findings were found during the inspection. The final inspection report is pending at the present time. An amendment report will be issued if there are substantive changes in the final inspection report.

2. Regis P. de Latour, M.D./Site 6001
Hospital Saint Louis
Paris Cedex 10, Paris 75475
France

Inspection dates: July 10-13, 2023

Twelve subjects were screened, and 10 subjects were enrolled and randomized into the study. All 10 subjects completed the treatment phase of the study to Day 168. There were no deaths, and no subject was lost to follow-up.

Ethics committee approvals, study correspondence, drug accountability, facility adequacy, staff qualifications, and monitoring procedures were reviewed. This inspection covered the safety of study subjects along with serious adverse event reporting, protocol deviations, subject eligibility, overall protocol compliance, and the verification of source documentation related to study endpoint criteria.

Adverse event and serious adverse reporting appeared adequate and consistent with the study protocol requirement and the case report form reports. The primary efficacy endpoint was verifiable. There was no evidence of under-reporting of adverse events.

Three discussion items, however, were mentioned at the FDA's closeout inspection meeting related to comprehensive documentation: (1) The principal investigator did not document all inclusion and exclusion criteria to ensure all subjects meet eligibility, (2) Not all protocol required procedures were documented within the source records, for example, the method of birth control; how long the subject was on standard of care before randomization; documentation if patient cards were given and trained on the e-patient reported outcome device, and (3) adverse events needed to be consistently documented within the source record when stated as clinically significant and when treatment was given to treat the condition. All AEs appeared to have been captured but greater details and explanation of the event were needed.

Reviewer's Comment: The above discussion items appeared mainly related to comprehensive documentation. All enrolled subjects met inclusion and exclusion criteria. Transfusion dates and reasons for blood transfusion were documented in the medical records. There was no observed underreporting of adverse events. The closeout inspectional discussion items at this clinical site did not have a significant impact on the efficacy or safety results of the study.

3. NOVARTIS PHARMACEUTICAL CORP
1 Health Plaza
East Hanover, NJ 07936

Inspection dates: August 7-21, 2023

The sponsor inspection involved comprehensive onsite review of study monitor selection, site and clinical investigator selection, clinical site monitoring, financial disclosures, safety

reporting and handling, data monitoring committee activities, study documents, standard operating procedures, data collection and handling, protocol deviations, and investigational product disposition. Monitoring actions taken for those clinical investigators who did not comply with the investigational plan were evaluated.

The FDA closeout inspection discussion items at Novartis included the following: (1) Documents essential to sponsor oversight was not available to the sponsor or available in the local country language; for instance, source records in local language discussing adverse events were partially translated by local country person. (2) FDA inspection staff noted due to Novartis's lack of identifying the appropriate personnel to provide information and requested documentation being incomplete, incomplete sponsor documentation provided to FDA resulted in repetitive requests. (3) Due to inadequate study records, FDA inspection staff noted that discussions leading to decisions in study conduct were not documented comprehensively. For example, discussions pertaining to protocol deviations in subject case report forms which were not recorded. Sponsor discussions and the medical monitor regarding protocol deviations were informal and unrecorded.

The inspection found that the Sponsor's monitor failed to ensure the investigational product, dispensed to Subject # (b) (6) was properly stored at 2-8 degrees Celsius as required, at a monitoring visit in April 2021. An additional four IP kits stored at room temperature were dispensed to Subject # (b) (6) prior to identification of the temperature excursions and there were no protocol deviations documented for the subject exposure to these four kits.

Reviewer's Comment:
Sponsor responded adequately to the FDA on September 9, 2023. Sponsor explained that the investigational product showed adequate stability. Subject # (b) (6) 's safety in this clinical investigation did not appear to have been impaired. In addition, this finding was isolated and should not have a significant impact on the overall study results.

