# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

# 214998Orig1s000

| | |
|---|---|
| ***Trade Name:*** | Camzyos capsules |
| ***Generic or Proper Name:*** | mavacamten |
| ***Sponsor:*** | MyoKardia, Inc. |
| ***Approval Date:*** | April 28, 2022 |
| ***Indication:*** | for the treatmentof adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms. |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# 214998Orig1s000

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214998Orig1s000

# APPROVAL LETTER

NDA 214998

**NDA APPROVAL**

MyoKardia, Inc.
Attention: Stephanie Chan, MS
Associate Director, Regulatory Strategy
1000 Sierra Point Parkway
Brisbane, CA 94005

Dear Ms. Chan:

Please refer to your new drug application (NDA) dated January 28, 2021, received January 28, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Camzyos (mavacamten) capsules.

We acknowledge receipt of your major amendment dated November 8, 2021, which extended the goal date by three months.

This NDA provides for the use of Camzyos (mavacamten) capsules for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms.

## 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]

[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.

The SPL will be accessible via publicly available labeling repositories.

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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214998**." 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 Camzyos (mavacamten) capsules shall be 30 months from the date of manufacture when stored at 20°C to 25°C.

## ADVISORY COMMITTEE

Your application for Camzyos was not referred to an FDA advisory committee because the application did not raise significant or controversial safety or efficacy issues that would have benefited from a public advisory committee discussion.

## 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 (1) assess a

signal of serious risks of pregnancy and maternal complications, adverse effects on the developing fetus and neonates, and adverse effects on lactation and the breastfed infant, and (2) identify an unexpected serious risk of carcinogenicity.

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 these serious risks.

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

4257-1 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Camzyos (mavacamten) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Assess infant outcomes through at least the first year of life. Specify the minimum number of patients in the protocol.

The timetable you submitted on February 11, 2022, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 10/2022 |
| Final Protocol Submission: | 04/2023 |
| Interim /Other[3]: | 10/2025 |
| Study Completion: | 04/2027 |
| Final Report Submission: | 10/2027 |

4257-2 Complete the 2-year Good Laboratory Practice (GLP) carcinogenicity study of mavacamten by oral gavage in Sprague Dawley rats, per the Special Protocol Assessment Agreement letter issued on June 14, 2018, and submit the final audited study report and proposed labeling update for Agency review.

The timetable you submitted on April 26, 2022, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Report Submission: | 09/2022 |

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.[4]

[3] Interim or “other” milestones may include interim report submission or subject accrual milestones.
[4] 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.

Submit clinical protocol(s) to your IND 121904 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).**

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 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 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 Camzyos (mavacamten) capsules to ensure the benefits of the drug outweigh the risk of heart failure due to systolic dysfunction.

Your proposed REMS must also include the following:

**Elements to assure safe use:** Pursuant to 505-1(f)(1), we have determined that Camzyos (mavacamten) capsules can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of heart failure due to systolic dysfunction 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
- Each patient using the drug is subject to certain monitoring

**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 is dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on January 28, 2021 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 Camzyos (mavacamten) capsules into interstate commerce.

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

Program Outreach and Communication (provide data at the 1-year assessment only)

1. REMS Program Website
   a) Date REMS website went live
   b) Number of total visits and unique visits to the REMS Program Website
   c) Number and type of Camzyos REMS materials downloaded or accessed

Program Implementation and Operations

2. REMS Call Center Reports (provide data for two previous reporting periods, the current reporting period, and cumulatively)
   a) Number of calls by stakeholder type (patient, healthcare provider, designee, pharmacy, wholesalers-distributors, other)
   b) Summary of reasons for calls (e.g., enrollment question) and stakeholder type (patients, healthcare provider, designee, pharmacy, other). Limit the summary to the top five reasons for calls by each stakeholder group.
   c) If the summary reason for the call(s) indicates a complaint, include details on the nature of the complaint(s) and whether the caller indicated potential REMS burden or patient access issues
   d) If the summary reason for the call(s) indicates an adverse event related to heart failure or a contraindicated drug or drug interaction, include details and the outcome of the call(s)

e) Percentage of calls to the REMS Call Center that were answered within 20 minutes
f) The shortest wait time for a call to be answered, the longest wait time for a call to be answered and the median time for a call to be answered
g) Percentage of calls to the REMS Call Center where the caller abandoned the call before the call was answered
h) The shortest wait time at which a call was abandoned, the longest wait time before the call was abandoned and the median wait time for a call to be abandoned

