CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204819Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Addendum to the Risk Evaluation and Mitigation Strategy (REMS)
Final Review

Date:	October 7, 2013
Reviewer:	Somya Dunn, M.D. Division of Risk Management (DRISK) Joan Blair, R.N., M.P.H. Health Communications Analyst, DRISK
Team Leader:	Kimberly Lehrfeld, Pharm.D., DRISK
Division Director	Claudia Manzo, Pharm.D., DRISK
Drug Name(s):	Adempas® (riociguat) BAY 63-2521
Therapeutic Class:	Soluble Guanylate Cyclase Stimulator
Dosage and Route:	1 mg three times a day to a maximum dose of 2.5 mg three times a day Oral tablet strengths: 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg
Application Type/Number:	NDA 204-819
Submission Number:	Supporting Document (SD) 1 (Sequence 0000), SD 36 (Sequence 0035), SD 37 (Sequence 0036), SD 38 (Sequence 0037), SD 41 (Sequence 0040), SD 42 (Sequence 0041), SD 43 (Sequence 0042)
Applicant/sponsor:	Bayer HealthCare Pharmaceuticals
OSE RCM #:	2013-969

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

The purpose of this review is to amend the Division of Risk Management's (DRISK) review (Reviewer: Somya Dunn Sept. 5, 2013) of Bayer HealthCare Pharmaceutical's Risk Evaluation and Mitigation Strategy (REMS) for Adempas® oral tablets. The New Drug Application (NDA 204-819) was submitted and received on February 8, 2013 and amended with the final REMS document, REMS appended materials and REMS Supporting Document on Oct. 7, 2013.

1.1 BACKGROUND

Adempas, riociguat, is a new molecular entity and a proposed first-in-class medication; it is a soluble guanylate cyclase (sGC) stimulator that increases vascular sensitivity to nitric oxide (NO). Guanlyate cyclase is an enzyme in the cardiopulmonary system and is also the receptor for NO. It acts along a pathway that leads to increased intracellular cGMP which plays an important role in regulating vascular tone, proliferation, fibrosis and inflammation. Adempas results in pulmonary vasodilation and also has a cellular antiproliferative effect.

Several drugs are approved to treat PAH-WHO Group 1 for improvement in symptoms and delay in clinical worsening. There are a variety of therapies including oral agents (bosentan, ambrisentan, sildenafil, tadalafil), inhaled agents (iloprost, treprostinil) and parenteral agents (epoprostenol, treprostinil). Though the population of patients with PAH and CTEPH is not large, treatment options for PAH are limited. In addition, there are currently no medications available to treat CTEPH. Expected duration of treatment would be chronic administration as these conditions have no cure, have significant morbidity and mortality and can result in right heart failure.

Of note, both bosentan and ambrisentan, classified as endothelin receptor antagonists (ERAs), were found to be teratogens in animal studies. In animal studies, ERAs were associated with abnormalities of the lower jaw, hard and soft palate, malformation of the heart and great vessels and failure of formation of the thymus and thyroid. Adempas will be a first-in-class medication and it is not an ERA; however, it is targeted at the same patients that are taking ERAs (PAH patients). The teratogenic signal seen in Adempas in preclinical studies is different than that seen with the ERAs. Adempas was found to be associated with ventricular septal defects (VSDs) and bone malformations in rat studies.

Dr. Preston Dunnmon's primary review of Adempas states his concurrence that the risk of teratogenicity rises to the level to necessitate a REMS. The review team agrees that a REMS is necessary for Adempas.

1.2 SUBMISSIONS

The Sponsor's final REMS proposal, received on October 7, 2013 (Sequence 0042)

1.3 OTHER MATERIALS INFORMING THIS REVIEW

Primary Clinical Review for Adempas (P. Dunnmon July 8, 2013)
DRISK Interim Comments #1 (S. Dunn July 19, 3013)
DRISK Interim Comments #2 (S. Dunn September 6, 2013)

2 DISCUSSION

The REMS document and all appended REMS materials were still in the process of being finalized when DRISK's REMS review was completed on Sept. 5, 2013. The significant changes that have been made to the REMS document since September 5, 2013 are described below.

On Aug. 13, 2013, Bayer proposed including inpatient pharmacies in the REMS program so that they can stock Adempas. They proposed an inpatient pharmacy enrollment form and also proposed a "limited quantity" of Adempas to be dispensed in cases where the inpatient pharmacy was not enrolled in the REMS. The Agency clarified to the Sponsor that inpatient pharmacies would need to be certified by completing education, attesting to the REMS requirements and completing an enrollment form. However, in cases where this may not occur in a timely manner and may cause patient treatment interruption, the REMS would allow Bayer to provide a fourteen day temporary supply to the inpatient pharmacy for a specific inpatient.

On Sept. 17, 2013, Bayer proposed having the contraceptive implant as part of the Long-Acting Reversible Contraceptive group. The Agency discussed this with the Maternal Health Team and found that this was acceptable. This will also be reflected in labeling.

On Sept. 27, 2013, Bayer proposed a change to dispense more than a seven day supply of Adempas to patients being discharged from an inpatient facility. Their rationale was that if patient treatment is interrupted for more than three days after discharge, the patient would have to restart titratation of Adempas (as outlined in the Adempas Prescribing Information (PI)). This could cause a significant burden on patients and could also result in treatment interruptions. On Oct. 1, 2013, the Agency agreed to extend this to fifteen days. In addition, to be consistent within the REMS document and with other similar REMS, the Agency changed the inpatient temporary supply to fifteen days.

