NDA 204819/S013 **GENERAL ADVICE**

Bayer HealthCare Pharmaceuticals Inc.
Attention: Joseph Quintavalla, PhD
Director, Regulatory Affairs
100 Bayer Boulevard
Whippany, NJ 07981-0915

Dear Dr. Quintavalla:

Please refer to your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adempas (riociguat) 0.5-, 1-, 1.5-, 2-, 2.5 mg Tablets.

We also refer to our approval letter date November 30, 2020, which contained an error and the November 30, 2020 General Advice letter that corrected the error.

The approval letter did not have the REMS materials attached, and the file attached to the General Advice letter was missing pages.

This General Advice letter acknowledges the error described above and incorporates the correction of the error. The effective approval date will remain November 30, 2020, the date of the original approval letter.

If you have any questions, call Lori Anne Wachter, Regulatory Project Manager, at 301 796-3975.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Attachment: REMS Materials

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

/s/

MARY R SOUTHWORTH
12/01/2020 10:51:18 AM

NDA 204819/S013 **GENERAL ADVICE**

Bayer HealthCare Pharmaceuticals Inc.
Attention: Joseph Quintavalla, PhD
Director, Regulatory Affairs
100 Bayer Boulevard
Whippany, NJ 07981-0915

Dear Dr. Quintavalla:

Please refer to your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adempas (riociguat) 0.5-, 1-, 1.5-, 2-, 2.5 mg Tablets.

We also refer to our approval letter date November 30, 2020, which contained an error.

The approval letter did not have the REMS materials attached.

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If you have any questions, call Lori Anne Wachter, Regulatory Project Manager, at 301 796-3975.

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{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Attachment: REMS

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

/s/

MARY R SOUTHWORTH
11/30/2020 07:00:43 PM

NDA 204819/S013

SUPPLEMENT APPROVAL

Bayer HealthCare Pharmaceuticals Inc.
Attention: Joseph Quintavalla, PhD
Director, Regulatory Affairs
100 Bayer Boulevard
Whippany, NJ 07981-0915

Dear Dr. Quintavalla:

Please refer to your supplemental new drug application (sNDA) dated and received July 12, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adempas (riociguat) 0.5-, 1-, 1.5-, 2-, 2.5 mg Tablets.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Adempas (riociguat) risk evaluation and mitigation strategy (REMS).

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Adempas (riociguat) was originally approved on October 8, 2013, and the most recent REMS modification was approved on February 10, 2020. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS establishes a single shared system (SSS) REMS for the elements to assure safe use and the implementation system required for the reference listed drug (RLD) Adempas (riociguat) and ANDAs referencing Adempas (riociguat), called the Riociguat REMS Program, which will become applicable on the date of full approval of the first ANDA joining a shared system with Adempas (riociguat). The modification being approved results in a two-part REMS consisting of: (1) the requirements of the previously approved Adempas (riociguat) REMS, and (2) the new SSS REMS for riociguat products. The requirements of the previously approved Adempas (riociguat) REMS will remain applicable until full approval of the first ANDA joining a shared system with Adempas (riociguat), at which time, those requirements will automatically be replaced by the requirements of the single, shared system.

Your proposed modified REMS, submitted on July 12, 2018, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on October 8, 2013, until full approval of the first ANDA joining a shared system with Adempas (riociguat). Upon full approval of the ANDA joining a shared system with Adempas (riociguat), you must submit REMS assessments to the FDA 12 months from the effective date of the SSS REMS, and annually thereafter.

The REMS assessment plan applicable to the previously approved Adempas REMS must include, but is not limited to, the following:

Program Implementation and Operations:

