

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204819Orig1s000**

**CHEMISTRY REVIEW(S)**

## Adempas (riociguat) Tablets

NDA 204-819

### Summary Basis for Recommended Action Chemistry, Manufacturing, and Controls

**Applicant:** Bayer Healthcare Pharmaceuticals, Inc.,  
P.O. Box. 1000  
Montville, NJ 07045-1000

**Indication:** For the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH).

**Presentation:** The product will be available in five different strengths; 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg. The different strength tablets are differentiated by color, and strength identifier numbers on one side of the tablets. The tablets will be packaged in HDPE bottles and blisters.

**EER Status:** Overall recommendation is “Acceptable” as of 14-Feb-2013.

**Consults:** ONDQA Biopharmaceutics – Acceptable as per Dr. Kareen Riviere’s review dated 11-Jun-13.

Methods Validation – The methods were sent to FDA labs and were found to be acceptable for quality control and regulatory purposes (2-Jul-2013).

EA – Categorical exclusion granted.

**Post-Approval Agreements:** None

### **Drug Substance:**

The drug substance, riociguat, is a new molecular entity. The drug substance is a white to yellowish crystalline solid with a melting point of 268° C for the thermodynamically stable morphic form. The drug substance is non-hygroscopic and practically insoluble in water. (b) (4)

In addition, (b) (4)

Based on the quality target product profile (QTPP) of riociguat immediate release tablets, a set of CQAs for the micronized drug substance has been compiled. These CQAs are influenced by critical process parameters (CPPs) and synthetic steps containing CPPs are considered critical. It is stated that all steps in the synthesis except (b) (4) are critical since they have an impact on at least one CQA. The overall control strategy partially relies on executing the synthetic steps within the limits of the established proven acceptable ranges (PARs).

Additionally, the drug substance quality is ensured through in-process controls throughout the manufacturing process and the appropriate final drug substance specification. The drug substance release specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., description, identification, assay, impurities, particle size distribution, polymorph confirmation, residual solvents, heavy metals, and residual palladium. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a retest period of (b) (4)

### **Drug product:**

Riociguat is an immediate release film-coated tablet product to be marketed in five different strengths. The drug product formulation uses standard compendial excipients with all tablets having the same weight. Lactose monohydrate is adjusted to (b) (4)

Even though the applicant has used QbD principles to gain enhanced understanding of the manufacturing process, the applicant has not claimed any design space. The applicant has used conventional strategy using a process validation approach and end product testing to control the quality of the drug product. The end product specification includes testing for appearance, identification, assay, content uniformity, dissolution, microbial purity and degradation products. The analytical procedures for the drug product are adequately described and validated. The provided stability data support a 36-month expiration period for this product.

The drug product is stored at (b) (4) -25°C (68-77°F). Excursions permitted 15-30°C (59-86°F).

