NDA 218276

NDA 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 Dr. Shah:

Please refer to your new drug application (NDA) dated and received April 5, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fabhalta (iptacopan) capsules.

This NDA provides for the use of Fabhalta (iptacopan) capsules for the treatment of adults with paroxysmal nocturnal hemoglobinuria.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on November 6, 2023, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 218276**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Fabhalta (iptacopan) capsules shall be 24 months from the date of manufacture when stored at 20°C to 25°C.

ADVISORY COMMITTEE

Your application for Fabhalta was not referred to an FDA advisory committee because this is not the first complement inhibitor approved for this specific indication and the application did not raise efficacy, safety, or public health questions requiring advice from external experts.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a

known serious risk of bacterial infections caused by encapsulated organisms and lack of information about the long term safety of Iptacopan.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4553-1 Provide data from a registry that characterizes the long-term safety of Fabhalta in adults with paroxysmal nocturnal hemoglobinuria (PNH), with up to 5 years of follow-up.

The timetable you submitted on December 4, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2024
Final Protocol Submission:	08/2024
Interim Report Submission #1:	12/2025
Interim Report Submission #2:	12/2026
Interim Report Submission #3:	12/2027
Interim Report Submission #4:	12/2028
Final Report Submission:	07/2030

Submit yearly interim report submissions that include safety follow-up data and a summary of the major safety findings for all patients and all serious infections with encapsulated bacteria. The final study report submission must include an integrated safety dataset and patient level data, including data on Fabhalta dosing, meningococcal, pneumococcal, and H. influenza vaccination status, serious infections with encapsulated bacteria, and concomitant medications.

4553-2 Complete Study APPLY-PNH (CLNP023C12302): “A randomized, multicenter, active-comparator controlled, open-label trial to evaluate efficacy and safety of oral, twice daily LNP023 in adult patients with PNH and residual anemia, despite treatment with an intravenous anti-C5 antibody”.

The timetable you submitted on November 2, 2023, states that you will conduct this trial according to the following schedule:

Final Report Submission:	07/2024

Include an updated summary of safety and efficacy analyses for this trial, and datasets at the time of final clinical study report submission.

4553-3 Complete Study APPOINT-PNH (CLNP023C12301): “A multicenter, single-arm, open-label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult PNH patients who are naive to complement inhibitor therapy”.

The timetable you submitted on November 2, 2023, states that you will conduct this trial according to the following schedule:

Final Report Submission: 07/2024

Include an updated summary of safety and efficacy analyses for this trial, and datasets at the time of final clinical study report submission.

4553-4 Complete Study CLNP023C12001B PNH REP: An open label, multicenter roll-over extension program (REP) to characterize the long-term safety and tolerability of iptacopan (LNP023) in patients with paroxysmal nocturnal hemoglobinuria (PNH) who have completed PNH phase 2 and phase 3 studies with iptacopan.

The timetable you submitted on November 2, 2023 states that you will conduct this trial according to the following schedule:

Final Report Submission: 05/2029

Include an updated summary of safety and efficacy analyses for this trial, and datasets at the time of final clinical study report submission.

FDA considers the term *final protocol submission* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocols to your IND 134655 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocols for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Fabhalta (iptacopan) to ensure the benefits of the drug outweigh the risk of serious infections caused by encapsulated bacteria.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Fabhalta (iptacopan) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of serious infections caused by encapsulated bacteria listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies that dispense the drug be specially

certified and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on April 5, 2023, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Fabhalta (iptacopan) into interstate commerce.

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 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 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, provide a narrative 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, provide the following information, as available:
    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 provided 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.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess your REMS program be submitted for FDA review as follows:

i. Submit your proposed audit plan and non-compliance plan for FDA review within 60 days of this letter.

ii. Submit your proposed protocol for the knowledge survey(s) for FDA review within 90 days of this letter.

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)**

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). 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, proposed 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 the 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 a REMS modification*, provide a rationale for why the REMS does not need to be modified.

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 REVISION 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[7].

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[7] https://www.uspnf.com/

If you have any questions, contact Courtney Hamilton, Regulatory Project Manager at 301-796-6849 or at Courtney.Hamilton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling
- REMS

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/s/

HYLTON V JOFFE
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