1. Report on utilization of the REMS: Provide the following data for each reporting period and cumulatively:
   a. Pharmacies
      i) Number of enrolled pharmacies by pharmacy type (inpatient and specialty)
      ii) Reason for inactivation of inpatient and specialty pharmacies
      iii) Identity of the specialty pharmacies
   b. Prescribers
      i) Number of enrolled prescribers, and the number and percentage of enrolled health care providers who have prescribed Adempas stratified by medical specialty
      ii) Reason for inactivation of prescribers
   c. Patients
      i) Number and percentage of enrolled patients by patient type:
         (1) Females of reproductive potential (FRP)
         (2) Pre-pubertal females (as classified on the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form) (PPF)
         (3) Females of non-reproductive potential (FNRP)
      ii) Number of patients, new and total, by patient type grouped by the following age ranges
         1) < 6
         2) 6 - < 18
         3) 18 - < 65
         4) 65+
   d. Number of outpatient prescriptions dispensed for FRPs and FNRPs stratified by
      i) Prescriber Specialty
      ii) Reproductive Status (FRP or FNRP)
      iii) Patient age as outlined in 1.c.ii above
   e. Number and identity of the enrolled wholesaler(s) / distributor(s)
   f. Number of sample packs provided by prescribers to patients
      i) Number of times more than one sample pack was provided to a patient at one time

2. Report on Pharmacy and Distributer Audit Summary for the current reporting period and cumulatively
    a. Provide a report of audit activities for enrolled specialty pharmacies; enrolled inpatient pharmacies, the REMS Coordinating Center, distributors and companies that distribute Adempas sample packages during the reporting period to include:
        i) The number of audited sites in each category listed directly above
        ii) A summary of critical and major (define both categories) observations identified during audits and corrective actions taken to address any non-compliance including whether any required corrective and preventative action (CAPA) plans were initiated and satisfactorily completed.
            1. Use a unique ID for stakeholder that had deviations to track deviation by stakeholder over time
            2. The audit is to confirm documentation of completion of training for relevant pharmacy staff as well as the existence of documented processes and procedures for complying with the REMS
        iii) A comparison of the findings to findings of previous audits and an assessment whether any trends are observed
        iv) A copy of the site-audit plan

3. Evaluation of the compliance with the Adempas REMS for each reporting period and cumulatively:
    a. Provide a copy of the Non-Compliance plan with every assessment report which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS

    b. The number of enrolled pharmacies and the number of enrolled prescribers for which non-compliance was detected, and what action(s) were taken in response

    c. Number of Adempas prescriptions dispensed that were written by non-enrolled or deactivated prescribers, source of report(s), actions taken to prevent future occurrences, and the outcome of such actions

    d. Number of prescriptions dispensed by non-enrolled pharmacies, source of report(s), actions taken to prevent future occurrences, and outcome of such actions

    e. Number of shipments sent to non-enrolled pharmacies, source of report(s), actions taken to prevent future occurrences, actions taken to

recover the Adempas from the certified non-enrolled pharmacy, and outcome of such actions

f. Number of samples sent to non-enrolled prescribers, actions taken to prevent future occurrences, actions taken to recover the samples from the prescribers, and the outcome of such actions

g. The number of enrolled prescribers and/or pharmacies that have had their certification suspended or revoked (disenrolled), including the reasons for such action

h. An evaluation of dispensing delays which resulted in an actual treatment interruption (defined as a delay in treatment of one or more days) focusing especially on delays on pregnancy testing with a root cause analysis to identify why pregnancy testing wasn't completed or the source of the prescriber and/or pharmacy error. Further include:

   i. The mean and median duration (including the standard deviation) of the observed treatment interruptions
   ii. Any adverse events resulting from the treatment interruption.
   iii. The protocol used to conduct this root cause analysis

i. Number of prescriptions dispensed of greater than 30-day supply and reasons for such dispensations, including any corrective actions as appropriate

j. Noncompliance with the REMS requirements, source of report(s), and any corrective action(s) or resolution(s)

4. REMS Coordinating Center

   a. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, wholesaler/distributors, other)

   b. Summary of reasons for calls (e.g. enrollment question, location of a pharmacy) and by reporter (authorized representative, pharmacy, prescriber, patient, other)

   c. Summary of frequently asked questions (FAQ) by stakeholder type

   d. Summary report of REMS-related problems identified and resulting corrective actions

5. REMS Website (per reporting period and cumulatively)

a. Number of visits and unique visits to the REMS website

b. Number of REMS materials downloaded or printed for each material

Safe Use Behaviors

6. Report on Reproductive Potential Status Changes (for each reporting period and cumulatively):

Both in a flowchart and in the report narrative, report the following regarding the Adempas REMS Change in Reproductive Potential Status and Prepubertal Annual Verification Forms including:

a. Number of forms received, including the number of forms received in error and the reasons these were classified as errors

b. Number of status changes to FRP status, including rationale for the change as indicated on the form. Also report:

i) Time between receipt of form and confirmation that monthly pregnancy testing occurred (time reported as a mean, median and standard deviation)

ii) Verification that routine monthly pregnancy tests of all FRPs occurred prior to the next dispense following a change in status to FRP.