**Conclusion:** Adequate from CMC perspective.

**Additional Items:**

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

**Overall Conclusion:** The application is recommended for “**Approval**” from CMC perspective.

Ramesh K. Sood, Ph.D.  
Acting Director, DPA I/ONDQA

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

/s/  
-----

RAMESH K SOOD  
08/20/2013

# **NDA 204819**

## **ADEMPAS (riociguat) Tablets**

***[Drug Substance Review]***

**Bayer HealthCare Pharmaceuticals, Inc.**

**Monica D. Cooper, Ph.D.  
Office of New Drug Quality Assessment  
DNDQA 1/Branch 1**

**Reviewed for the Division of Cardiovascular and Renal  
Products (HFD-110)**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>4</b>
<b>The Executive Summary .....</b>	<b>8</b>
I. Recommendations .....	8
A. Recommendation and Conclusion on Approvability .....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s) .....	8
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block .....	10
<b>Chemistry Assessment .....</b>	<b>11</b>
I. Review Of Common Technical Document-Quality (CTD-Q) Module 3 .....	11
S DRUG SUBSTANCE [riociguat, Bayer HealthCare Pharmaceuticals] .....	11
S.1 General Information [riociguat, Bayer HealthCare Pharmaceuticals, Inc.] .....	11
S.2 Manufacture [riociguat, Bayer HealthCare Pharmaceuticals, Inc.].....	13
S.3 Characterization [riociguat, Bayer HealthCare Pharmaceuticals, Inc.].....	68
S.4 Control of Drug Substance [riociguat, Bayer HealthCare Pharmaceuticals, Inc.] .....	83
S.5 Reference Standards or Materials [riociguat, Bayer HealthCare Pharmaceuticals].....	123
S.6 Container Closure System [riociguat, Bayer HealthCare Pharmaceuticals, Inc.] .....	125
S.7 Stability [riociguat, Bayer HealthCare Pharmaceuticals, Inc.] .....	127
P DRUG PRODUCT [Adempas (riociguat) Tablets] .....	141
A APPENDICES .....	141
A.1 Facilities and Equipment (biotech only).....	141
A.2 Adventitious Agents Safety Evaluation.....	141
A.3 Novel Excipients .....	141

R	REGIONAL INFORMATION .....	141
R.1	Executed Batch Records.....	141
R.2	Comparability Protocols.....	142
R.3	Methods Validation Package.....	142
II.	Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....	142
A.	Labeling & Package Insert.....	142
B.	Environmental Assessment Or Claim Of Categorical Exclusion .....	143
III.	Establishment Evaluation Report.....	144
IV.	List of Deficiencies .....	144

# Chemistry Review Data Sheet

1. NDA 204819
2. REVIEW #: 1 (for Drug Substance)
3. REVIEW DATE: 03-Jul-2013
4. REVIEWER: Monica D. Cooper, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA 204819	08-Feb-2013
Amendment (0005) – MV Package	22-Mar-2013
Amendment (0011) – Response to 74-Day Letter	18-Apr-2013
Amendment (0018) – Response to IR Letter	28-May-2013
Amendment (0027) – Response to IR Letter	27-Jun-2013

7. NAME & ADDRESS OF APPLICANT:

<b>Name</b>	Bayer HealthCare Pharmaceuticals, Inc.
<b>Address</b>	P.O. Box 1000 Montville, NJ 07045-1000
<b>Representative</b>	Carmen Leung, R. Ph. Deputy Director, Global Regulatory Affairs
<b>Telephone</b>	973-487-2687
<b>Fax</b>	973-487-2016
<b>E-Mail</b>	carmen.leung@bayer.com

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

<b>Proprietary Name</b>	Adempas
<b>Non-Proprietary Name (USAN)</b>	riociguat
<b>Code Names</b>	BAY 63-2521
<b>Chemistry Type</b>	1
<b>Submission Priority</b>	P

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Soluble guanylate cyclase (sGC) stimulator for treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH)

11. DOSAGE FORM: Film-Coated Tablet

12. STRENGTH/POTENCY: 5 Strengths – 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

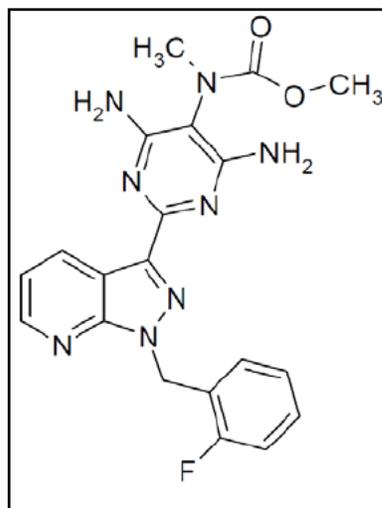
## Chemistry Review Data Sheet

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: (1) Methyl-4,6-diamino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate

(2) Carbamic acid, *N*-[4,6-diamino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-pyrimidinyl]-*N*-methyl-, methyl ester

US Adopted Name (USAN): riociguat  
International Nonproprietary Name (INN): riociguat  
Laboratory Code: BAY 63-2521  
Structural Formula:



Molecular Formula:  $C_{20}H_{19}FN_8O_2$   
Molecular Weight: 422.42 g/mol  
CAS Number: 625115-55-1

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

There are no DMFs related to the drug substance. Please see the CMC drug product review by Pei-I Chu, Ph.D. for a list of DMFs related to the drug product.

## Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	75,629	BAY 63-2521

## 18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	ACCEPTABLE	14-Feb-2013	T. Sharp
Pharm/Tox	N/A	----	----
Biopharmaceutics	ACCEPTABLE	11-Jun-2013	K. Riviere
LNC	N/A	----	----
Methods Validation	ACCEPTABLE	02-Jul-2013	M. Trehy
DMEPA	Tradename: Adempas Acceptable	09-May-2013	K. DeFronzo
EA	Categorical Exclusion: Acceptable	27-Jun-2013	P.I. Chu (See CMC Drug Product Review)
Microbiology	N/A	----	----

# The Chemistry Review for 204819

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This new drug application (204819) (drug substance section) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls.

*Note:* This review covers only the drug substance, riociguat micronized. The drug product (Adempas Tablets) was reviewed separately by Pei-I Chu, Ph.D. (please see her review dated 27-Jun-2013 in DARRTS).

The Office of Compliance has given an acceptable recommendation for the manufacturing and testing facilities (see the CMC drug product review by Pei-I Chu, Ph.D. dated 27-Jun-2013 for the Establishment Evaluation Summary).

The Division of Pharmaceutical Analysis (St. Louis Laboratory) verified the Method Validation for the drug substance method for particle size (by laser diffraction) and the drug product method for assay, content uniformity, and degradation products (by HPLC). The results of samples tested by these methods met the proposed specification limits and the methods were found acceptable for control and regulatory purposes (see Method Validation Reviews by Michael Trehy dated 02-Jul-2013 in DARRTS).

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Riociguat is the first of a new class of compounds, the soluble guanylate cyclase (sGC) stimulators, and may represent a novel therapeutic principle for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). Riociguat is used in a micronized form as the drug substance for riociguat film-coated tablets (0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg) for oral use.

## Executive Summary Section

Drug Substance

Riociguat drug substance is a chemically synthesized small molecule with no stereocenters (achiral). It is manufactured by Bayer Pharma AG, Wuppertal, Germany. The micronization is performed at Bayer Pharma AG, Berlin, Germany. Riociguat micronized drug substance is a white to yellowish crystalline solid. The drug substance is non-hygroscopic and practically insoluble in water. (b) (4)

In addition, (b) (4)

The proposed (b) (4) **retest date is acceptable for the drug** (b) (4)  
substance when stored in (b) (4)

Drug Product

The drug product is a film-coated tablet for oral use. Riociguat coated tablets were developed as an immediate release formulation with strengths of 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg. (b) (4)

The riociguat coated tablet 0.5 mg is a white, round, biconvex tablet – it is de-bossed on the top side with R 0.5 and on the bottom side with the Bayer cross. The 1 mg tablet is a pale yellow, round, biconvex tablet, de-bossed on the top side with R 1 and the bottom side with the Bayer cross. Riociguat 1.5 mg tablet is a yellow-orange, round, biconvex tablet, de-bossed on the top side with R 1.5 and on the bottom side with the Bayer cross. The 2 mg tablet is a pale orange, round, biconvex tablet, de-bossed on the top side with R 2 and on the bottom side with the Bayer cross. Riociguat 2.5 mg tablet is a red-orange, round, biconvex tablet, de-bossed on the top side with R 2.5 and on the bottom side with the Bayer cross.

