NDA 218037

NDA APPROVAL

Alexion Pharmaceuticals, Inc.
Attention: Vinayak Rajana
Associate Director, Global Regulatory Affairs
121 Seaport Blvd.
Boston, MA 02210

Dear Vinayak Rajana:

Please refer to your new drug application (NDA) dated and received March 30, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Voydeya (danicopan) tablets.

This NDA provides for the use of Voydeya (danicopan) tablets indicated as add-on therapy to ravulizumab or eculizumab for the treatment of extravascular hemolysis (EVH) in adults with paroxysmal nocturnal hemoglobinuria (PNH).

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, 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 218037**." 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 Voydeya (danicopan) tablets shall be 24 months from the date of manufacture when stored at 20°C to 25°C.

ADVISORY COMMITTEE

Your application for Voydeya was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

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 increased susceptibility to serious infections caused by encapsulated bacteria.

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:

4601-1 Establish a registry to characterize the long-term safety of danicopan in adults with paroxysmal nocturnal hemoglobinuria (PNH), with at least 5 years of follow-up. Yearly safety follow-up data should include a summary of the major safety findings for all patients and all serious infections with encapsulated bacteria. The final study report should include an integrated safety dataset and patient level data, including data on danicopan dosing, meningococcal and pneumococcal vaccination status, and concomitant medications.

The timetable you submitted on March 13, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2024
Final Protocol Submission:	12/2024
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:	12/2029

FDA considers the term *final* 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 protocol to your IND 127367 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) 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 protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute

[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.

clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4601-2 Complete Study ALXN2040-PNH-301: A phase 3 study of danicopan (ALXN2040) as add-on therapy to a C5 inhibitor (eculizumab or ravulizumab) in patients with paroxysmal nocturnal hemoglobinuria who have clinically evident extravascular hemolysis (EVH). Include an updated summary of efficacy and safety analyses and datasets at the time of final clinical study report submission

The timetable you submitted on March 13, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2026

4601-3 Complete Study ACH471-101: A phase 2 open-label study of ACH0144471 in patients with paroxysmal nocturnal hemoglobinuria (PNH) who have an inadequate response to eculizumab monotherapy. Include an updated summary of efficacy and safety analyses and datasets at the time of final clinical study report submission

The timetable you submitted on March 13, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2024

Submit clinical protocols to your IND 127367 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

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 Voydeya 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 Voydeya 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 October 30, 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 Voydeya into interstate commerce.

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

For each metric, 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 VOYDEYA
    b. Date of VOYDEYA REMS launch
    c. Date when the VOYDEYA **REMS Website** became live and fully operational
    d. Date when healthcare providers (HCPs) who can prescribe could become certified in the VOYDEYA REMS
    e. Date when pharmacies were able to complete the VOYDEYA REMS certification process
    f. Date of first prescriber certification
    g. Date of first pharmacy certification
    h. Date when the REMS Call Center was established and fully operational

2. REMS Certification and Enrollment Statistics
    a. Healthcare Provider Certification
        i. The number of HCPs certified: total, newly certified, and active (prescribed VOYDEYA 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, Doctor of Pharmacy), medical specialty (e.g., Hematology/Oncology, Immunology, Internal medicine, Nephrology, Neurology, Rheumatology, and Other), and geographic region (as defined by US Census)
        ii. Method of HCP certification (e.g., fax, online, email)
        iii. The number of HCPs who were unable to become certified, accompanied by a summary of the reason(s) why they were unable to be certified
    b. Pharmacy Certification (stratify by inpatient and outpatient)
        i. The number and identity of certified dispensing pharmacies: total, and newly certified and active (dispensed VOYDEYA at least once

during the reporting period) and by geographic region (as defined by US Census)
   ii. Method of pharmacy certification (e.g., fax, email)
   iii. The number of pharmacies that were unable to become certified, accompanied by a summary of the reason(s) why they were unable to become certified

3. Patient Statistics
   a. The number and percent of new patients treated with VOYDEYA
   b. The number of patients treated with VOYDEYA stratified by sex, age, diagnosis, and geographic region (as defined by US Census)