3. Program Implementation (provide data at the 1-year assessment only)
   a) Date of first commercial availability of Camzyos
   b) For each stakeholder (healthcare providers, designees, pharmacies, patients), the date when they could become certified
   c) Date when the Camzyos REMS Call Center was established and fully operational

4. REMS Certification and Enrollment (provide data for two previous reporting periods, the current reporting period and cumulatively)
   a) Healthcare Providers
      i. Number of newly certified healthcare providers and number of active (i.e., who have prescribed at least once during the reporting period) healthcare providers stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), specialty (e.g., Cardiology, Electrophysiology, Geneticist, Other), and geographic region (defined by US Census). If "Other" accounts for >10% of respondents, provide the most common specialties identified. Specifically identify and categorize if a specialty is within cardiology or non-cardiology
   b) Number of designees stratified by role (e.g., RPh/PharmD, RN, NP, or PA)
      i. Method of healthcare provider and designee certification (online or fax)
   c) Pharmacies
      i. Number of newly certified pharmacies
      ii. Number of active pharmacies (i.e., have dispensed Camzyos)
   d) Patients
      i. Number of newly enrolled patients and number of active (i.e., received at least one dispense of Camzyos) patients stratified by a combined variable of age and gender and geographic region. Provide the minimum and maximum age of enrolled patients. For gender/age variable use age ranges of less than 18, 18-40, 41-60, 61 years and older
   e) Wholesalers-distributors
      i. Number of newly contracted wholesalers-distributors and number of active (i.e., have shipped Camzyos) wholesalers-distributors

5. REMS Compliance (provide data for two previous reporting periods, the current reporting period, and cumulatively)
   a) A copy of the non-compliance plan, including the criteria for non-compliance

for healthcare providers, pharmacies, and wholesalers-distributors, actions taken to address noncompliance for each case, and which events lead to decertification from the Camzyos REMS (Beginning with the 1-year assessment and annually thereafter)

b) Audits
   i. A copy of the audit plan for pharmacies and wholesalers/distributors
   ii. Report of audit findings for each stakeholder (pharmacies and wholesalers-distributors)
   iii. Number of audits expected, and the number of audits performed.
   iv. Documentation of completion of training for relevant staff
   v. Documentation of processes and procedures in place for complying with the Camzyos REMS
   vi. Verification for each audited stakeholder's site that the designated Authorized Representative remains the same. If different, document that the pharmacy has re-certified with the name and contact information for the new Authorized Representative
   vii. Number and types of deficiencies noted for each group of audited stakeholders as a percentage of audited stakeholders.
   viii. For each Audited Pharmacy, number of the following deficiencies (numerator) divided by the number of dispenses audited at that pharmacy (denominator):
      1. Healthcare provider not certified, and prescription dispensed
      2. Patient not enrolled and prescription dispensed
      3. Drug Interaction and Counseling Checklist not completed, and prescription dispensed
      4. Audit of Drug Interaction and Counseling Checklist forms that identified a drug was dispensed but a required action not taken
      5. Authorization denied and prescription dispensed
   ix. For stakeholders with deficiencies noted, the number that successfully completed a Corrective and Preventative Action (CAPA) plan and as a percentage of those for which a CAPA plan was requested
   x. For any stakeholders who did not complete the CAPA Plan, a description of actions taken

c) Healthcare provider noncompliance (For each non-compliance event, the source of the report, a description of the event, the root cause analysis of the event, and corrective actions taken)
   i. Number of healthcare providers who were non-compliant with the Camzyos REMS program requirements. Provide as a percentage of active healthcare providers.
   ii. Number of healthcare providers who were de-certified and reasons for de-certification, also provided as a percentage of active healthcare providers. Include if any healthcare providers were re-certified.

d) Pharmacies (For each non-compliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions

taken)

i. Number of pharmacies for which non-compliance with the Camzyos REMS is detected (numerator) divided by all pharmacies dispensing Camzyos (denominator)
ii. The number of non-certified pharmacies that dispensed Camzyos (numerator) divided by all pharmacies that dispensed Camzyos (denominator). A compliance rate of 99.9% is expected.
iii. Number of Camzyos prescriptions dispensed by non-certified pharmacies (numerator) divided by all Camzyos prescriptions dispensed (denominator) and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected
iv. Number of Camzyos prescriptions dispensed that were written by non-certified healthcare providers (numerator) divided by all dispensed prescriptions (denominator). For prescriptions dispensed that were written by non-certified healthcare providers, provide the root cause analysis and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected.
v. Number of Camzyos prescriptions dispensed to non-enrolled patients (numerator) divided by all dispensed prescriptions (denominator). For prescriptions dispensed to non-enrolled patients provide a root cause analysis and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected.
vi. Number of Camzyos prescriptions dispensed to non-enrolled patients based on a prescription from a non-certified healthcare provider (numerator) divided by all dispensed prescriptions (denominator). For prescriptions dispensed to non-enrolled patients based on a prescription from a non-certified healthcare provider provide a root cause analysis and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected.
vii. Number of times a Camzyos prescription was dispensed because a certified pharmacy bypassed the Camzyos REMS authorization processes (numerator) divided by all certified pharmacies (denominator). Provide a root cause analysis and include a description of how the events were identified and any corrective actions taken. A compliance rate of 99.9% is expected.
viii. Number of pharmacies decertified, reasons for decertification, and actions to address non-compliance. Provide as a ratio the number of pharmacies decertified (numerator) divided by all certified pharmacies (denominator).

e) Wholesalers-distributors (For each non-compliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions taken)

i. Number of contracted wholesalers-distributors for which non-compliance with the Camzyos REMS is detected (numerator) divided by the number

of contracted wholesalers-distributors (denominator)

ii. Number of wholesalers-distributors suspended from distributing, reasons for the suspension, and actions to address non-compliance

iii. Number of times Camzyos was distributed to a non-certified pharmacy (numerator) divided by the number of distributions of Camzyos (denominator)

6. Utilization Data (provide data for two previous reporting periods, the current reporting period, and cumulatively)
   a) Number of prescriptions (new and refills) dispensed, stratified by:
      i. Healthcare provider degree/credentials and geographic region
      ii. Patient demographics (age and gender, and geographic region)
   b) The number of prescriptions received and denied (not authorized), stratified by:
      i. Reasons and number of denials (numerator) divided by all denials (denominator)
         1. Healthcare provider not certified
         2. Prescription written by designee
         3. Patient not enrolled
         4. Patient status form documenting echocardiogram not submitted on appropriate schedule
         5. Drug Interaction and Counseling Checklist not completed
         6. Drug interaction or contraindicated drug identified, and appropriate actions not taken
         7. Other reasons for denial not categorized above
      ii. Healthcare provider degree/credentials and geographic region
   c) Number of unique healthcare providers who wrote prescriptions dispensed in the reporting period (active healthcare providers)
   d) Number of unique patients receiving Camzyos, stratified by age, gender, and geographic region

7. Burden to the Healthcare System and/or Barriers to Patient Access
   Reports to the Camzyos REMS Call Center indicating a burden to the healthcare system or barriers to patient access. Assessment of whether burden is attributable to the REMS, insurance, health care availability, other

Safe Use Behavior

8. Patient Status Forms (provide data for two previous reporting periods, current reporting period and cumulatively)
   a) Number of Patient Status Forms expected, received, and outstanding as of the REMS assessment cut-off date
   b) Number of first patient shipments sent prior to receipt of a Patient Enrollment Form (numerator) divided by all patients who were dispensed Camzyos (denominator). A compliance rate of 99.9% is expected.
   c) Number of unique patients who had a Patient Status Form submitted who the healthcare provider confirmed reviewing the echocardiogram for (numerator)

divided by number of unique patients who had a Patient Status Form submitted (denominator)

d) Number of unique patients who had a Patient Status Form submitted who the healthcare provider authorized treatment for (numerator) divided by number of unique patients who had a patient status form submitted (denominator)
e) Number of Patient Status Forms outstanding from previous reporting periods that were completed in the current reporting period (numerator) divided by the number of outstanding Patients Status Forms from the previous reporting period (if applicable)
f) Number of patients whose echocardiogram was completed off drug as a result of an authorization denial and reason (e.g., drug not dispensed due to missing Patient Status Form, insurance issues prevented drug dispensing, transportation issues prevented patient from obtaining echocardiograms)
g) Number of Patient Status Forms on which the healthcare provider indicated that the patient experienced a clinical heart failure event requiring hospitalization
h) Number of Patient Status Forms on which the healthcare provider indicated the patient experienced a decrease in LVEF to <50%
i) Number of patients who were not authorized to receive Camzyos as indicated on the Patient Status Form