In general, the sponsor's oversight and monitoring of this clinical study appear to be acceptable.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Office of Scientific Investigations

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Clinical Outcome Assessment Review Memorandum

From	Julia Ju, Pharm.D., Ph.D. Clinical Outcome Assessment (COA) Reviewer Division of Clinical Outcome Assessment (DCOA) Selena Daniels, Pharm.D., Ph.D. Deputy Division Director DCOA David Reasner, Ph.D. Division Director DCOA
To	Division of Non-malignant Hematology (DNH)
COA tracking number	C2023131
NDA# / Referencing IND#	NDA 218276/ IND 134655
Drug Sponsor	Novartis Pharmaceuticals Corporation
PDUFA Goal Date:	December 5, 2023
Indication:	Treatment of (b) (4) paroxysmal nocturnal hemoglobinuria (PNH) ☐ Pediatric ☒ Rare Disease/Orphan Designation
Instrument(s) reviewed:	1. Functional Assessment of Chronic Illness Therapy – Fatigue Scale ☒ Patient-reported outcome (PRO)

This Clinical Outcome Assessment (COA) consult review is provided as a response to a request for consultation by the Division of Non-malignant Hematology (DNH) regarding NDA 218276 (DARRTS Reference ID: 5162669). In this submission, the applicant is seeking approval of iptacopan[1] for the treatment of (b) (4) paroxysmal nocturnal hemoglobinuria (PNH)[2]. The specific COA-related labeling claims are related to the improvement of fatigue, which is derived from two multi-center, open-label, 24-week, phase 3 studies (Studies CLNP023C12301 and CLNP023C12302; hereon referred to as APPOINT-PNH and APPLY-PNH, respectively). The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA-related labeling claims related to the concept of interest.

The secondary efficacy COA endpoint proposed for labeling is:

- Change from baseline in Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) scores as mean of visits between Day 126 and Day 168

[1]Iptacopan is a novel, oral, small molecular weight compound that inhibits factor B (a key protease of the complement alternative pathway).

[2] PNH is a rare, acquired, life-threatening disease of the blood. The disease is characterized by destruction of red blood cells, blood clots, and impaired bone marrow function. Chronic hemolysis (destruction of red blood cells) is central to all the symptoms and physical findings associated with PNH.

APPOINT-PNH study is a single arm study and there was no formal hypothesis testing for the secondary efficacy COA endpoint.

The data from APPLY-PNH studies demonstrated that iptacopan had statistically significant improvement in FACIT-Fatigue scores compared to anti-C5 treatment (active comparator) between baseline and mean of visits between Day 126 and 168. Despite achievement of statistical significance in the FACIT-Fatigue score, the data is difficult to interpret due to the given study design (refer to Issues Identified section for more details).

From a COA perspective, fatigue is a clinically relevant concept for PNH. However, due to the design of Studies APPOINT-PNH and APPLY-PNH, there is concern the data from this instrument cannot be communicated in labeling in a way that is accurate, interpretable and not misleading.

Review Conclusions

The applicant submitted an evidence dossier for the FACIT-Fatigue and patient-reported outcome (PRO) reports for both clinical trials. Note that this instrument has previously been accepted and labeled for the context of PNH. As such, this instrument was not reviewed for content validity and other measurement properties.

Review Summary

- The FACIT-Fatigue measures some important aspects of fatigue in patients with PNH.
- The content validity and other measurement properties have been established in other PNH development programs.
- Because of the issues related to data interpretability (See Key Issues Identified section), the FACIT-Fatigue was not reviewed for meaningful within-patient change.

Key Issues Identified

Issue 1: Data interpretability

- The FACIT-Fatigue results are difficult to interpret due to the small sample size and study design (APPLY-PNH (n= 95); APPOINT-PNH (n=40)). Given the open-label trial design, patient's knowledge of treatment assignment may lead to systematic overestimation or underestimation of the treatment effect, the magnitude of which is currently unknown.

Recommendations for Future Studies

For future clinical trials in this indication, we recommend sponsors to engage FDA early (e.g., Pre-IND) and throughout drug development to discuss COA endpoint strategy to ensure the selected instruments are fit-for-purpose and the studies are designed appropriately for the context of use prior to initiation of pivotal studies. Further, for sponsors who intend to seek a claim of treatment benefit (e.g., drug X improves disease symptoms or function), we recommend a clear endpoint definition and formal statistical testing with adjustment for multiplicity.