Excipients used in the tablet formulation include microcrystalline cellulose, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, hydroxypropylcellulose, propylene glycol and titanium dioxide. All excipients comply with pharmacopeia requirements. Riociguat coated tablets are manufactured (b) (4)

The primary packaging of the container closure system used for commercial distribution of riociguat tablets is a 45-cc, white HDPE bottle closed with a screw cap (b) (4) white, (b) (4) (b) (4) ) with sealing insert. The drug is also packaged in (b) (4)

The formal stability study of the NDA registration batches was conducted for three batches of each strength (0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg) and for each packaging configuration. The stability data show that the assay does not significantly deviate from the initial value. No significant change from the initial potency value was observed at 25°C/60% RH and 30°C/75% RH for 36 months or at 40°C/75% RH for 6 months. All unspecified

## Executive Summary Section

impurities are (b) (4) The appearance, dissolution, and microbial purity showed no changes over all the room temperature and accelerated storage conditions. The applicant requested a **36-month expiry for riociguat tablets**, which was found acceptable (see CMC drug product review by Pei-I Chu, Ph.D. dated 27-Jun-2013).

**B. Description of How the Drug Product is Intended to be Used**

The recommended starting dose of the drug is 1 mg taken 3 times daily (TID). Tablets should be taken approximately 6 to 8 hours apart with or without food. The dosage can be increased in approximately 2-week intervals by 0.5 mg increments.

**C. Basis for Approvability or Not-Approval Recommendation**

This new drug application (204819) (drug substance section) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. All of the CMC drug substance issues identified in the original submission were resolved in subsequent amendments.

**III. Administrative****A. Reviewer's Signature**

/s/ M.D. Cooper, Ph.D.

**B. Endorsement Block**

Chemistry Reviewer (Drug Substance):	Monica D. Cooper, Ph.D.
Chemistry Reviewer (Drug Product):	Pei-I Chu, Ph.D. (see separate review)
CMC Lead:	Kasturi Srinivasachar, Ph.D.
Branch Chief:	Ramesh Sood, Ph.D.
Project Manager (ONDQA):	Deborah Mesmer
Project Manager (OND):	Ed Fromm

**C. CC Block**

Original NDA 204819

134 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

MONICA D COOPER  
07/03/2013

RAMESH K SOOD  
07/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION REPORT SUMMARY**

**TO:** Monica D. Cooper, Ph.D., CMC Reviewer  
Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: monica.cooper@dpa.hhs.gov  
Phone: (301)-796-1661  
Fax: (301)-796-9747

**FROM:** FDA  
Division of Pharmaceutical Analysis  
Michael Trehy, MVP Coordinator  
Suite 1002  
1114 Market Street  
St. Louis, MO 63101  
Phone: (314) 539-3815

**Through:** John Kauffman, Acting Deputy Director  
Phone: (314) 539-2168

**SUBJECT:** Methods Validation Report Summary

---

Application Number: 204819

Name of Product: Adempas (riociguat) Tablets 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg

Applicant: Bayer HealthCare Pharmaceuticals, Inc.

Applicant's Contact Person: Carmen Leung, Deputy Director of Global Regulatory Affairs

Address: P.O.Box 1000, Montville, NJ 07045-1000

Telephone: (973) 487-2687 Fax: (973) 487-2016

---

Date Methods Validation Consult Request Form Received by DPA: 3/15/13

Date Methods Validation Package Received by DPA: 3/15/23

Date Samples Received by DPA: 4/24/13

Date Analytical Completed by DPA: 7/2/13

---

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.   
2. Methods are acceptable with modifications (as stated in accompanying report).   
3. Methods are unacceptable for regulatory purposes.

Comments: See attached memo for method summary and comments.



DEPARTMENT OF HEALTH & HUMAN SERVICES  
Food and Drug Administration

Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis  
St. Louis, MO 63101  
Tel. (314) 539-3866

Date: July 2, 2013  
To: Monica Cooper, Ph.D., CMC reviewer  
Through: John Kauffman, Acting Deputy Director, Division of Pharmaceutical Analysis  
From: Jamie D. Dunn, Chemist  
Daniel J. Mans  
Changning Guo  
Subject: Methods Validation for NDA 204819  
Riociguat 0.5 mg, 1.5 mg and 2.5 mg tablets  
Bayer AG

The following method was evaluated and is acceptable for quality control and regulatory purposes:

Riociguat Drug Substance Test Procedure 3.2.S.4.2

(b) (4) Laser Diffraction according to Ph. Eur.)

