CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204819Orig1s000

Trade Name: Adempas

Generic Name: Riociguat

Sponsor: Bayer Healthcare Pharmaceuticals Inc.

Approval Date: October 8, 2013

Indications: For the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) WHO Group 4, after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class; and 2) for the treatment of adults with pulmonary arterial hypertension (PAH) WHO Group 1, to improve exercise capacity, WHO functional class and to delay clinical worsening.

CENTER FOR DRUG EVALUATION AND RESEARCH

204819Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	**X**
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	**X**
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204819Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204819

NDA APPROVAL

Bayer Healthcare Pharmaceuticals Inc.
Attention: Ms. Carmen Leung
Deputy Director, Global Regulatory Affairs
100 Bayer Boulevard
Whippany, NJ 07981-0915

Dear Ms. Leung:

Please refer to your New Drug Application (NDA) dated February 8, 2013, received February 8, 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 March 8, 12, 13, 19, 22, 25 and 27, April 4, 8, 16, 18, 19, and 26, May 2, 17, 29, 23, 28, and 30, June 7, 10, 13, 14, 17, 18, 24 and 27, July 3, 9, 12, 16, 19, and 31, August 5, and September 13, 17, 19, 20, 23, 27, and October 1 and 7, 2013.

This new drug application provides for the use of Adempas (riociguat) Tablets for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) WHO Group 4, after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class; and 2) for the treatment of adults with pulmonary arterial hypertension (PAH) WHO Group 1, to improve exercise capacity, WHO functional class and to delay clinical worsening.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

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 the enclosed labeling (text for the package insert and Medication Guide). 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*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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 IMMEDIATE CONTAINER LABELS

We acknowledge your August 5, 2013, submission containing final printed carton and container labels.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Edward Fromm, R.Ph., RAC
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 4162
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code 20903 if shipping via United States Postal Service (USPS).
Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for these indications has an orphan drug designation, you are exempt from this requirement.

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 [section 505-1(a)].
In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Adempas (riociguat) to ensure the benefits of the drug outweigh the risks of teratogenicity.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Adempas (riociguat) poses a serious and significant

public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Adempas (riociguat). FDA has determined that Adempas (riociguat) is a product for which patient labeling could help prevent serious adverse effects, and that has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use Adempas (riociguat), and that the drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Adempas (riociguat).

Pursuant to 505-1(f)(1), we have also determined that Adempas (riociguat) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of teratogenicity that is listed in the labeling. The elements to assure safe use will minimize the risk of fetal exposure and adverse fetal outcomes among Females of Reproductive Potential (FRP) who are prescribed Adempas (riociguat) by certifying healthcare providers and pharmacies, and by documenting safe use conditions.

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.

Your proposed REMS, submitted on October 7, 2013, and appended to this letter, is approved. 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 REMS must be fully operational before you introduce Adempas (riociguat) into interstate commerce.

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

For the 6-month assessment and all subsequent REMS assessments submitted thereafter:

1. Assessment of the dispensing of the Medication Guide in accordance with 21 CFR 208.24
2. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
3. Number of dispensers and prescribers (stratified by medical specialty) certified, and patients enrolled during the current REMS assessment reporting period and during each previous REMS assessment reporting period
4. Patient demographics for the current REMS assessment reporting period and for previous REMS assessment reporting periods to include age, diagnosis, and the percentage number (%) of females of reproductive potential

5. The frequency and reasons for dispensing >30 day supply to females of reproductive potential
6. Report on Change of Reproductive Potential Status forms including:
    a. Number of forms received
    b. Number of status changes to a female of reproductive potential, including rationale for the change as indicated on the form and time between receipt of form and start of routine monthly pregnancy testing
    c. Number of status changes to a female of non-reproductive potential, including rationale for the change as indicated on the form
7. Reports of critical observations identified during operational monitoring, including results of distribution data reconciliation
8. Critical observations identified during Regulatory Compliance Audits and corrective actions taken to address any non-compliance.
9. An analysis of all cases of pregnancy reported in association with Adempas from any source (during the reporting period and cumulative) with attention to but not limited to:
    a. The number of pregnancy exposures reported (during the reporting period and cumulative) and stratified by source of exposure report. A cumulative summary of pregnancy cases worldwide should be provided and at a minimum, include the following information:
        i. Event identification number
        ii. Indication for Adempas
        iii. Birth control methods
        iv. Root cause of contraception failure
        v. Weeks gestation at termination if pregnancy terminated.
    b. Follow-up of outstanding pregnancy reports from previous assessment reporting period
    c. Root cause analysis of each reported pregnancy to determine the reason the Adempas REMS program failed to prevent the pregnancy exposure
10. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goal or whether the goal or such elements should be modified

For the 12-month and all subsequent REMS assessments submitted annually thereafter, the following assessment will also be included:

1. An evaluation of patients' awareness and understanding of teratogenicity associated with Adempas, including an evaluation of patient-reported compliance with contraceptive use and monthly pregnancy testing for females of reproductive potential

2. An evaluation of healthcare providers' awareness and understanding of:
    a. The risk of teratogenicity associated with Adempas
    b. The need to exclude a pregnancy before initiating Adempas therapy
    c. The need for patients to consistently use reliable birth control and what the reliable methods of contraception are

Under section 505-1(g)(2)(C), FDA may require the submission of a REMS assessment if FDA determines that that an assessment is needed to evaluate whether the approved strategy should be modified to ensure the benefits of the drug outweigh the risks of the drug or minimize the burden on the health care delivery system of complying with the strategy.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

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 CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - 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.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 204819 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 204819
PROPOSED REMS MODIFICATION

REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 204819
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

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

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

You will be contacted by ERG to schedule the interview following this action on your application; ERG will provide specifics about the interview process at that time. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, please call:

Edward Fromm, R.Ph., RAC
Regulatory Project Manager
(301) 796-1072

Sincerely,
{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
REMS
Carton and Container Labeling

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

/s/

ELLIS F UNGER
10/08/2013