On October 7, 2013, Bayer submitted the final REMS document, all appended REMS materials and the REMS Supporting Document. DRISK finds the proposed Adempas REMS, Adempas REMS appended materials and Adempas REMS Supporting Document acceptable.

3 RECOMMENDATIONS

DRISK recommends approval of the Adempas REMS and the attached materials.

ATTACHMENTS

1. REMS Document
2. REMS Patient Enrollment and Consent Form
3. REMS Patient Enrollment Guide
4. REMS Reproductive Status Form
5. REMS Prescriber Enrollment and Agreement Form
6. REMS Prescriber Guide
7. REMS Website
8. REMS Inpatient Enrollment Form

43 pages of "Risk Evaluation and Mitigation Strategy (REMS)" have been withheld in full immediately following this page as a duplicate copy of the "Risk Evaluation and Mitigation Strategy" dated 10/08/2013 which can be found in the REMS Review.

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/s/

SOMYA V DUNN
10/07/2013

CLAUDIA B MANZO
10/07/2013
concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ODE-1
Division of Cardiovascular and Renal Products

NDA #:	204819
Product:	Adempas (riociguat) 0.5, 1, 1.5, 2, and 2.5 mg tablets
APPLICANT:	Bayer
FROM:	Mary Ross Southworth, PharmD
DATE:	September 25, 2013

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Adempas (riociguat) to ensure that the benefits of the drug outweigh the risk of teratogenicity. In reaching this determination, we considered the following:

A. Adempas (riociguat) will be indicated for the treatment of two forms of pulmonary hypertension: chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). The exact number people affected with pulmonary hypertension in the United States is unknown; based on registry data prevalence rates are approximately 15 per million[1].

B. Pulmonary hypertension is associated with significant morbidity and mortality. Symptoms include decreased exercise tolerance, shortness of breath, and fatigue; patients are often hospitalized. Disease progression eventually leads to right ventricular heart failure. The mortality rate at 1 year is approximately 15%.

[1] ACCF/AHA Expert Consensus Document on Pulmonary Hypertension, 2009.

C. Adempas (riociguat) is indicated to improve exercise ability and functional class (a measure of how difficult daily activities are) in patients with CTEPH. Adempas (riociguat) is indicated to improve exercise ability, improve functional class, and delay clinical worsening in patients with PAH.

D. Although the studies supporting approval were short term (about 16 weeks), Adempas (riociguat) will probably be used chronically (life-long).

E. Adempas (riociguat) is associated with teratogenicity and embryotoxicity in animal studies. Its use is contraindicated in pregnancy. The background incidence of pregnancy in patients with PAH is unknown; however, such patients are generally discouraged from becoming pregnant because of the significant risk of maternal and neonatal morbidity and mortality.

F. Adempas (riociguat) is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Adempas (riociguat). 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 drug for which patient labeling could help prevent serious adverse effects and that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) 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.

The elements of the REMS will be a Medication Guide, elements to assure safe use, including:

- Healthcare providers will be certified.
- Pharmacies and other facilties that dispense Adempas (riociguat) will be certified.
- Adempas (riociguat) will be dispensed only with documentation of safe use conditions.

The elements of the REMS also include an implementation system and a timetable for submission of assessments of the REMS.

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/s/

MARY R SOUTHWORTH
10/07/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Interim Comments on Risk Evaluation and Mitigation Strategy (REMS) Set # 2

Date:	September 5, 2013
Reviewer:	Somya Dunn, M.D. Division of Risk Management (DRISK)
Team Leader:	Kimberly Lehrfeld, Pharm.D., DRISK
Division Director	Claudia Manzo, Pharm.D., DRISK
Drug Name(s):	Adempas® (riociguat)
	BAY 63-2521
Therapeutic Class:	Soluble Guanylate Cyclase Stimulator
Dosage and Route:	Applicant Proposal: 1 mg three times a day to a maximum dose of 2.5 mg three times a day
	Oral tablet strengths: 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg
Application Type/Number:	NDA 204-819
Submission Number:	Supporting Document 1 (Sequence 0000)
Applicant/sponsor:	Bayer HealthCare Pharmaceuticals
OSE RCM #:	2013-969

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CONTENTS

1 INTRODUCTION

The purpose of this review is to document interim comments for the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) for Adempas® oral tablets. The New Drug Application (NDA 204-819) was submitted by Bayer HealthCare Pharmaceuticals (Bayer). The NDA was submitted and received on February 8, 2013.

The application is currently under review in the Division of Cardiovascular and Renal Products (DCRP) for treatment of pulmonary arterial hypertension. The Sponsor included a proposed REMS for the risk of teratogenicity in the submission. One set of interim comments regarding the proposed REMS was sent to the Sponsor on July 19, 2013. The Sponsor responded with updated drafts of the REMS documents on August 13, 2013. These were reviewed by DRISK and are discussed in this document.

2 MATERIALS REVIEWED

Sponsor's Updated REMS Proposal including:

- Bayer HealthCare Pharmaceuticals Proposed REMS
- Bayer HealthCare Pharmaceuticals Prescriber Enrollment and Agreement Form
- Bayer HealthCare Pharmaceuticals Prescriber Guide, Patient Enrollment Guide
- Bayer HealthCare Pharmaceuticals Patient Enrollment and Consent Form
- Bayer HealthCare Pharmaceuticals Patient Re-enrollment Form
- Bayer HealthCare Pharmaceuticals REMS Supporting Document
- Bayer HealthCare Pharmaceuticals REMS Website

These updated documents were received on August 13, 2013.

3 SUMMARY OF APPLICANT'S PROPOSED REMS

The Sponsor has proposed a Medication Guide (MG) and the following Elements to Assure Safe Use (ETASU)

- ETASU A – Prescriber Certification
- ETASU B – Pharmacy Certification
- ETASU D – Documentation of safe use conditions

The Sponsor has updated their REMS proposal and related materials as advised by the Agency.