Regulatory Background and Materials Reviewed

- The sponsor received Orphan Drug Designation on July 31, 2020 for iptacopan.
- A Breakthrough Therapy Designation (BTD) was granted from FDA on December 1, 2020.
- The sponsor was denied ability to file for accelerated approval on March 9, 2021.
- There have been previous communications with the applicant regarding their COA measurement strategy, which included the following:
  - Advice Letter/Information Request dated October 24, 2022
    - Identified limitations with the selected anchor scales (i.e., misaligned concepts).
    - Provided specific comments regarding the meaningful change analyses.
  - Final Written Response dated July 27, 2021
    - Provided specific comments regarding exit interview protocol (including interview guide).
  - Type B Meeting Minutes dated October 28, 2020
    - Noted that PRO endpoints are not evaluable in a single-arm trial.
  -

Reviewer's comment(s): *DCOA was not consulted for the Type B Meeting. In a previous COA review[3], the reviewer commented that the open-label study design is a limitation to PRO data interpretation, as patients' knowledge of treatment assignment may lead to systematic overestimation or underestimation of the treatment effect, the magnitude of which is unknown. However, it is unknown whether this comment was ever communicated to the sponsor. Per an email communication dated 9/23/2020, Clinical stated "… we will place your recommendations as additional comments for the sponsor in the STP letter."*

- The applicant has proposed the following specific targeted COA-related labeling claims for adult and pediatric patients with cTTP (in *blue italicized text*):

"APPLY-PNH
Iptacopan was superior to anti-C5 treatment in fatigue assessed by FACIT-Fatigue (treatment difference of +8.29 points; p<0.001), and patients treated with iptacopan experienced clinically meaningful improvements in patient-reported fatigue from Baseline (FACIT-Fatigue score mean change from baseline +8.59; 95% CI 6.72, 10.47).

APPOINT-PNH
Patients treated with iptacopan experienced clinically meaningful improvements in patient-reported fatigue from Baseline (FACIT-Fatigue score mean change from baseline +10.8; 95% CI: 8.7, 12.8)."

[3] C2020382_IND 134655_Daniels dated October 2, 2020 [DARRTS Reference ID: 4675063]

Reviewer's comment(s):
After discussion with colleagues from Clinical, Biostatistics, and the Patient-Focused Statistical Scientists (PFSS) team, (b) (4)
FACIT-Fatigue results are difficult to interpret due to the study design and small sample size.

The sponsor mentioned (b) (4)
(b) (4)

The materials reviewed for this submission include the following:

- Clinical Outcome Assessment Dossier: Evidence Supporting the Functional Assessment of Chronic Illness Therapy – Fatigue Scale for Assessment of Fatigue in Patients with Paroxysmal Nocturnal Hemoglobinuria, dated March 13, 2023 (SDN:1, eCTD: 0000, date received April 5, 2023)
- Previous COA reviews:
    - C2022300-IND 134655 by Daniels dated October 21, 2022 (DARRTS Reference ID: 5060640)
    - Previous COA review C2020382-IND 134655 by Daniels dated October 2, 2020 (DARRTS Reference ID: 4675063)

Trial Design and Study Endpoints

The efficacy and safety of iptacopan administered orally in adult patients with PNH were evaluated in two multi-center, open-label, 24-week, phase 3 studies trials:

- an active comparator-controlled trial (APPLY-PNH; NCT04558918)
- a single arm study trial (APPOINT-PNH; NCT04820530).

APPLY-PNH

The APPLY-PNH study was a multi-center, randomized, open-label, active comparator-controlled, parallel group phase 3 study comprised of three periods:

- A screening period lasting up to 8 weeks (unless there is a need to extend it for vaccinations required for inclusion, vaccinations should be started at the earliest possible to avoid extension of the screening period)
- A 24-week randomized, open-label, active controlled, parallel group treatment period for the primary efficacy and safety analyses
- A 24-week open-label, LNP023 treatment extension period

The study enrolled adult patients with PNH patients with residual anemia (hemoglobin < 10 g/dL) despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization.