The Division of Pharmaceutical Analysis (DPA) has no comments pertaining to these methods. See attached sheet for summary of results.

A copy of the analysts' work sheets and data is available at  
<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880493f6f>

## Summary of Results

NDA 204819

Particle size distribution of Riociguat micronized drug substance

(b) (4)



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

/s/  
-----

MICHAEL L TREHY  
07/02/2013

JOHN F KAUFFMAN  
07/02/2013



**NDA 204819**

**Adempas (Riociguat 0.5mg, 1mg, 1.5mg, 2mg, 2.5mg  
Film Coated Tablet)**

**Bayer Health Care Pharmaceuticals**

**Pei-I Chu, Ph.D.**

**Office of New Drug Quality Assessment DPA1  
For Division of Cardio renal Drug Products**

**Review of Chemistry, Manufacturing, and Controls**

**Table of Contents**

<b>Table of Contents</b> .....	<b>2</b>
<b>Chemistry Review Data Sheet</b> .....	<b>2</b>
<b>The Executive Summary</b> .....	<b>7</b>
I. Recommendations .....	7
<b>A. Recommendation and Conclusion on Approvability</b> .....	<b>7</b>
<b>B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable</b> .....	<b>7</b>
II. Summary of Chemistry Assessments .....	7
<b>A. Description of the Drug Product(s) and Drug Substance(s)</b> .....	<b>7</b>
<b>B. Description of How the Drug Product is Intended to be Used</b> .....	<b>8</b>
<b>C. Basis for Approvability or Not-Approval Recommendation</b> .....	<b>8</b>
III. Administrative .....	8
<b>A. Reviewer’s Signature</b> .....	<b>8</b>
<b>B. Endorsement Block</b> .....	<b>9</b>
<b>C. CC Block</b> .....	<b>9</b>
<b>Chemistry Assessment</b> .....	<b>10</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:	
Body Of Data .....	10
<b>S DRUG SUBSTANCE [Name, Manufacturer]</b> .....	<b>10</b>
<b>P DRUG PRODUCT [Name, Dosage form]</b> .....	<b>13</b>
<b>A APPENDICES</b> .....	<b>28</b>
<b>R REGIONAL INFORMATION</b> .....	<b>59</b>
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1. ....	60
<b>A. Labeling &amp; Package Insert</b> .....	<b>60</b>
<b>B. Environmental Assessment Or Claim Of Categorical Exclusion</b> .....	<b>65</b>

## Chemistry Review Section

**Chemistry Review Data Sheet**

1. NDA 204819
2. REVIEW # 1
3. REVIEW DATE: March 23, 2013
4. REVIEWER: Pei-I Chu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

February 8, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Bayer HealthCare Pharmaceuticals  
Address: P O Box 1000 Montville, NJ 07045-1000  
Representative: Carmen Leung  
Telephone: 973-487-2150

8. DRUG PRODUCT NAME/CODE/TYPE: N/A

- a) Proprietary Name: Riociguat
- b) Non-Proprietary Name (USAN): Riociguat
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: P

## Chemistry Review Section

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)
10. PHARMACOL. CATEGORY: Soluble guanylate cyclase (sGC) stimulators for CTEPH and PAH
11. DOSAGE FORM: Film Coated Tablet
12. STRENGTH/POTENCY: 0.5mg, 1mg, 1.5mg, 2mg, 2.5mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:  X  Rx   OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed  
 X  Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl (methyl) carbamate

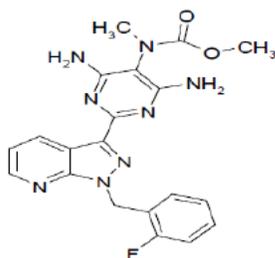
Carbamic acid, *N*-[4,6-diamino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-pyrimidinyl]-*N*-methyl-, methyl ester

*Molecular Formula:* C<sub>20</sub>H<sub>19</sub>FN<sub>8</sub>O<sub>2</sub>

*Molecular Weight:* 422.42 g/mol

Structural Formula

## Chemistry Review Section



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	03/26/2013	
	III			4			Sufficient information in application
	III			4			Sufficient information in application
	III			1	Adequate	12/10/2012	
	III			4			Sufficient information in application
	III			4			Sufficient information in application
	III			4			Sufficient information in application

