



NDA 204819/S-006

**SUPPLEMENT APPROVAL**

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

Dear Mr. Quintavalla:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 14, 2016, 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, 2.5 mg Tablets.

This supplemental new drug application provides for changes to the approved labeling and proposed modifications to the approved risk evaluation and mitigation strategy (REMS).

This Prior Approval supplemental new drug application provides for the following changes to the approved label for Adempas:

1. Under **DOSAGE AND ADMINISTRATION**, the following section was added:

**2.6 Transitioning to and from Adempas**

- Discontinue sildenafil at least 24 hours prior to administering Adempas [see Contraindications (4.3) and Drug Interactions (7)].
- Discontinue tadalafil at least 48 hours prior to administering Adempas [see Contraindications (4.3) and Drug Interactions (7)]. Consider initiating Adempas at a starting dose of 0.5 mg in patients at risk of hypotension [see Dosage and Administration (2.1)]. Monitor for signs and symptoms of hypotension on initiation.
  - Discontinue Adempas at least 24 hours prior to administering a PDE5-inhibitor [see Contraindications (4.3) and Drug Interactions (7)]. Monitor for signs and symptoms of hypotension on initiation.

2. Under **CONTRAINDICATIONS**, the following text was added to section 4.3 and section 4.4 was added:

#### **4.3 Phosphodiesterase Inhibitors**

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated [*see Dosage and Administration (2.6), Drug Interactions (7.1) Clinical Pharmacology (12.2)*]. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or 48 hours after tadalafil.

#### **4.4 Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias (PH-IIP)**

Adempas is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP).

3. Under **DRUG INTERACTIONS**, the following text was added:

##### **7.1 Pharmacodynamic Interactions with Adempas**

*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 (4.2) and Clinical Pharmacology (12.2)*].

*PDE Inhibitors:* Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or 48 hours after tadalafil. [*See Dosage and Administration (2.6)*]. Clinical experience with co-administration of Adempas and other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

4. Under **PATIENT COUNSELING**, the section was revised to read:

##### **Other Risks Associated with Adempas**

- Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
- Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
- Instruct patients on the dosing, titration, and maintenance of Adempas.
- Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). ~~Patients should~~ Instruct patients to report all current medications and new medications to their physician.
- Advise patients that antacids should not be taken within 1 hour of taking Adempas.

Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines [*see Adverse Reactions (6.1)*]. ~~They should~~ Advise patients to be aware of how they react to Adempas, before driving or operating machinery, and if needed, consult their physician. Patients should consult their physicians if fainting occurs, or dizziness gets worse with Adempas.

5. The revision date and version number were updated.

**In the Medication Guide:**

1. Under **Who should not take Adempas?**, the following bullet was added:
  - **you have pulmonary hypertension** associated with idiopathic interstitial pneumonias (PH-IIP).
2. Under **How should I take Adempas?**, the following text was added:
  - Do not take Adempas within 24 hours of sildenafil. Do not take Adempas 24 hours before or 48 hours after tadalafil.
3. The revision date was updated.

There are no other changes from the last approved package insert and Medication Guide.

**APPROVAL & LABELING**

We have completed our review of this supplemental 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, Medication Guide), with the addition of any labeling changes in pending “Changes Being Effectuated” (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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes 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 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).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

The REMS for Adempas was originally approved on October 8, 2013, and the most recent modification was approved on October 4, 2016. 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 modification to the REMS consists of a revised medication guide to include information regarding idiopathic hypertension and switching from a PDE5 inhibitor to Adempas and vice versa.

Your proposed modified REMS, submitted on January 12, 2017, 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.

There are no changes to the REMS assessment plan described in our December 4, 2015 letter.

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 of 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 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 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 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.

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**

**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 LABEL 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/BLA 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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 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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

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, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

## **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):  
Content of Labeling  
REMS



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
01/17/2017