The updated goals are as follows:

To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Adempas

1. To minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed Adempas
    a. Females who are pregnant must not be prescribed Adempas

b. Females taking Adempas must not become pregnant

The Sponsor has accepted the Agency's recommendations that the program enroll all females. In addition, they have accepted the updated terminology of females of reproductive potential and amended their documents accordingly. A website was submitted as requested.

Noteworthy changes were made to the Sponsor's proposal. The Sponsor now plans to enroll inpatient pharmacies, including long term care and prison facilities in the REMS program. (b) (4)

The Sponsor accepted the FDA's recommendations to use and define FRP but is proposing that the definition for Females of Non-Reproductive Potential (FNRP) (b) (4)

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Adempas REMS proposal be sent to the applicant. Please request that the applicant respond to these comments with text versions in one week in order to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA/BLA submission. They can submit formatted versions in two weeks.

The comments below are based on DRISK's preliminary review of the REMS proposal for Adempas. Appended to this review is the REMS proposal Bayer HealthCare Pharmaceuticals Proposed REMS Prescriber Enrollment and Agreement Form, Prescriber Guide, Patient Enrollment Guide, Patient Enrollment and Consent Form, Patient Re-enrollment Form, REMS Website and the REMS Supporting Document including our track changes and comments (see Attachments). The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

5 COMMENTS FOR THE APPLICANT

5.1 ELEMENTS TO ASSURE SAFE USE

5.1.1 Pharmacy certification

Inpatient Pharmacies

The Agency is internally discussing certification details regarding dispensing Adempas to inpatient pharmacies. This includes discussion of the certification process and how that impacts timeliness and delivery of the medication. We will send comments regarding this aspect of the REMS, including a draft of the inpatient pharmacy enrollment form, in the next two weeks. However, all pharmacies that dispense Adempas will be certified; enrollment is part of the certification process. Audit plans should include all types of certified pharmacies, including inpatient settings.

Pharmacy Enrollment Expectations

(b) (4)

[redacted]

5.1.2 Definitions of FRP and FNRP

You have proposed (b) (4) [redacted] The Agency is currently recommending that there be two subcategories under FNRP. One is Prepubertal, the other is the Menopausal. These definitions need to remain consistent with those used in similar REMS programs. The definitions throughout your REMS document, REMS Supporting Document, and all educational materials should include the definitions as described in the first set of Interim Comments as follows:

Females of Reproductive Potential

- Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause (as defined below).
- For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)

Females of Non- Reproductive Potential (FNRP)

- Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Post-Menopausal Female: Females who have passed through menopause

Menopause

Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or postsurgical from bilateral oophorectomy.

Revise all REMS documents with these definitions accordingly.

5.2 WEBSITE

Edits were made to the website for consistency with information and language contained in other Adempas materials for patients and prescribers. The Agency will provide more comments when you provide screen shots and the layout for the website. Use bullets, white space, and fewer lines of text when possible when developing your website. Provide links when referencing other materials.

5.3 GENERAL COMMENTS

See all the attached REMS draft materials for further comments and instruction on how to design these materials and what information should be included.

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Adempas with attached materials and the REMS Supporting Document; this should be submitted officially to the NDA. In addition, provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. For the REMS document, the tracked changes version was used to make comments and edits. New FDA comments are in red text. For the REMS materials, the clean versions were used to make comments and edits. For all documents, please accept changes and work in tracked changes for the next version.

Submit the REMS and the REMS Supporting Document as two separate MS Word documents. 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 be in a single MS Word document.

Please refer to the attachments for detailed edits and recommendations.

6 REMS SUPPORTING DOCUMENT

The REMS Supporting Document must be consistent with all changes made to the REMS document.

ATTACHMENTS

1. REMS Document
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/s/

SOMYA V DUNN
09/05/2013

KIMBERLY LEHRFELD
09/06/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	September 5, 2013
Reviewer:	Somya Dunn, M.D. Division of Risk Management (DRISK)
Team Leader:	Kim Lehrfeld, Pharm.D., DRISK
Division Director	Claudia Manzo, Pharm.D., DRISK
Drug Name(s):	Adempas® (riociguat)
	BAY 63-2521
Therapeutic Class:	Soluble Guanylate Cyclase Stimulator
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Submission Number:	Supporting Document 1 (Sequence 0000)
Applicant/sponsor:	Bayer HealthCare Pharmaceuticals
OSE RCM #:	2013-969

CONTENTS

EXECUTIVE SUMMARY

1 INTRODUCTION

The purpose of this review is to evaluate the need for a Risk Evaluation and Mitigation Strategy (REMS) for Adempas® (riociguat) oral tablets. The New Drug Application (NDA 204-819) was submitted by Bayer HealthCare Pharmaceuticals (Bayer). The NDA was submitted and received on February 8, 2013.

The application is currently under review in the Division of Cardiovascular and Renal Products (DCRP) for treatment of pulmonary arterial hypertension (PAH). If approved, Adempas will be indicated to treat persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) after surgical treatment, or to treat inoperable CTEPH to improve exercise capacity and WHO functional class. It will also be indicated for Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.

The Sponsor has included a proposed REMS in the submission for the risk of teratogenicity based upon request by the FDA at a PreNDA meeting.