Patients were randomized in 8:5 ratio either to receive iptacopan 200 mg orally twice daily (n = 62) or to continue anti-C5 treatment (eculizumab n = 23 or ravulizumab n = 12) throughout the duration of the 24-week randomized controlled period (RCP). Randomization was stratified based on prior anti-C5 treatment and transfusion history within the last 6 months. Following completion of the 24-week RCP, all patients were eligible to enroll in a 24-week treatment extension period and receive iptacopan monotherapy. Subsequently, patients were eligible to enter a separate long-term extension study.

APPOINT-PNH

The APPOINT-PNH study was a multicenter, single-arm, open-label trial in adult PNH patients who are naive to complement inhibitor therapy, including anti-C5 antibody treatment. This study is comprised of three periods:

- A Screening period lasting up to 8 weeks (unless there is a need to extend it for vaccinations required for inclusion, vaccinations should be started at the earliest possible to avoid extension of the screening period)
- A 24-week single arm, open-label Core treatment period for the primary efficacy and safety analysis
- A 24-week open-label, iptacopan treatment Extension period

This study enrolled patients with PNH (RBC clone size ≥ 10%) with hemoglobin < 10 g/dL and LDH > 1.5 ULN, who are naive to complement inhibitor therapy, including anti-C5 antibody treatment with approximately 40% of all participants having received at least one (1) packed-RBC transfusion within 6 months prior to starting study treatment. All patients received iptacopan 200 mg orally twice daily during the 24-week open-label core treatment period. Subsequently, patients were eligible to enroll in a 24-week treatment extension period and continue to receive iptacopan, followed by a separate long-term extension study.

The study endpoints for both clinical trials are:

Primary efficacy endpoint

- Response defined as having an increase from Baseline in Hb ≥2 g/dL assessed between Day 126 and Day 168, in the absence of packed red blood cell transfusions between Day 14 and Day 168. (APPLY-PNH and APPOINT-PNH)
- Response defined as having Hb ≥12 g/dL between Day 126 and Day 168 in the absence of packed-red blood cell transfusions between Day 14 and Day 168. (APPLY-PNH)

Secondary efficacy COA endpoint

- Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168 (APPLY-PNH and APPOINT-PNH)

Refer to the clinical study reports for the corresponding trial for more details on the trial design and study endpoints.

Reviewer's comment(s):
During the trials, PRO questionnaires were completed prior to any procedure or clinical assessment.

COA Description(s)

Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue)
The FACIT-Fatigue is a 13-item patient-reported outcome (PRO) questionnaire designed to assess fatigue-related symptoms and impacts. Each item is rated on a five-point verbal rating scale (VRS) ranging from "Not at all," to "Very much." The recall period is the previous 7 days ("past 7 days"). The FACIT-Fatigue was administered electronically at Screening and at baseline Day 1, Day 7, Day 14, Day 42, Day 84, Day 126, Day 140, Day 154, and Day 168 in both trials.

The FACIT-Fatigue generates a total score ranging from 0 to 52, where a higher score equates to less fatigue.

Reviewer's comment(s):
The literature review conducted by the Applicant found that fatigue is a relevant and important symptom of patients with PNH. Additionally, exit interviews with participants were scheduled within 14 days of their Week 24 study visit for both trials. All interviews were conducted by telephone and lasted approximately 60 minutes.

- *A total of 17 patients in the APPLY-PNH trial participated in the qualitative interviews. The results suggest that the FACIT-Fatigue measures relevant and important aspects of the fatigue experience in patients with PNH.*
- *A total of 22 patients in the APPOINT-PNH trial participated in the qualitative interviews. Consistent with what is reported above from APPLY-PNH, the results also suggest that the FACIT-Fatigue measures relevant and important aspects of the fatigue experience in patients with PNH.*

The published literature provides evidence of the convergent validity, ability to detect change, and ability to distinguish known groups of the FACIT-Fatigue among patients with PNH. Psychometric analyses using data from APPLY-PNH and APPOINT-PNH appear to

support that the FACIT-Fatigue demonstrated internal consistency and test-retest reliability, and construct validity.

Anchor Scales

The applicant utilized the Patient Global Impression of Severity (PGIS) scale as an anchor for the FACIT-Fatigue-based endpoints. The PGIS is a single question assessing the overall severity of fatigue within the 7-day recall period. The response was collected asking patients a single question to rate their overall symptoms of fatigue during the past seven days. The scale is an ordinal 5-point scale ranging from 0 (none) to 4 (very severe). The PGIS was administered at the same visit as the FACIT-Fatigue in both Study APPLY-PNH and Study APPOINT-PNH. A summary of the anchor scale is shown in Table 1.

Table 1. Summary of Anchor Scales

Endpoint concept/attribute (COA type/name if any)	Anchor (concept)	Anchor response scale	Recall period (target/anchor)	Timing (target/anchor)
FACIT-Fatigue (fatigue-related symptoms and impacts)	PGIS (fatigue severity)	5-point verbal rating scale (VRS): None/Mild/Moderate/ Severe/Very Severe	7 days/7 days	Day 126-168/Day 126-168

FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; PGIS= Patient Global Impression of Severity

Appendices

Appendix A. FACIT-Fatigue

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 10/17/2023

To: Courtney Hamilton, PharmD, BCPS, Senior Regulatory Project Manager
Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling
(DNH)

From: Louiza Bako, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for FABHALTA® (iptacopan) capsules, for oral use

NDA: 218276

Background:
In response to DNH's consult request dated April 20, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for the original NDA submission for FABHALTA® (iptacopan) capsules, for oral use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on October 4, 2023, and our comments are provided below.

Medication Guide:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on October 12, 2023.

Thank you for your consult. If you have any questions, please contact Louiza Bako at (301) 796-3970 or Louiza.Bako@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 12, 2023
To:	Courtney Hamilton, PharmD, BCPS Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Louiza Bako, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	FABHALTA (iptacopan)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 218276
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On April 5, 2023, Novartis Pharmaceuticals Corporation submitted for the Agency's review an original New Drug Application (NDA) 218276 for FABHALTA (iptacopan) capsules, proposed for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on April 20, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for FABHALTA (iptacopan) capsules.

2 MATERIAL REVIEWED

- Draft FABHALTA (iptacopan) capsules MG received on April 5, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 4, 2023.
- Draft FABHALTA (iptacopan) capsules Prescribing Information (PI) received on April 5, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 4, 2023.
- Approved EMPAVELI, ULTOMIRIS, SOLIRIS, comparator labeling dated September 28, 2023, July 22, 2022, and November 20, 2020, respectively.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 2, 2023
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 218276
Product Name, Dosage Form, and Strength:	Fabhalta (iptacopan) capsule, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation (Novartis)
FDA Received Date:	April 5, 2023, June 30, 2023 and September 12, 2023
TTT ID #:	2023-4374
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Fabhalta (iptacopan) capsule, we reviewed the proposed Fabhalta Prescribing Information (PI), Medication Guide (MG) and container labels for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Novartis is submitting an original 505(1)(b) New Drug Application (NDA) for iptacopan capsule 200 mg as a treatment of (b) (4) paroxysmal nocturnal hemoglobinuria (PNH).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, MG and container labels to identify deficiencies that may lead to medication errors and other areas of improvement.

We note the dosage form statement in the Highlights of PI (HPI) and full PI is (b) (4) (b) (4) "capsules". We defer to Office of Pharmaceutical Quality (OPQ) regarding the acceptability of this statement. In addition, we note that the strength statement contains an asterisk symbol on the container labels and the MG states to store the product in the original container; however, this information is not in the PI or container labels. We reached out to OPQ to clarify if the product requires to be stored and dispensed in the original container, if the asterisk symbol in the strength statement is necessary and if it is advisable to include a statement in the PI to "Swallow capsules whole. Do not open, break, or chew capsules". OPQ confirmed the asterisk is unnecessary and agreed with including a statement in the PI to "Swallow capsules whole. Do not open, break, or chew capsules". In addition, (b) (4)

(b) (4) OPQ agreed with including a statement in the PI and on the container labels to "store and dispense in the original container."