iii) Number of times Adempas was dispensed prior to the patient getting their first pregnancy test following the status change to FRP, any resulting adverse events, and corrective action

c. Number of status changes to a FNRP, including rationale for the change as indicated on the form

d. The number of Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms returned reporting annual verification that a patient remains a Pre-Pubertal Female

e. The expected number of Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms returned reporting annual verification that a patient remains a Pre-Pubertal Female

f. Number of shipments suspended as a result of the prescriber's failure to return the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form for pre-pubertal females

g. Number of instances where a prescriber did not report a change or misclassification in the reproductive status of any female patient within 10 business days after the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form is signed

h. Conduct a root cause analysis of all cases of reproductive status misclassifications and include the protocol used to conduct this root cause analysis.

Health Outcomes and/or Surrogates of Health Outcomes

7. An analysis of all cases of pregnancy reported in association with Adempas from any source (for each reporting period and cumulative) with attention to but not limited to:

    a. The number of pregnancy exposures reported and stratified by source of exposure report (spontaneous report, for example).

    b. A cumulative summary of both U.S. and worldwide pregnancy cases should be provided and at a minimum, include the following information:

        i) Event identification number
        ii) Indication for Adempas
        iii) Contraceptive methods used
        iv) Weeks gestation at termination if pregnancy terminated
        v) Outcome for each Pregnancy
        vi) Age of patient

    c. Follow-up of outstanding pregnancy reports from previous assessment reporting period
    d. Root cause analysis of each reported pregnancy to determine the reason the REMS failed to prevent the pregnancy exposure. This root cause analysis should include patient interviews as a component. Include the protocol utilized to conduct this root cause analysis.

Knowledge

8. Evaluation of Knowledge of the Adempas REMS and Risks of Adempas/Surveys per reporting period:

    a. An evaluation of enrolled prescribers' knowledge of:

        i) The risks of embryo-fetal toxicity associated with Adempas
        ii) The need for appropriate baseline and monthly monitoring

iii) The need to counsel patients about these risks; the need to use reliable contraception; and the need for appropriate monitoring, and;
iv) The need to enroll patients in the Adempas REMS.

b. An evaluation of enrolled inpatient and outpatient pharmacy authorized representatives' and trained pharmacists' knowledge of:

i) the risks of embryo-fetal toxicity associated with Adempas; and
ii) the need to confirm that appropriate patient monitoring and counseling occur before dispensing Adempas.

c. An evaluation of patients' knowledge of:

i) the risks of embryo-fetal toxicity associated with Adempas
ii) the need for appropriate baseline and monthly monitoring; and
iii) effective contraception

9. 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.

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

Program Implementation and Operations

1. REMS Implementation (1-year assessment only)
   a. Date of first commercial distribution of generic riociguat
   b. Date when the Riociguat REMS website became live and fully operational
   c. Date with healthcare providers could become certified
   d. Date when pharmacies could become recertified
   e. Date when patients could become enrolled
   f. Date when the REMS Coordinating Center was established and fully operational

2. REMS Certification and Enrollment Statistics (provide for each reporting period and cumulatively)
   a. Pharmacies
      i. Number and percentage of recertified (i.e. recertified from the Adempas REMS), newly certified and active (i.e. have dispensed riociguat) pharmacies stratified by pharmacy type (i.e. inpatient and outpatient), facility type (i.e. hospital, long-term care, prison, Other) for inpatient pharmacies, and geographic region (as defined by US Census

b. Healthcare Providers
   i. Number and percentage of previously certified (i.e. transitioned from the Adempas REMS), newly certified and active (i.e. who have prescribed riociguat) healthcare providers stratified by provider credentials (e.g. Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), medical specialty (e.g. Cardiology, Pulmonology, Other), and geographic region (as defined by US Census region)

c. Patients
   i. Number and percentage of previously enrolled (i.e. transitioned from previous program), newly enrolled and active (i.e. have received riociguat) patients stratified by geographic region (as defined by US Census) and patient type:
   (1) Females of reproductive potential (FRP)
   (2) Pre-pubertal females (as classified on the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form) (PPF)
   (3) Females of non-reproductive potential (FNRP)

d. Wholesaler/Distributors
   i. Number and percentage of re-enrolled (i.e. re-enrolled from the Adempas REMS), newly enrolled and active (i.e., have shipped riociguat) wholesaler(s)/distributor(s)