1.1 BACKGROUND

Adempas, riociguat, is a new molecular entity and a proposed first-in-class medication; it is a soluble guanylate cyclase (sGC) stimulator that increases vascular sensitivity to nitric oxide (NO). Guanlyate cyclase is an enzyme in the cardiopulmonary system and is also the receptor for NO. It acts along a pathway that leads to increased intracellular cGMP which plays an important role in regulating vascular tone, proliferation, fibrosis and inflammation. Adempas results in pulmonary vasodilation and also has a cellular antiproliferative effect.

Several drugs are approved to treat PAH-WHO Group 1 for improvement in symptoms and delay in clinical worsening. There are a variety of therapies including oral agents (bosentan, ambrisentan, sildenafil, tadalafil), inhaled agents (iloprost, treprostinil) and parenteral agents (epoprostenol, treprostinil). Though the population of patients with PAH and CTEPH is not large, treatment options for PAH are limited. In addition, there are currently no medications available to treat CTEPH. Expected duration of treatment would be chronic administration as these conditions have no cure, have significant morbidity and mortality and can result in right heart failure.

Of note, both bosentan and ambrisentan, classified as endothelin receptor antagonists (ERAs), were found to be teratogens in animal studies. In animal studies, ERAs were associated with abnormalities of the lower jaw, hard and soft palate, malformation of the heart and great vessels and failure of formation of the thymus and thyroid. Adempas will be a first-in-class medication and it is not an ERA; however, it is targeted at the same patients that are taking ERAs (PAH patients). The teratogenic signal seen in Adempas in preclinical studies is different than that seen with the ERAs. Adempas was found to be associated with ventricular septal defects (VSDs) and bone malformations in rat studies.

Adempas was studied in patients with CTEPH, WHO Group 4 and PAH, WHO Group 1. The primary endpoint in both populations was change from baseline in 6 Minute Walk Distance (6MWD). The drug product proposed for marketing is an immediate release, film-coated tablet for oral use. The proposed dosing is 1 mg three times a day. This dose can be increased in 0.5 mg increments at two week intervals to a maximum dose of 2.5 mg three times a day. The tablet strengths are 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg.

1.2 REGULATORY HISTORY

- October 2008 End of Phase II meeting held at FDA—The Sponsor presented the clinical development program for Adempas. They put forth their planned program for two randomized, double-blind, placebo-controlled clinical trials. Important topics that were agreed upon included statistical plans and the primary endpoint of a six minute walk distance (6MWD) for CTEPH.
- Nov 2012 and Dec 2012—Pre NDA meeting comments provided and subsequent teleconference occurred. The Sponsor was informed that a REMS would likely be necessary to ensure that the benefits of the drug outweigh the risk of embryo-fetal toxicity. The Sponsor was encouraged to submit a proposed REMS in the NDA.
- February 8, 2013—Application received
- March 10, 2013—Application filed
- May 10, 2013—The Agency had a post mid-cycle teleconference with the Sponsor. The Sponsor was informed that the need for a REMS was being discussed internally and that their proposed REMS was under review. They were also informed that comments regarding the REMS were forthcoming.
- July 11, 2013—Late-Cycle Meeting with Sponsor
- July 19, 2013—DRISK first set of REMS comments provided to Sponsor
- August 29, 2013—Wrap Up Meeting
- August 6, 2013—Advisory Committee meeting
- October 8, 2013—PDUFA action date

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The Sponsor's REMS proposal received on February 8, 2013 as part of the NDA was reviewed in full.

Other materials that informed this review were:

- Bayer HealthCare Pharmaceuticals. Clinical Overview for Adempas (riociguat), received February 8, 2013.
- Bayer HealthCare Pharmaceuticals. Summary of Clinical Safety for Adempas (riociguat), received February 8, 2013.
- Bayer HealthCare Pharmaceuticals. Summary of Clinical Efficacy for Adempas (riociguat), received February 8, 2013.
- Bayer HealthCare Pharmaceuticals. Draft Labeling for Adempas (riociguat), received February 8, 2013.

2.2 ANALYSIS TECHNIQUES

The need for a REMS and the proposed REMS were reviewed and evaluated under the provisions of Title IX, Subtitle A, section 901, of the Food and Drug Administration Amendments Act of 2007 (FDAAA).

In order to evaluate the need for a REMS and the REMS proposal, the prospective dispensing processes for Adempas, the safety profile of the drug and other drugs that have a REMS in place for teratogenicity were considered.

3 RESULTS OF REVIEW OF PROPOSED ADEMPAS RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM

The Adempas phase III clinical development program consisted of separate efficacy and safety studies in patients with CTEPH (Study 11348 [CHEST-1]) and PAH (Study 12934 [PATENT-1]). There were long term extension studies in both patient groups as well (studies 11349 [CHEST-2] and12935 [PATENT-2]) for evaluation of long term safety.

The efficacy of Adempas for the treatment of CTEPH and PAH is primarily based on CHEST-1 and CTEPH. Both studies had a similar design and used the same efficacy endpoints (primary endpoint change in baseline in 6MWD) which are widely accepted and used in the PAH population. The Sponsor asserts that both studies consistently demonstrated that treatment with Adempas was superior to placebo with respect to the primary endpoint 6MWD and to their pre-defined secondary endpoints. Please see Dr. Preston Dunnmon's review for the details on both the efficacy and safety of Adempas.

The main safety population in placebo controlled phase III studies consisted of 490 Adempas treated patients and 214 subjects with placebo from both phase III studies. This pool was referred to by the Sponsor as POOL-1.

The safety database of the CHEST and PATENT extension studies included 319 subjects with treatment duration of at least 48 weeks, 121 subjects with at least 96 weeks and 3 subjects with at least 144 weeks. These extension studies are ongoing.