9. Drug Interaction and Counseling Checklist for Pharmacies (provide data for two previous reporting periods, current reporting period and cumulatively)

a) Number of unique patients who had a Drug Interaction and Counseling Checklist completed prior to their initial dispensing of Camzyos (numerator) divided by the number of patients who initiated therapy with Camzyos (denominator). A compliance rate of 99.9% is expected.
b) Number of prescriptions dispensed that had a Drug Interaction and Counseling Checklist completed prior to dispensing (numerator) divided by the number of prescriptions dispensed for Camzyos (denominator). A compliance rate of 99.9% is expected.
c) Number of Drug Interaction and Counseling Checklists that identified a concurrent contraindicated medicine (numerator) divided by the total number of Drug Interaction and Counseling Checklists completed (denominator)
d) For those Drug Interaction and Counseling Checklists that identified a concurrent contraindicated medicine indicate the source of the drug interaction and action taken after healthcare provider was contacted including:
    i. Source
        1. Interacting drug prescribed by Camzyos certified healthcare provider/designee
        2. Interacting drug prescribed by other healthcare provider
        3. Interacting drug purchased over the counter by patient
    ii. Action taken
        1. Camzyos discontinued

2. Contraindicated drug discontinued

e) Number of Drug Interaction and Counseling Checklists that identified a concurrent medicine that required a dosage reduction (numerator) divided by the total number of Drug Interaction and Counseling Checklists completed (denominator)

f) For those Drug Interaction and Counseling Checklists that identified a concurrent medicine that required a dosage reduction, indicate the source of the drug interaction and action taken after healthcare provider was contacted including:

i. Source

1. Interacting drug prescribed by Camzyos certified healthcare provider/designee
2. Interacting drug prescribed by other healthcare provider
3. Interacting drug purchased over the counter by patient

ii. Action taken

1. Camzyos discontinued
2. Camzyos dose decreased
3. Other medicine(s) discontinued

g) Any information obtained from audits, or self-reported by pharmacies that indicated that a patient received a contraindicated medicine, while taking Camzyos expressed by the number of patients who received at least one shipment (dispensing) of Camzyos who were also taking a concurrent contraindicated medicine (numerator) divided by the total number of patients with at least one shipment (dispensing) of Camzyos (denominator). For all occurrences, include the contraindicated drug name, dose, and duration of therapy.

10. Knowledge Assessments (provide data at the 1-year and 2-year assessment reports only)

a) Number of completed Healthcare Provider Knowledge Assessments, including the method of completion and number of attempts to complete

b) A summary of the most frequently missed Healthcare Provider Knowledge Assessment questions

c) A summary of potential comprehension or perception issues identified with the Healthcare Provider Knowledge Assessment

d) Number of completed Pharmacy Authorized Representative Knowledge Assessments, including the method of completion and number of attempts to complete

e) A summary of the most frequently missed Pharmacy Authorized Representative Knowledge Assessment questions

f) A summary of potential comprehension or perception issues identified with the Pharmacy Authorized Representative Knowledge Assessment

11. Report on Key Performance Indicator (KPI)

The KPI is the number of prescriptions dispensed with an authorization from the REMS program when the prescription:

i. Will be dispensed from a Certified pharmacy

ii. Written by a Certified prescriber
iii. Written for an Enrolled patient
iv. Has a completed Patient Status form that documents an appropriately timed echocardiogram
v. Has a completed Drug Interaction and Counseling Checklist that documents appropriate actions were taken prior to authorization.

The threshold for the KPI is that 99.9% of dispenses are associated with an approved authorization.

Overall Assessment of REMS

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:

Submit your proposed audit plan, non-compliance plan and root cause analysis plan for FDA review within 60 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 214998 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 214998 REMS ASSESSMENT**

***or***

**NEW SUPPLEMENT FOR NDA 214998/S-000**
**CHANGES BEING EFFECTED IN 30 DAYS**
**PROPOSED MINOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA 214998/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED MAJOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA 214998/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 214998/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 214998**

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**

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).

For more 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.*[5]

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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

## 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.

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

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager, at (301) 796-0442.

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/

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