Chemistry Review Section

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under “Comments”)

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	075629	Commercial

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	NA	John Lawrence
EES	Acceptable	2/14/2013	Office of compliance
Pharm/Tox	Acceptable pending clinical benefit	6/19/2013	Elizabeth Hausner
Biopharm	Acceptable	6/11/2013	Karen Riviere
LNC	NA	NA	NA
Methods Validation	Pending		Michael Trehy
OPDRA	NA	NA	
DMEPA	Acceptable	05/09/2013	Cherye Milburn
EA	NA	NA	NA
Microbiology	NA	NA	NA

## Chemistry Review Section

**The Chemistry Review for NDA 204819****The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

NDA 204819 has been reviewed for the chemistry, manufacturing, and controls section. This review covers the drug product portion. It is determined that the CMC information provided for the drug product is adequate. The drug substance review has been performed by Monica Cooper, Ph.D. Office of compliance has determined that the drug substance, drug product and packaging facilities are acceptable based on profile. The drug product CMC section of this NDA is recommended for approval.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

None as per this review.

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)****Drug Product**

Riociguat (BAY 63-2521) is the first of a new class of compounds, the soluble guanylate cyclase (sGC) stimulators. It may represent a novel therapeutic principle for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). The drug product is a film-coated immediate release tablet for oral use.

(b) (4)  
Riociguat coated tablet 0.5 mg is a white, round, biconvex tablet. The tablet is de-bossed on the top side with R 0.5 and on the bottom side with the Bayer cross. The 1 mg tablet is a pale yellow, round, biconvex tablet. It is de-bossed on the top side with R 1 and the bottom side with the Bayer cross. Riociguat 1.5 mg tablet is a yellow - orange, round, biconvex tablet. It is de-bossed on the top side with R 1.5 and on the bottom side with the Bayer cross. The 2 mg tablet is a pale orange, round, tablet. The tablet is de-bossed on the top side with R 2 and on the bottom side with the Bayer cross. Riociguat 2.5 mg tablet is a red-orange, round, biconvex tablet. The tablet is de-bossed on the top side with R 2.5 and on the bottom side with the Bayer cross.

Excipients used in the tablet formulation include microcrystalline cellulose, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, hydroxypropylcellulose, propylene glycol, ferric oxide yellow, ferric oxide red and titanium dioxide. All excipients complied with the

## Chemistry Review Section

pharmacopeia requirement. Riociguat coated tablets are manufactured as immediate-release formulations (b) (4)

The primary packaging components of container closure system used for commercial distribution of Riociguat tablet are 45-cc, white HDPE bottles closed with screw cap (b) (4) white (b) (4) with sealing insert. The drug is also packaged in (b) (4) (b) (4)

The formal stability study of the NDA registration batches was conducted for three batches of each strength (0.5mg, 1mg, 1.5 mg, 2mg and 2.5 mg) and for each packaging configuration. The stability data shows that the assay does not significantly deviate from the initial value. No significant change from the initial potency value was observed at 25° C/60% RH, 30°C/75% RH for 36 months or at 40°C/75% RH for 6 months. All unspecified impurity is (b) (4) (b) (4). The appearance, dissolution microbial purity showed no changes over all the room temperature or accelerated storage conditions. The applicant has requested a 36 months expiry for Riociguat tablets.

**Drug Substance (From Monica Cooper Ph.D.'s review)**

370 Riociguat drug substance is a chemically synthesized small molecule with no stereocenters (achiral). It is manufactured by Bayer Pharma AG, Wuppertal, Germany. The micronization is performed at Bayer Pharma AG, Berlin, Germany. Riociguat micronized drug substance is a white to yellowish crystalline solid. The drug substance is non-hygroscopic and practically insoluble in water (b) (4)

(b) (4) In addition, (b) (4) (b) (4) A (b) (4) retest date is proposed for the drug (b) (4) substance when stored in (b) (4) (b) (4)

**B. Description of How the Drug Product is Intended to be Used**

The drug should be initiated at 1 mg 3 times daily (TID), 6 to 8 hours apart with or without food. Increase dosage by 0.5 mg increments in approximately 2-week intervals.