3.2 SAFETY CONCERNS

In the CTEPH patients, differences in adverse events (AEs) ≥5% between the treatment groups, with higher incidence rates in the Adempas treatment group were reported for: headache (25% Adempas versus 14% placebo), dizziness (23% vs. 13%), dyspepsia (18% vs. 8%), nasopharyngitis (15% vs. 9%), diarrhea (10% vs. 5%), vomiting (10% vs. 3%), and hypotension (9% vs. 3%). In the PAH treated patients, AE differences ≥5% between the treatment groups, with higher incidence rates in the Adempas treatment group were headache (27% vs. 20%), dyspepsia (19% vs. 8%), peripheral edema (17% vs. 11%), anemia (8% vs. 2%), and hypotension (10% vs. 2%). Some AEs such as gastrointestinal effects and hypotension are expected due to the mechanism of action (smooth muscle dilating/relaxing).

There were a total of 12 deaths in the CHEST-1 and PATENT-1 studies; this was in POOL-1. Five of these were in Adempas treated patients. The causes/AEs leading to death in these five patients were cardiac failure, acute renal failure /deterioration of right heart failure, sepsis, right ventricular failure and hemoptysis. In the pooled analysis of both studies, serious adverse events (SAEs) other than death were reported for 15% of all Adempas treated subjects and for 17% of placebo subjects. The most common SAEs with an incidence rate ≥ 1% were syncope (1.4% Adempas vs. 3.7% placebo), right ventricular failure (2.2% Adempas vs. 1.9% placebo), and hemoptysis (1.0% Adempas vs. 0% placebo). Of note, there were three SAEs of renal failure in Adempas treated patients other than the one that led to death. There were also two cases that were SAEs of hypotension in Adempas treated patients and none in placebo. One of the cases was in a patient in a drug/drug interaction study with Adempas and nitroglycerin.

Overall, in POOL-1, the incidence rate of hypotension related events was 10.0% in all Adempas treated subjects versus 3.7% in all placebo subjects. As mentioned, two of these cases were SAEs. The vast majority of subjects in both treatment groups had one single hypotension event. The mean duration of the hypotension event was longer for Adempas treated subjects than for placebo (51 hours all Adempas vs. 1 hour placebo).

Treatment-emergent gastrointestinal disorders in POOL-1were reported in 52% of subjects in all Adempas treated subjects and 34% in the placebo group. Most of these events were non-serious. As mentioned, these types of event are likely related to mechanism of action as a smooth muscle dilator.

The mechanism is unclear, but there is a bleeding risk with Adempas (note the one SAE of hemoptysis); the Sponsor reports that in POOL-1, the incidence rate of bleeding events was 15.7% in all Adempas treated subjects versus 14.5% in placebo subjects. The AE of anemia had a higher rate in the Adempas group (7.8%) compared to placebo (1.9%).

Preclinical data suggests that Adempas affects cardiac formation and bone metabolism. In rat studies, there were VSDs and incomplete ossification of the 4^{th} vertebral arches. The incidence of wavy ribs was increased in all drug-treated groups although not in a dose response manner. Please see Dr. Elizabeth Hausner's review for full details. Overall, the bone findings are difficult to characterize, but Adempas is definitively considered a teratogen. In addition, the safety in terms of bone metabolism effects in growing children is unknown.

The Sponsor discusses these safety concerns in the proposed label draft. They propose to include respiratory tract bleeding under *Warnings and Precautions*. They also contraindicate Adempas with nitrates or nitric oxide medications; this is due to the increased risk of hypotension. Under *Use in Specific Populations*, they propose including a recommendation for patients with low blood pressure, renal impairment and women of childbearing potential. The labeling proposal is still under review in DCRP. Most of the safety concerns will be addressed with labeling and post marketing study requirements; however, the details of the label and the specific post marketing study requirements (PMRs) are still under discussion.

3.3 RATIONALE FOR THE ADEMPAS REMS FOR TERATOGENICITY

The Adempas REMS is necessary to ensure the benefits outweigh the risk of teratogenicity. The risk of teratogenicity is particularly concerning as there are females of reproductive age affected by PAH, though fewer are affected by CTEPH. In addition, there are PAH affected pediatric patients whose reproductive status changes with onset of puberty. VSD and bone effects in animal studies may translate to similar, less or worse effects in humans. There is no human data to evaluate. If the VSDs seen in animal studies occurred in human fetuses, infants may experience failure to thrive, resultant growth and development issues, or could eventually suffer from congestive heart failure. The bone effects may result in growth problems or bone fragility in developing fetuses. These potential adverse effects may impact quality of life for these children for years to come.

Expected benefit of Adempas outweighs the risk of teratogenicity if there is a program in place that can potentially minimize fetal exposure. Labeling provides information to the practitioner but does not offer any active processes to reduce risk. In this case, a REMS program will evoke a behavioral change, both to the patient (by taking pregnancy tests and using birth control) and in prescribing practices (by requiring education and certification). These interventions serve to mitigate the risk of teratogenicity. Furthermore, there are two approved treatments for PAH with REMS for teratogenicity (ERAs). These medications are prescribed by the same prescribing population that will prescribe Adempas. Therefore, they are familiar with the requirements of this type of REMS.

3.4 PRODUCTS WITH SIMILAR REMS PROGRAMS

Letairis® and Tracleer®, two ERAs approved for treatment of PAH, have REMS programs for teratogenicity.