3. Program Utilization Data (provided for each reporting period and cumulatively)
   a. Number and percentage of unique patients who received riociguat, new and total, by patient type grouped by the following age ranges:
      i. < 6
      ii. 6 - < 18
      iii. 18 - 49
      iv. 50+
   b. Number of outpatient prescriptions (new and refill) dispensed for FRPs and FNRPs stratified by:
      i. Healthcare Provider Specialty
      ii. Reproductive Status (FRP or FNRP)
      iii. Patient age as outlined in 3a above
   c. Number of sample packs provided by healthcare providers to patients
      i) Number of unique patients who received samples packs

4. REMS Infrastructure and Performance (provide for each reporting period and cumulatively)
   a. REMS Coordinating Center
      i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, wholesaler(s)/distributor(s), other)
      ii. Summary of reasons for calls (e.g., enrollment question, location of a pharmacy) and by reporter (authorized representative, pharmacy, healthcare provider, patient, other)

iii. Summary of frequently asked questions (FAQ) by stakeholder type
iv. Summary report of REMS-related problems identified and resulting corrective actions

b. REMS Website
   i. Number of visits and unique visits to the REMS website
   ii. Number of REMS materials downloaded or printed for each material

5. Riociguat REMS Compliance (provide for each reporting period and cumulatively)
   a. Provide a summary of non-compliance identified, including but not limited to:
      i. A copy of the Non-Compliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified 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 noncompliance, report the following information:
         1) The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
         2) The source of the noncompliance data
         3) The results of root cause analysis
         4) What action(s) were taken in response and whether any follow up is planned
   b. Number of riociguat prescriptions dispensed that were written by non-certified or deactivated (including previously certified) healthcare providers, source of report(s), actions taken to prevent future occurrences, and the outcome of such actions
   c. Number of prescriptions dispensed by non-certified pharmacies, source of report(s), actions taken to prevent future occurrences, and outcome of such actions
   d. Number of shipments sent to non-certified pharmacies, source of report(s), actions taken to prevent future occurrences, actions taken to recover the riociguat from the non-certified pharmacy, and outcome of such actions
   e. Number of samples sent to non-certified healthcare providers, actions taken to prevent future occurrences, actions taken to recover the samples from the healthcare providers, and the outcome of such actions
   f. The number of certified healthcare providers and/or pharmacies that have had their certification suspended or revoked (disenrolled), including the reasons for such action
   g. An evaluation of dispensing delays which resulted in an actual treatment interruption (defined as a delay in treatment of five or more days) focusing

especially on delays on pregnancy testing with a root cause analysis to identify why pregnancy testing was not completed or the source of the healthcare provider and/or pharmacy error. Further include:

i. The mean and median duration (including the standard deviation) of the observed treatment interruptions
ii. Any adverse events resulting from the treatment interruption.
iii. The protocol used to conduct this root cause analysis

h. Number of prescriptions dispensed of greater than 30-day supply and reasons for such dispensings, including any corrective actions as appropriate
i. Noncompliance with the REMS requirements, source of report(s), and any corrective action(s) or resolution(s)

6. Report on Pharmacy and Distributor Audits (provide for each reporting period and cumulatively)
   a. Report of audit findings for each stakeholder (e.g. enrolled pharmacies; enrolled inpatient pharmacies, the REMS Coordinating Center, wholesaler(s)/distributor(s) and companies that distributed riociguat sample packages) including but not limited to:
      i. A copy of the audit plan for each stakeholder
      ii. The number of audits expected, and the number of audits conducted
      iii. The number and type of deficiencies noted for each group of audited stakeholders
      iv. For those with deficiencies noted, report the number that successfully completed a corrective and preventative action (CAPA) plan within the timeline specified in the audit plan.
      v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
      vi. Use a unique ID for stakeholder that had deviations to track deviations by stakeholder over time
      vii. Confirm documentation of completion of training for relevant staff
      viii. Verify the existence of documented processes and procedures for complying with the REMS
      ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