**C. Basis for Approvability or Not-Approval Recommendation**

The drug product section of this NDA is recommended for approval from the perspective of chemistry, manufacturing and controls.

**II. Administrative****A. Reviewer's Signature**

Pei-I Chu, Ph.D.

## Chemistry Review Section

**B. Endorsement Block**

Chemist Name:	Pei-I Chu, Ph.D.
Chemistry CMC Lead:	Kasturi Srinivasachar, Ph.D.
Chemistry Branch Chief :	Ramesh Sood, Ph.D.
Chemistry Project Manager :	Deborah Mesmer

**C. CC Block**

Orig. NDA-204819

60 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

PEI-I CHU  
06/27/2013

RAMESH K SOOD  
06/27/2013



# CHEMISTRY REVIEW

## Chemistry Review Section

### III. Establishment Evaluation Report

#### FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 204819/000  
 Org. Code: 110  
 Priority: 1  
 Stamp Date: 08-FEB-2013  
 PDUFA Date: 08-OCT-2013  
 Action Goal:  
 District Goal: 08-JUN-2013

Sponsor: BAYER HLTHCARE  
 1000  
 MONTVILLE, NJ 07045

Brand Name: Riociguat

Estab. Name:

Generic Name:

Product Number; Dosage Form; Ingredient; Strengths

001; TABLET (IMMED./COMP. RELEASE), FILM COATED;  
 RIOCIQUAT; 5MG  
 002; TABLET (IMMED./COMP. RELEASE), FILM COATED;  
 RIOCIQUAT; 1MG  
 003; TABLET (IMMED./COMP. RELEASE), FILM COATED;  
 RIOCIQUAT; 1.5MG  
 004; TABLET (IMMED./COMP. RELEASE), FILM COATED;  
 RIOCIQUAT; 2MG  
 005; TABLET (IMMED./COMP. RELEASE), FILM COATED;  
 RIOCIQUAT; 2.5MG

FDA Contacts:	V. SHAH	Facility Reviewer	(HFD-320)	3017961750
	P. CHU	Prod Qual Reviewer		3017963887
	D. MESMER	Product Quality PM	(HFD-800)	3017964023
	E. FROMM	Regulatory Project Mgr		3017961072
	K. SRINIVASACHAR	Team Leader		3017961760

Overall Recommendation:	ACCEPTABLE	on 14-FEB-2013	by T. SHARP	()	3017963208
	PENDING	on 13-FEB-2013	by EES_PROD		
	PENDING	on 13-FEB-2013	by EES_PROD		
	PENDING	on 13-FEB-2013	by EES_PROD		

Establishment: CFN: 9610135 FEI: 3002806462

BAYER PHARMA AG  
 CHEMPARK  
 LEVERKUSEN, GERMANY

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER  
 FINISHED DOSAGE PACKAGER  
 FINISHED DOSAGE RELEASE TESTER  
 FINISHED DOSAGE STABILITY TESTER

Profile: TABLETS, PROMPT RELEASE

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-FEB-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION



# CHEMISTRY REVIEW



## Chemistry Review Section

### FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

**Establishment:** CFN: 9610496 FEI: 3003229486  
 BAYER PHARMA AG  
 217-333 FRIEDRICH-EBERT STRASSE  
 WUPPERTAL, GERMANY

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE RELEASE TESTER  
 DRUG SUBSTANCE STABILITY TESTER

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 14-FEB-2013

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

**Establishment:** CFN: 9611633 FEI: 3002908063  
 BAYER PHARMA AG  
 MAX DORN STRASSE 8-10  
 BERLIN, GERMANY

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE MICRONIZER  
 DRUG SUBSTANCE PACKAGER -

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 13-FEB-2013

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE