DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204819/S-009

SUPPLEMENT APPROVAL

Bayer HealthCare Pharmaceuticals Inc.
Attention: Joseph Quintavalla, PhD.
Deputy Director, Regulatory Affairs
100 Bayer Boulevard
P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Quintavalla:

Please refer to your Supplemental New Drug Application (sNDA) dated and, received June 8, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adempas (riociguat) 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg Tablets.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Adempas 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 was originally approved on October 8, 2013, and the most recent REMS modification was approved on January 17, 2017. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of:

- Modifying the REMS to accommodate for certified prescribers' dispensing of Adempas to new patients. This modification results in changes to the following:
  - REMS document
  - Prescriber Enrollment Form
  - Patient Enrollment Form
  - Prescriber and Pharmacy Guide
- An update to the REMS document to correspond to the current format
- Modifications to the Guide for Females Who Can Get Pregnant to incorporate information on females who cannot get pregnant and retitle it as Guide for Female Patients
- Editorial changes throughout to replace "teratogenicity" with "embryo-fetal toxicity" and replace "reliable" with "effective"

In accordance with section 505-1 of the FDCA, we have determined that the following REMS modifications are necessary to minimize burden on the healthcare delivery system of complying with the REMS:

REMS Goals: The overall goal of the Adempas REMS remains the same; however, the presentation of the REMS goals were updated to better articulate how the REMS is structured to mitigate the risk.

Medication Guide: We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Adempas outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on June 8, 2018, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on October 8, 2013.

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

The REMS Assessment Plan for the Adempas REMS should include, but is not limited to the following:

1. Report on utilization of the REMS: Provide the following data for each reporting period and cumulatively:
    a. Pharmacies
        i. Number of certified pharmacies by pharmacy type (inpatient or specialty)
    b. Prescribers
        i. Number of certified prescribers, and the number and percentage of enrolled prescribers who have prescribed Adempas stratified by medical specialty.
    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 prescriptions dispensed for FRPs and FNRPs
e. Number of samples provided by the prescriber to patients

2. 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 potential FRP status, including rationale for the change as indicated on the form and also:
      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 dispensing of Adempas following a change in status to a FRP.
      iii) Number of times Adempas was dispensed prior to the patient getting her 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 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 of becoming aware of the change
   h. Conduct a root cause analysis of all cases of reproductive status misclassifications and include the protocol used to conduct this root cause analysis.

3. Report on Pharmacy and Distributer Audit Summary for the current reporting period, the previous reporting period, and cumulatively
   a. Provide a report of audit activities for certified specialty pharmacies; certified inpatient pharmacies, the REMS Coordinating Center, distributors and companies that distribute Adempas samples during the reporting period to include:
      i. The number of audited sites in each category listed directly above
      ii. A summary of critical 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
iii. A comparison of the findings to findings of previous audits and an assessment whether any trends are observed
iv. Submit a new site-audit plan whenever changes are made to the plan.

4. Evaluation of the compliance with the Adempas REMS for each reporting period and cumulatively:
    a. 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
    b. Number of prescriptions dispensed by noncertified pharmacies, source of report(s), actions taken to prevent future occurrences, and outcome of such actions
    c. Number of shipments sent to noncertified pharmacies, source of report(s), actions taken to prevent future occurrences, actions taken to recover the Adempas from the noncertified pharmacy, and outcome of such actions
    d. 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
    e. The number of certified prescribers and/or pharmacies that have had their certification suspended or revoked, including the reasons for such action
    f. An evaluation of dispensing delays which resulted in an actual treatment interruption (defined as a delay in treatment of one of more days) due either to the absence of pregnancy test results of due to pharmacy and/or prescriber error
        i. The mean and median duration (including the standard deviation) of the observed treatment interruptions
        ii. A root cause analysis to identify why pregnancy testing wasn't completed, or the source of the pharmacy and/or prescriber error.
        iii. Any adverse events resulting from the treatment interruption.
    g. Number of prescriptions dispensed of greater than 30-day supply and reasons for such dispensations
    h. Noncompliance with the REMS requirements, source of report(s), and any corrective action(s) or resolution(s)

5. An analysis of all cases of pregnancy reported in association with Adempas from any source (for each reporting period and cumulatively) 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:
        a. Event identification number
        b. Indication for Adempas
        c. Contraceptive methods used
        d. Root cause of contraception failure
        e. Weeks gestation at termination if pregnancy terminated
        f. Outcome for each Pregnancy

g. Age

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

6. Evaluation of Knowledge of the Adempas REMS Program and Risks of Adempas/Surveys:
    a. An evaluation of certified 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 the risks and need for monitoring, and
        iv. The need to enroll patients in the Adempas REMS program.
    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 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 embryo-fetal toxicity associated with Adempas
        ii. The need for appropriate baseline and monthly monitoring; and
        iii. appropriate contraception.

7. 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:

NDA204819 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/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 204819/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 204819/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

REMS REVISIONS FOR NDA 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
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
REMS

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

/s/

MARY R SOUTHWORTH
12/06/2018