Currently, these programs consist of the following:

- Medication Guide (MG)
- Elements to Assure Safe Use
    - Prescriber Certification
    - Pharmacy Certification
    - Documentation of Safe Use Conditions
- Implementation System
- Timetable for Submission of Assessments

3.5 PROPOSED ADMEPAS REMS

The Sponsor has proposed a REMS with identical components as the ERA REMS for teratogenicity that are currently approved. The proposed REMS consists the following:

- MG
- Elements to Assure Safe Use
    - Prescriber Certification

Prescribers must complete a Prescriber Enrollment and Agreement Form and agree to:

- Read the full prescribing information (PI) and MG
- Review MG with each patient
- (b) (4)
- Educate (b) (4) about risk of embryo-fetal toxicity and the need for reliable contraception
- Order pregnancy test prior to and monthly during treatment
- Counsel (b) (4) patient if not compliant with testing or contraception
- Report AEs/pregnancies to FDA
- Monitor for changes in childbearing potential status

o Pharmacy Certification

- (b) (4)
- Counsel and inform (b) (4) on risks and need for monthly pregnancy test
- Notify Sponsor of AEs or reports of pregnancy

o Documentation of Safe Use Conditions

Patients are enrolled by completing a Patient Enrollment Form.

(b) (4) must agree to:

- Pregnancy testing
- Be counseled on REMS requirements and risks
- Be contacted by Sponsor should she become pregnant while taking the medication or within 30 days after discontinuing
- (b) (4)

- Implementation System

The Sponsor plans to:

- Maintain a database of certified dispensers, prescribers, and enrolled patients
- Ensure the drug is only distributed to certified dispensers

- Track dispensing
- Monitor and evaluate the REMS and take steps to improve as needed
- Monitor certified dispensers to ensure compliance

- Assessments

  The proposed assessment plan includes surveys designed to assess prescribers' and patients'awareness of the REMS materials and requirements. The plan also includes evaluation of prescriber and pharmacy noncompliance with the REMS program and a root cause evaluation of noncompliance.

  The Timetable for Submission of Assessments is proposed to be provided at six months, 12 months and then annually thereafter from the date of initial approval of the REMS.

Although the REMS components proposed for Adempas are identical to that of the ERAs, some specifics of the program will be different and these are discussed in detail below.

3.5.1 Enrollment of at-risk patient population

(b) (4)

The Agency held a DSaRM Advisory Committee meeting (AC) in December 2012 which focused on teratogenicity. One of the topics discussed involved the target population for REMS that are in place for teratogenicity. The AC recommendation was to target the REMS to the affected population (in this case, females). These discussions expanded through the Agency and involved senior management. Overall, the Agency recommends that the REMS should be targeted to the at-risk population. Furthermore, the Agency recommends the PAH REMS programs should be aligned since they treat similar patient populations and all address the risk of teratogenicity.

Reviewer Comments— (b) (4) *he program should be targeted at the at-risk population—females; males will not need to be enrolled in the REMS program. Enrolling all females may help prevent misclassification errors, and ensure females who have not yet undergone puberty are adequately counseled. All females should be enrolled but REMS requirements will be directed at females that fall within specific classification categories.*

3.5.2 Terminology utilized for female reproductive status

The Sponsor used the previously agreed upon definition to define females of reproductive potential (FRP), (b) (4)

Reviewer Comments: *These definitions have been clarified by the Agency after discussions at the aforementioned December 2012 AC. The following categories should*

be used to define FRP and females of non-reproductive potential (FNRP) and will be utilized by the Sponsor to guide the prescriber and pharmacies in the REMS.

Females of Reproductive Potential (FRP)

- Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause (as defined below).

- For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)

Females of Non Reproductive Potential (FNRP)

- Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential

- Post-Menopausal Female: Females who have passed through menopause

3.5.3 Reassess female reproductive status annually

(b) (4)

3.5.4 Goals

The Sponsor proposed the following goal for the riociguat REMS program:

To minimize the risk of fetal exposure and adverse fetal outcomes in (b) (4) prescribed riociguat:

a. (b) (4) who are pregnant should not be prescribed riociguat

b. (b) (4) taking riociguat should not become pregnant

Reviewer Comments: This program should also have a goal to inform prescribers, patients and pharmacists about the serious risk of teratogenicity. This is an essential part of the REMS as information and education are key to ensuring safe use of this medication

and for making informed decisions, both for providers and patients. The revised Goal is as follows:

> The risk minimization goals of the Adempas Risk Evaluation and Mitigation Strategy (REMS) are:
>
> 1. To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Adempas
> 2. To minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential prescribed Adempas
>   a. Females who are pregnant should not be prescribed Adempas
>   b. Females taking Adempas should not become pregnant

4 DISCUSSION

Adempas is a first in class medication currently under review for the treatment of PAH and CTEPH. It has the risk of teratogenicity similar to other treatments for PAH despite the different mechanism of action. Though the actual teratogenic signal was different with the ERAs, the REMS can be designed similarly. The risk of teratogenicity rises to the need for a REMS to ensure that the benefits of use outweigh this risk.

Other risks seen in the clinical program such as hypotension, gastrointestinal disorders and drug interaction risks can be conveyed in labeling. Safety in special populations, such as pediatrics and/or bone safety may need to be further assessed in PMRs.

As with the ERAs, each ETASU element will serve a significant role in mitigation of the risk of teratogenicity.

- Prescriber certification ensures that prescribers are aware of the serious risk, understand how to appropriately mitigate the risk, and educate their patients who are at risk about how the risk can be mitigated.

- Pharmacy certification ensures that riociguat is only dispensed for female patients who are enrolled in the program and receive a prescription from a REMS certified physician. The pharmacy is also responsible for ensuring that appropriate pregnancy testing is completed prior to dispensing drug by contacting the patient. The limited day supply ensures that FRPs are contacted prior to receiving additional medication.

- Documentation of Safe Use ensures all female patients are enrolled in the program and appropriate classified into one of three categories (described above). Based on the category they are assigned to, the certified physician ensures they receive appropriate counseling regarding the risk of teratogenicity. Additionally, the Patient Enrollment Form ensures patients are adequately informed about the risk of teratogenicity. For females of reproductive potential, pregnancy testing and contraception use is documented to mitigate the risk of teratogenicity while receiving riociguat.

Limitations of this program include the lack of direct communication between the pharmacy that is dispensing the medication and the physician that is reviewing the pregnancy test, i.e., there is no confirmation that the test is negative when the medication is dispensed. This checkpoint is not in place and may not be practical to implement due to burden on pharmacy and physician. Thus far, however, the assessment information from Letairis and Tracleer do not indicate that this process needs to be revised as this time.

DRISK has been in discussion with DCRP regarding the REMS and are in agreement. The proposed REMS and the DRISK/DCRP recommendations were presented to senior management on June 19, 2013and they are in agreement with the DRISK/DCRP recommendations.

5 CONCLUSION/RECOMMENDATIONS

In conclusion, the proposed REMS for Adempas® (riociguat; BAY 63-2521), NDA 204-819 (Sequence 0000), contains the appropriate REMS components. These include a Medication Guide and three ETASU—prescriber certification, pharmacy certification and documentation of safe use. [redacted] (b) (4) . In addition, the terminology for female reproductive potential status has been revised to reflect current Agency thinking. The REMS Supporting Document will outline the information and content that the applicant will use to assess the effectiveness of Adempas REMS in achieving the goals.

The OSE DRISK recommends a REMS for Adempas for the risk of teratogenicity. Review and evaluation regarding details of the REMS program and the assessment plan and metrics are still underway. Our recommendations for the Action Letter will be forthcoming. An addendum to this review will contain the final REMS document, all appended materials as well the finalized assessment plan.

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

/s/

SOMYA V DUNN
09/05/2013

CLAUDIA B MANZO
09/05/2013
concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Interim Comments on Risk Evaluation and Mitigation Strategy (REMS) Set # 1

Date:	July 18, 2013
Reviewer:	Somya Dunn, M.D. Division of Risk Management (DRISK)
Team Leader:	Kimberly Lehrfeld, Pharm.D., DRISK
Division Director	Claudia Manzo, Pharm.D., DRISK
Drug Name(s):	Adempas® (riociguat)
	BAY 63-2521
Therapeutic Class:	Soluble Guanylate Cyclase Stimulator
Dosage and Route:	Applicant Proposal: 1 mg three times a day to a maximum dose of 2.5 mg three times a day
	Oral tablet strengths: 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg
Application Type/Number:	NDA 204-819
Submission Number:	Supporting Document 1 (Sequence 0000)
Applicant/sponsor:	Bayer HealthCare Pharmaceuticals
OSE RCM #:	2013-969

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

1 INTRODUCTION

The purpose of this review is to document interim comments for the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) for Adempas® oral tablets. The New Drug Application (NDA 204-819) was submitted by Bayer HealthCare Pharmaceuticals (Bayer). The NDA was submitted and received on February 8, 2013.

The application is currently under review in the Division of Cardiovascular and Renal Products (DCRP) for treatment of pulmonary arterial hypertension. The Sponsor has included a proposed REMS for the risk of teratogenicity in the submission.

2 MATERIALS REVIEWED

Sponsor's REMS Proposal including:

- Bayer HealthCare Pharmaceuticals Proposed REMS
- Bayer HealthCare Pharmaceuticals Prescriber Enrollment and Agreement Form
- Bayer HealthCare Pharmaceuticals Prescriber Guide, Patient Enrollment Guide
- Bayer HealthCare Pharmaceuticals Patient Enrollment and Consent Form
- Bayer HealthCare Pharmaceuticals Patient Re-enrollment Form
- Bayer HealthCare Pharmaceuticals REMS Supporting Document

All REMS related documents were received as part of the NDA on February 8, 2013

3 SUMMARY OF APPLICANT'S PROPOSED REMS

The goal of the Sponsor's proposed riociguat REMS program is:

To minimize the risk of fetal exposure and adverse fetal outcomes in (b) (4)

a. (b) (4) who are pregnant should not be prescribed riociguat

b. (b) (4) taking riociguat should not become pregnant

The Sponsor has proposed a Medication Guide (MG) and the following Elements to Assure Safe Use (ETASU)

- ETASU A – Prescriber Certification
- ETASU B – Pharmacy Certification
- ETASU D – Documentation of safe use conditions

The Sponsor proposed an Implementation System that includes a tracking system. They also proposed a Timetable for Submission of Assessments which are planned to be provided at six months, 12 months and then annually thereafter from the date of initial approval of the REMS.

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Adempas REMS proposal be sent to the applicant. Please request that the applicant respond to these comments in two weeks in order to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA/BLA submission.

The comments below are based on DRISK's preliminary review of the REMS proposal for Adempas. Appended to this review is the REMS proposal Bayer HealthCare Pharmaceuticals Proposed REMS Prescriber Enrollment and Agreement Form, Prescriber Guide, Patient Enrollment Guide, Patient Enrollment and Consent Form, Patient Re-enrollment Form and the REMS Supporting Document including our track changes and comments (see Attachments). The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

5 COMMENTS FOR THE APPLICANT

5.1 GOALS

You propose the goal of minimizing the risk of fetal exposure and related outcomes. This program should also have a goal to inform prescribers, patients and pharmacists about the serious risk of teratogenicity. This is an essential part of the REMS as information and education are key to ensuring safe use of this medication and for making informed decisions, both for providers and patients.

Revised Goals:

The risk minimization goal of the Adempas Risk Evaluation and Mitigation Strategy (REMS) is:

1. To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Adempas
2. To minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed Adempas
    a. Females who are pregnant should not be prescribed Adempas
    b. Females taking Adempas should not become pregnant

5.2 ELEMENTS TO ASSURE SAFE USE

We agree with the proposed ETASU. However, the following modifications will need to be made to your proposed plan.

(b) (4)

- All females should be enrolled in the Adempas REMS to prevent misclassification errors and ensure females who have not yet undergone puberty are adequately counseled. This recommendation is consistent the recommendations from the FDA Drug Safety and Risk Management (DSaRM) Advisory Committee meeting in December 2012 to target the REMS at the at-risk population.

- Your proposed REMS uses (b) (4) and previously agreed upon definitions. The term (b) (4) has been changed to FRP (females of reproductive potential). In addition, the Agency has further clarified these definitions based on the DSaRM Advisory Committee meeting in December 2012. These definitions are as follows:

Females of Reproductive Potential

- Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause (as defined below).
- For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)

Females of Non- Reproductive Potential (FNRP)

- Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Post-Menopausal Female: Females who have passed through menopause

Menopause

Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or postsurgical from bilateral oophorectomy.

- As part of the ETASU for both Prescriber and Pharmacy certification, there will need to be educational materials. Comments related to these materials are below.

  – Website (see Attachment 7)

  In addition to what you proposed, you will need to develop an Adempas REMS website to provide information that both providers and patients can use to inform themselves about the REMS. We recommend that you include a prominent link on the product website's homepage for REMS materials. This link should direct users to a separate REMS dedicated website that provides the information that both providers and patients can use to inform themselves about the REMS. Please note, the Adempas REMS website should also be accessible directly through a search engine. We have included a mock up example of what your REMS website could look like, and the links that it should include (Attachment 7).

The FOR PRESCRIBERS link should bring the provider to goals and overview of the REMS and include a way to download REMS materials.

The FOR FEMALE PATIENTS link should bring the patient to a description of the rationale behind the REMS and the rules that the patients must follow. There should also be a link to download patient materials.

– Patient and Prescriber Guides (see Attachments 3 and 6 for detailed comments regarding these documents)

Please note the attached Contraceptive Table (Attachment 8) shows the concept of birth control options for patients. We recommend using these concepts in the patient and prescriber materials as appropriate, to explain the acceptable forms of birth control, replacing the current contraception charts. Bayer should use the options concept as shown, but create a user friendly design (e.g., using colors, layout, formatting) that makes the charts easy to follow and will match the look and feel of your current program materials.

5.3 IMPLEMENTATION SYSTEM

No comments.

5.4 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

No comments.

5.5 INFORMATION NEEDED FOR ASSESSMENT

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

4. An evaluation of healthcare providers' awareness and understanding of:

    a. The risk of teratogenicity associated with riociguat

    b. The need to exclude a pregnancy before initiating riociguat therapy

    c. The need for patients to consistently use effective birth control and what the effective methods of contraception are

    d. The need to promptly discontinue riociguat therapy in the event of a pregnancy

5. 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

6. Patient demographics for the current REMS assessment reporting period and for previous REMS assessment reporting periods to include gender, age, diagnosis, and the percentage number (%) of females of reproductive potential

7. An evaluation of any shipment holds due exclusively to the absence of pregnancy test results, which resulted in an actual treatment interruption and a summary of root cause analysis and any adverse events resulting from the treatment interruption.

8. The frequency and reasons for dispensing >30 day supply to females of reproductive potential

9. 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

10. Reports of critical observations identified during operational monitoring, including results of distribution data reconciliation

11. Critical observations identified during Regulatory Compliance Audits and corrective actions taken to address any non-compliance.

12. An analysis of the post-marketing cases of pregnancy reported in association with Riociguat (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 cumulatively) and stratified by source (spontaneous report, reported via the REMS call center, enrolled in the pregnancy registry), age, and other demographics.

    b. The pregnancy outcome for each exposed pregnancy reported (during the reporting period and cumulative).

    c. Follow-up of outstanding pregnancy reports from the previous assessment reporting period;

    d. Root cause analysis of each reported pregnancy to determine the reason the REMS failed to prevent the pregnancy exposure; and

    e. Discussion of any new information provided in the most recent Periodic Safety Update Report (PSUR) regarding pregnancy. In the electronic REMS assessment submission, include a hyperlink to the most recent PSUR that provides information on worldwide pregnancies.

        *All pregnancy exposures reported to the sponsors from any source should be reported and analyzed as part of the REMS assessment. Pregnancy exposures will be recorded within the REMS database as well as the global safety database, with appropriate linkage to allow matching of the

cases reported in the REMS database to cases in the global safety database.

13. 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

5.5.1 Surveys

Surveys should be designed to gather the data needed for assessments.

5.6 GENERAL COMMENTS

See all the attached REMS draft materials for further comments and instruction on how to design these materials and what information should be included.

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Adempas with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents. 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 be in a single MS Word document.

6 REMS SUPPORTING DOCUMENT

The REMS Supporting Document must be consistent with all changes made to the REMS document. See Attachment 9.

ATTACHMENTS

1. Proposed REMS
2. REMS Patient Enrollment and Consent Form
3. REMS Patient Enrollment Guide
4. REMS Patient Re-enrollment Form
5. REMS Prescriber Enrollment and Agreement Form
6. REMS Prescriber Guide
7. Riociguat REMS Website Example
8. Riociguat Contraception Options Chart
9. REMS Supporting Document

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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.

/s/

SOMYA V DUNN
07/19/2013

KIMBERLY LEHRFELD
07/19/2013