4. VOYDEYA Utilization Data (stratify by inpatient and outpatient)
   a. The number of VOYDEYA shipments sent to pharmacies overall and stratified by quantity per shipment, and by geographic region (as defined by US Census)
   b. For certified pharmacies, the number of prescriptions dispensed stratified by:
      i. Prescriber specialty, degree/credentials, and geographic region
      ii. Patient demographics (e.g., age, sex), and geographic region (as defined by US Census)
      iii. Whether the prescription was new or a refill
   c. Percentage (%) of VOYDEYA dispenses corresponding to prescriptions written by REMS certified HCPs
   d. The number of prescriptions not dispensed, accompanied by a listing and summary of all reasons for not dispensing the prescription (e.g., HCP not certified, REMS related issue)

5. REMS Compliance
   a. A summary report of non-compliance identified, associated corrective and preventive action (CAPA) plans, and the status of CAPA plans. Provide a summary of non-compliance identified, including, but not limited to:
      i. A copy of the non-compliance plan, including the criteria for determination of non-compliance for prescribers, outpatient pharmacies and inpatient pharmacies, actions taken to address non-compliance for each case, and what events led 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, the following information will be reported:
         a) The unique identification (ID) of the stakeholder(s) associated with the non-compliance event or deviation to enable tracking over time
         b) The source of the non-compliance data
         c) The results of root cause analysis
         d) The action(s) taken in response to non-compliance

iii. The number and percentage of prescribers who prescribed VOYDEYA but were not certified as identified by the certified pharmacy
iv. The specific reasons why prescribers were not certified at the time of prescribing and whether these prescribers subsequently became certified
v. The number and percentage of outpatient and inpatient pharmacies who obtained VOYDEYA that were not certified
vi. The specific reasons for the drug distributions to outpatient and inpatient pharmacies that were not certified
vii. The number of outpatient and inpatient pharmacies who became decertified, accompanied by a summary of reasons for decertification

6. Audits: Summary of audit activities including but not limited to:
   a. A copy of the audit plan used for each audited stakeholder (i.e., outpatient and inpatient pharmacies, REMS Call Center)
   b. The number of audits expected, and the number of audits performed for each stakeholder
   c. The number and category of observations noted, stratified by category
   d. A unique ID for each stakeholder that had observations to track observations by stakeholder over time
   e. Documentation of completion of training for relevant staff
   f. A summary report of documented processes and procedures for complying with the REMS requirements including how certified pharmacies obtain patient vaccination status from HCPs
   g. Verification that at each audited pharmacy site, the designated Authorized Representative is up to date. If the Authorized Representative has changed, include the number of new Authorized Representatives and verification of each site's recertification.
   h. Describe any corrective actions taken for any non-compliance (audit observation) identified during the audits, as well as preventative measures that were developed from uncovering these non-compliance events
      i. For those with deficiencies noted, report the number that successfully completed a CAPA plan by the due date
      ii. For any that did not complete the CAPA plan by the due date, describe additional actions taken

7. REMS Infrastructure and Performance
   a. REMS Website
      i. The number of visits and unique visits to the **REMS Website**
      ii. The number of REMS materials downloaded or printed for each material
   b. REMS Call Center Report
      i. The number of contacts by stakeholder type (patient/caregiver, healthcare provider, etc.)
      ii. A table summarizing the reasons for calls (e.g., enrollment question) by stakeholder type

iii. If the reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
iv. A summary report of corrective actions resulting from issues identified

Safe Use Behaviors

8. Safe Use Behaviors

Determination of patient's vaccination and antibacterial drug prophylaxis compliance is made using data collected via the certified pharmacies documenting the patient's vaccination status.

a. Methods utilized to determine whether or not patients received meningococcal and pneumococcal vaccines in accordance with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving a complement inhibitor. Include vaccine serogroup (if applicable), dosing (i.e., first vaccine dose, second vaccine dose and booster doses), and timing of the vaccinations, when the information is provided.
b. Data on the number and percentage of new patients treated with VOYDEYA who report receiving meningococcal and pneumococcal vaccines out of the total number of patients who received VOYDEYA. 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 Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal and pneumococcal vaccinations in patients receiving a complement inhibitor
    ii. Did not receive vaccines in accordance with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal and pneumococcal vaccinations in patients receiving a complement inhibitor
c. Data on the number and percentage of new patients treated with VOYDEYA who reported not receiving meningococcal and pneumococcal vaccines out of the total number of patients who received VOYDEYA
d. Whether the patient received antibacterial drug prophylaxis, and timing of antibacterial drug prophylaxis in relation to the dosing of VOYDEYA (if available)
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. Healthcare provider did not respond to pharmacy queries
f. The number and percentage of patients dispensed VOYDEYA 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 Advisory Committee on Immunization Practices (ACIP) recommendations in patients receiving a complement inhibitor and antibacterial drug prophylaxis, if needed, before the first dispense.

g. The number and percentage of patients dispensed VOYDEYA who received at least one dose of pneumococcal vaccines according to the most current Advisory Committee on Immunization Practices (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 VOYDEYA 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 Advisory Committee on Immunization Practices (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 meningococcal and pneumococcal vaccines when starting treatment, report the number and percentage who, for 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

9. Summary of cases of meningococcal and pneumococcal infections in patients receiving VOYDEYA:
    a. For US, cases are summarized as follows:
        i. In the most recent Periodic Safety Update Report (PSUR) submitted to the VOYDEYA New Drug Application (NDA) with reference to the PSUR corresponding with the reporting interval
        ii. 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, the following information is provided:
        i. MedWatch or other case report number
        ii. Date of event and date of report to FDA
        iii. Patient age, race, and sex
        iv. Indication for VOYDEYA treatment
        v. Meningococcal and pneumococcal vaccination status
            a) Date of vaccine(s) [i.e., all of the meningococcal vaccines (serogroups: A, C, W, Y, and B); and pneumococcal vaccine(s) doses that a patient receives including the first vaccine dose, second vaccine dose, and booster doses, as applicable]
            b) Name of vaccine(s)
            c) Timing in relation to VOYDEYA (i.e., the dates or duration that a patient receives VOYDEYA 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 receives VOYDEYA in relation to antibacterial drug prophylaxis)

e) Clinical course
    1) Outcome and causative encapsulated bacteria (include serogroup where applicable)
    2) Include the 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 antibacterial drug, antibacterial drug regimen (dose/frequency/duration), and route(s) of administration
    b) The timing of the course of the antibacterial drug prophylaxis in relation to VOYDEYA 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, if applicable, the following information is provided:
    i. Case report number
    ii. Patient age and sex
    iii. Indication for VOYDEYA treatment
    iv. Meningococcal and pneumococcal vaccination status if known
    v. Outcome
    vi. If associated with any clinical trials

10. Meningococcal and Pneumococcal Infections Rate (per year and cumulatively)
    a. Among patients who received VOYDEYA in the US and worldwide, if applicable:
        i. The number of reported cases of meningococcal and pneumococcal infections per 100,000 patient-years of post-marketing exposure to VOYDEYA; reporting rate, summarized cumulatively since the approval of VOYDEYA and also by year and relevant age subgroup (≤18 years, 19-55 years, and >55 years)

Knowledge

11. 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. Assess HCP and patient 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 the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving a complement inhibitor and receive antibacterial drug prophylaxis if needed
        b) The early signs and symptoms of serious encapsulated bacterial infections
        c) The need for immediate medical evaluation

Overall Assessment of REMS Effectiveness

12. 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 a 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 surveys 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 218037 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 218037 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 218037/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 218037/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 218037/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 218037/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 218037

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, 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).

REQUESTED ENHANCED PHARMACOVIGILANCE

We request that for Voydeya you submit all serious domestic and foreign cases of hepatic injury as 15-day “Alert reports” (described under 21 CFR 314.80(c)(1)).

We also request that you provide a separate narrative summary including analysis of all serious cases of hepatic injury reported with the use of Voydeya as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

under 21 CFR 314.80(c)(2)], quarterly during the first 3 years post-approval and annually thereafter, through the 5th year following the initial U.S. approval date.

Your analysis should include interval and cumulative data relative to the date of approval of Voydeya for all serious cases of hepatic injury reported with the use of Voydeya; and provide an assessment of causality, with documentation of indication (including all labeled and off-label use), temporal association, duration of therapy, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

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].

[7] https://www.uspnf.com/

If you have any questions, contact Carleveva Thompson, Regulatory Project Manager, at 301-796-1403 or Carleveva.Thompson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, MD, MMSc
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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