We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. For the Division, we recommend including the conditionally acceptable proprietary name and instructions to swallow capsules whole in the PI and MG. In addition, we recommend including information to store and dispense in original container in the PI. For the Applicant, we recommend including the location of the lot number and expiration date, the product identifer, revising the recommended dosage statement, decreasing the prominence of manufacturer information, as well as including instructions to swallow capsules whole and to store and dispense in the original container. We provide our proposed recommendations in Section 4.1 for the Division and in Section 4.2 for Novartis.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed PI, MG, container labels that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Novartis to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Prescribing Information and Medication Guide
    1. As currently presented, the proprietary name is denoted by the placeholder "Brandname". We recommend replacing the placeholder "Brandname" with the conditionally acceptable proprietary name, Fabhalta.
B. Prescribing Information (Section 2 Dosage and Administration)
    1. To ensure appropriate administration of the capsule, we recommend including the statement "Swallow the capsules whole. Do not open, break, or chew capsules." after the recommended dose statement in Section 2.2. For example, revise Section 2.2 to:
    "The recommended dosage of Fabhalta is 200 mg orally twice daily without regard to food.
    Swallow capsules whole. Do not open, break, or chew capsules.".
C. Prescribing Information (Section 16 How Supplied/Storage and Handling)
    1. The Medication Guide contains the statement (b) (4) however, this statement not in the Prescribing Information. To ensure appropriate storage of the medication, we recommend adding the statement "Store and dispense in the original container." after the storage statement.
D. Medication Guide
    1. To ensure appropriate administration of the capsule, we recommend including the statement "Swallow the capsules whole. Do not open,

break, or chew capsules." in the "How should I take BRANDNAME?" section as separate bullet after "Take one Fabhalta capsule 2 times each day (with or without food) (b) (4)

4.2 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORPORATION

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. The location of the lot number and expiration date is not currently presented. Confirm the location of this information and include the format of the expiration date. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date. Ensure that there are no other numbers located in close proximity to the lot number or expiration date where it can be mistaken as the lot number or the expiration date.
2. The product identifier is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.
3. The terminology within the statement of dosage statement (b) (4) (b) (4) is inconsistent with the terminology in the Prescribing Information. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the statement of dosage statement to read, "Recommended Dosage: see Prescribing Information.".
4. The manufacturer information (e.g., manufacturer name and logo) competes in prominence from critical product information (e.g., proprietary name,

established name, strength). Critical product information such as the proprietary name, established name, and product strength should appear as the most prominent information on the principal display panel in accordance with 21 CFR 201.15. Reduce the prominence of the manufacturer information so it does not compete with the prominence of important product information on the principal display panel.

5. We note the product should be stored and dispensed in the original container. To ensure appropriate storage of the medication, we recommend adding "Store and dispense in the original container." next to the storage statement.
6. To ensure appropriate administration of the capsule, we recommend including the statement "Swallow the capsules whole. Do not open, break, or chew capsules." on the principal display panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Fabhalta received on April 5, 2023 from Novartis Pharmaceuticals Corporation.

Table 2. Relevant Product Information for Fabhalta	
Initial Approval Date	N/A
Active Ingredient	iptacopan
Indication	Treatment of (b) (4) paroxysmal nocturnal hemoglobinuria (PNH)
Route of Administration	oral
Dosage Form	capsule
Strength	200 mg
Dose and Frequency	200 mg orally twice daily with or without food
How Supplied	200 mg (b) (4) capsules: pale yellow opaque, (b) (4))
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 23, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, “iptacopan”. Our search identified zero previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Fabhalta labels and labeling submitted by Novartis Pharmaceuticals Corporation.

- Container labels received on September 13, 2023
- Prescribing Information and Medication Guide (Images not shown) received on June 30, 2023, available from \\CDSESUB1\EVSPROD\nda218276\0017\m1\us\proposed.pdf

F.2 Label and Labeling Images

Container Labels

(b) (4)

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

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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