NDA 218276/S-003

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Shivani Shah, PharmD, MBA
Senior Global Regulatory Manager
Regulatory Affairs
One Health Plaza, Building 337
East Hanover, New Jersey 07936-1080

Dear Shivani Shah:

Please refer to your supplemental new drug application (sNDA) dated and received March 20, 2024, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fabhalta (iptacopan) capsules.

This Prior Approval sNDA provides for proposed modifications to the approved Fabhalta risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Fabhalta was originally approved on December 5, 2023. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS include the following:

- Updates to the REMS Document, including the REMS goal, and materials to conform to the Safety Labeling Changes approved on March 26, 2024 which included removal of the requirement to assess and vaccinate against *Haemophilus influenzae* type B (Hib) and editorial changes for clarity
- Changes to the “Inpatient Pharmacy Location” field options on the *Inpatient Pharmacy Enrollment Form*
- Addition of language to the REMS Website Outpatient Pharmacy page to provide more detail on the process for outpatient pharmacy enrollment

Your proposed modified REMS, submitted on March 20, 2024, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on December 5, 2023.

The revised 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 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, 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, 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, and by geographic region (as defined by US Census)
   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 noncompliance 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 non-compliance 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 non-compliance 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
         a) Specific reasons for the drug distributions to inpatient and outpatient pharmacies that are not certified
      v. 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 from HCPs
vii. Verification that at each audited pharmacy site the designated Authorized Representative is up to date. If the Authorized Representative changes, 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 or printed 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. Methods utilized to collect data on whether patients received meningococcal and pneumococcal vaccinations in accordance with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving a complement inhibitor.

b. The number and percentage of new patients treated with Fabhalta who received vaccination against encapsulated bacteria (*Neisseria meningitidis* serogroups A, C, W, Y and B; and *Streptococcus pneumoniae*) out of the total number of patients who received Fabhalta. Of those who reported receiving meningococcal and pneumococcal vaccines, provide the number and percentage of patients who:

    i. Received vaccines in accordance with the most current ACIP recommendations for meningococcal and pneumococcal vaccinations in patients receiving a complement inhibitor
    ii. Did not receive vaccines in accordance with the most current ACIP recommendations for meningococcal and pneumococcal vaccinations in patients receiving a complement inhibitor
    iii. Did not have all the information necessary for determining compliance with current ACIP recommendations for patients receiving a complement inhibitor

c. Stratified by vaccine type, provide the number and percentage of new patients who did not receive vaccination against encapsulated bacteria (*Neisseria meningitidis* serogroups A, C, W, Y and B; and *Streptococcus pneumoniae*) in accordance with the current ACIP recommendations or received antibacterial drug prophylaxis if needed, prior to initiating treatment with Fabhalta, out of the total number of patients who received Fabhalta

d. For all new patients who received antibacterial drug prophylaxis, include the timing (mean, median, range) of when antibacterial drug prophylaxis was given in relation to the initiation of Fabhalta

e. If any of the above information is missing, the reasons why this information is missing such as:
    i. Healthcare provider records do not include this information
    ii. Healthcare provider declined to provide information
    iii. Pharmacy unable to get healthcare provider to respond to queries

f. Number and percentage (%) of patients dispensed Fabhalta who received at least one dose of meningococcal vaccines (against all of the following serogroups: A, C, W, Y, and B) according to the most current ACIP recommendations in patients receiving a complement inhibitor and antibacterial drug prophylaxis, if needed, before the first dispense

g. Number and percentage (%) of patients dispensed Fabhalta who received at least one dose of pneumococcal vaccine according to the most current ACIP recommendations in patients receiving a complement inhibitor and antibacterial drug prophylaxis, if needed, before the first dispense

h. The number and percentage of new patients treated with Fabhalta who completed or were up to date with meningococcal vaccinations (against all of the following serogroups: A, C, W, Y and B) and pneumococcal vaccinations as per the most current ACIP recommendations in patients receiving a complement inhibitor at the time of first dose

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

   i. Completed meningococcal and pneumococcal vaccines
   ii. Did not complete meningococcal and pneumococcal 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 and pneumococcal 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 and pneumococcal 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 and pneumococcal vaccination status, to include the specific vaccines and the dates they were administered
         a) Date of vaccine(s) (i.e., all of the meningococcal (A, C, W, Y and B) and pneumococcal vaccine 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 and pneumococcal infection rate (per year and cumulatively):
   a. Among patients who received Fabhalta in the US and worldwide, the number of reported cases of meningococcal and pneumococcal 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; and *Streptococcus pneumoniae*) 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.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether

the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 218276 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block

or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 218276 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 218276/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 218276/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 218276/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 218276/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 218276

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Caden Brennen, Safety Regulatory Project Manager at 301-796-6591 or at Caden.Brennen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rosanna Setse, MD, MPH, PhD.
Deputy Director for Safety
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE(S):

- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROSANNA W SETSE
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