DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204819/S-002

SUPPLEMENT APPROVAL

Bayer Healthcare Pharmaceuticals Inc.
Attention: Sharon W. Brown
Director, Global Regulatory Affairs
100 Bayer Boulevard
Whippany, NJ 07981-0915

Dear Ms. Brown:

Please refer to your Supplemental New Drug Application (sNDA) dated December 18, 2013., received December 18, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adempas (riociguat) 0.5, 1, 1.5, 2, and 2.5 mg Tablets.

We acknowledge receipt of your amendments dated December 18, 2013, January 10, April 15, and April 25, 2014.

This "Prior Approval" supplemental new drug application provides for revisions as follows (additions noted in underline, deletions noted in strikethrough):

In the **DRUG INTERACTIONS** section, subsection **7.1 Pharmacodynamic Interactions with Adempas,** of the package insert

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension *[see Contraindications (~~4.1~~4.2) and Clinical Pharmacology (12.2)]*.

PDE Inhibitors: Co-administration of Adempas with ~~phosphodiesterase (PDE) inhibitors, including~~ specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension *[see Contraindications (4.3) and Clinical Pharmacology (12.2)]*. Clinical experience with co-administration of Adempas and other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

In the **USE IN SPECIFIC POPULATIONS** section, subsection **8.1 Pregnancy,** of the package insert:

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately ~~3 times~~ 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at ~~5 times~~ 4 times the human exposure and fetal toxicity ~~at doses~~ with exposures approximately ~~15 times~~ 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Boxed Warning and Contraindications (4.1)]*.

Animal Data

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately ~~0.15 times~~ 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time- concentration curve (AUC) for unbound drug in rat and humans. Plasma exposure at the highest dose (25 mg/kg/day) is approximately ~~3 times~~ 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/day) is approximately ~~0.5 times~~ 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were ~~5 times and 15 times~~ 4 times and 13 times, respectively, the human ~~dose~~ exposure at the MRHD ~~respectively~~.

In the **USE IN SPECIFIC POPULATIONS** section, subsection **8.4 Pediatric Use,** of the package insert:

Safety and effectiveness of Adempas in pediatric patients have not been established *[see NonclinicalToxicology (13.2)]*.

In addition, minor editorial and formatting changes were proposed for other sections of the label.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below.

1. In Highlights, in the Product Title Section, only the first letter of Adempas should be capitalized.
2. The Full Prescribing Information (FPI), the following subsections have cross-references back to the Boxed Warning: 2.3, 4.1, 5.1, 5.2, 8.1, and 8.6. Cross-references back to the Boxed Warning should not appear in the FPI.
3. In subsection 8.6, the ending parenthetical is missing after the cross-reference to subsection 8.1.
4. Ensure the "Revised" month listed at the end of Highlights is the same as the supplement approval month.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to, except with the revisions indicated, the enclosed labeling (text for the package insert) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, 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 titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes with the revisions indicated above approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration

Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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 Wayne Amchin, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
05/06/2014