Safe Use Behaviors

7. Report on Reproductive Potential Status Changes (for each reporting period and cumulatively) Both in a flowchart and in the report narrative, report the following regarding the Riociguat REMS Change in Reproductive Potential Status and Prepubertal Annual Verification Forms including:
   a. Number of forms received, including the number of forms received in error and the reasons these were classified as errors
   b. Number of status changes to FRP status, including rationale for the change as indicated on the form. Include:

i. Time between receipt of form and confirmation that monthly pregnancy testing occurred (time reported as a mean, median and standard deviation)
ii. Verification that routine monthly pregnancy tests of all FRPs occurred prior to the next dispense following a change in status to FRP.
iii. Number of times riociguat was dispensed prior to the patient getting their first pregnancy test following the status change to FRP, any resulting adverse events and corrective action

c. Number of status changes to a FNRP, including rationale for the change as indicated on the form
d. The number of Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms returned reporting annual verification that a patient remains a Pre-Pubertal Female
e. The expected number of Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms returned reporting annual verification that a patient remains a Pre-Pubertal Female:
   i. For any forms expected for a Pre-Pubertal female, but not received, conduct follow-up in order to determine the cause, outcome and any corrective actions taken.
f. Number of shipments suspended as a result of healthcare provider's failure to return the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form for pre-pubertal females
g. Number of instances where a healthcare provider did not report a change or misclassification in the reproductive status of any female patient within 10 business days after the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form is signed.
h. Conduct a root cause analysis of all cases of reproductive status misclassifications and include the protocol used to conduct this root cause analysis.

Health Outcomes and/or Surrogates of Health Outcomes

8. Each manufacturer will provide in their submission an analysis of all cases of pregnancy reported in association with riociguat from any source including but not limited to (provide for each reporting period and cumulatively):

   a. The number of pregnancy exposures reported and stratified by source of exposure report (spontaneous report, reported via the REMS, etc.).
   b. Pregnancy rate
   c. A cumulative separate summary of both U.S. and worldwide pregnancy cases, including but not limited to the following information:
      i. Event Identification Number
      ii. Indication for riociguat
      iii. Contraceptive methods used

iv. Weeks gestation at termination if pregnancy terminated
v. Outcome for each pregnancy
vi. Age of patient

d. Follow-up of outstanding pregnancy reports from the previous assessment reporting period
e. Root cause analysis of each reported pregnancy to determine the reason the REMS failed to prevent the pregnancy exposure. This root cause analysis should include patient interviews as a component. Include the protocol utilized to conduce this root cause analysis

Knowledge

9. Evaluation of Knowledge of the Riociguat REMS and Risks of Riociguat Stakholder/Surveys (provided for each reporting period)
    a. An evaluation of enrolled healthcare providers' knowledge of:
        i. the risks of embryo-fetal toxicity associated with riociguat
        ii. the need for appropriate baseline and monthly monitoring
        iii. the need to counsel patients about these risks; the need to use appropriate contraception and the need for appropriate monitoring
        iv. the need to enroll patients in the Riociguat REMS

    b. An evaluation of certified inpatient and outpatient pharmacy authorized representatives' and trained pharmacists' knowledge of:
        i. the risks of embryo-fetal toxicity associated with riociguat
        ii. the need to confirm that appropriate patient monitoring and counseling occur before dispensing riociguat.
    c. An evaluation of patients' knowledge of:
        i. the risks of embryo-fetal toxicity associated with riociguat
        ii. the need for appropriate baseline and monthly monitoring
        iii. appropriate contraception.

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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

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

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

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

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

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

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

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

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

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

NDA 204819 REMS ASSESSMENT METHODOLOGY

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 204819 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 204819/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 204819
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 204819
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 204819
REMS ASSESSMENT

PROPOSED REMS MODIFICATION (if included)

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

REMS REVISIONS FOR NDA 204819

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

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

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.

REPORTING REQUIREMENTS

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

If you have any questions, please call:

Lori Anne Wachter, RN, BSN, RAC
Regulatory Project Manager for Safety
301 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE(S):

- REMS

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/s/

MARY R SOUTHWORTH
11/30/2020 04:28:28 PM