HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ADEMPAS safely and effectively. See full prescribing information for ADEMPAS.

ADEMPAS (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: EMBRYO-FETAL TOXICITY
See full prescribing information for complete boxed warning

- **Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)**
- **Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, 8.6)**
- **For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration	
Recommended Dosage in Adult Patients (2.1)	2/2017
Transitioning to and from Adempas (2.6)	1/2017
Contraindications (4.4)	1/2017

---------- INDICATIONS AND USAGE ----------

Adempas is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with:

- Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class. (1.1)
- Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening. (1.2)

---------- DOSAGE AND ADMINISTRATION ----------

- Initiate treatment at 1 mg taken three times a day. (2.1)
- For patients who may not tolerate the hypotensive effect of Adempas, consider a starting dose of 0.5 mg, three times a day. (2.1)
- Increase dosage by 0.5 mg at intervals of no sooner than 2-weeks as tolerated to a maximum of 2.5 mg three times a day. (2.1)
- Tablets may be crushed and mixed with water or soft foods for patients who have difficulty swallowing. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg (3)

---------- CONTRAINDICATIONS ----------

- Pregnancy (4.1)
- Use with nitrates or nitric oxide donors in any form (4.2, 7.1)
- Use with PDE inhibitors (2.6, 4.3, 7.1)
- Pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP) (4.4)

---------- WARNINGS AND PRECAUTIONS ----------

- Symptomatic hypotension (5.3)
- Bleeding (5.4)
- Pulmonary edema in patients with pulmonary veno-occlusive disease. If confirmed, discontinue treatment (5.5)

---------- ADVERSE REACTIONS ----------

Adverse reactions occurring more frequently (≥3%) on Adempas compared to placebo are headache, dyspepsia/gastritis, dizziness, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Strong CYP and P-gp/BCRP inhibitors: For patients receiving strong CYP and P-gp/BCRP inhibitors, consider a starting dose of 0.5 mg three times a day. Monitor for hypotension. (7.2)
- Antacids: Separate administration by at least 1 hour. (7.2)

---------- USE IN SPECIFIC POPULATIONS ----------

- Nursing mothers: Discontinue drug or breastfeeding. (8.3)
- Renal impairment: Not recommended in patients with creatinine clearance <15 mL/min or on dialysis. (8.7)
- Hepatic impairment: Not recommended in patients with severe (Child Pugh C) hepatic impairment. (8.8)
- Smoking: May require dosages higher than 2.5 mg three times a day if tolerated. Dose decrease may be required in patients who stop smoking. (2.4, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 02/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas to a pregnant female because it may cause fetal harm *[see Contraindications (4.1), Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception *[see Dosage and Administration (2.3), Warnings and Precautions (5.1, 5.2),and Use in Specific Populations (8.6)]*.

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program *[see Warnings and Precautions (5.1, 5.2)]*.

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class *[see Clinical Studies (14.1)]*.

1.2 Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Adult Patients

The recommended starting dosage is 1 mg taken 3 times a day. For patients who may not tolerate the hypotensive effect of Adempas, consider a starting dose of 0.5 mg taken three times a day. If systolic blood pressure remains greater than 95 mmHg and the patient has no signs or symptoms of hypotension, up-titrate the dose by 0.5 mg taken three times a day. Dose increases should be no sooner than 2 weeks apart. The dose can be increased to the highest tolerated dosage, up to a maximum of 2.5 mg taken three times a day. If at any time, the patient has symptoms of hypotension, decrease the dosage by 0.5 mg taken three times a day.

Crushed Tablets

For patients who are unable to swallow whole tablets, Adempas may be crushed and mixed with water or soft foods (such as applesauce) immediately before administration *[see Clinical Pharmacology (12.3)]*.

2.2 Dosage Interruption

If a dose is missed, advise patients to continue with the next regularly scheduled dose.

In case Adempas is interrupted for 3 days or more, re-titrate Adempas.

2.3 Pregnancy Testing in Females of Reproductive Potential

Obtain pregnancy tests prior to initiation and monthly during treatment *[see Use in Specific Populations (8.6)]*.

2.4 Use in Patients who Smoke

Consider titrating to dosages higher than 2.5 mg three times a day, if tolerated, in patients who smoke. A dose decrease may be required in patients who stop smoking *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

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2.5 Strong CYP and P-gp/BCRP Inhibitors

Consider a starting dose of 0.5 mg, three times a day when initiating Adempas in patients receiving strong cytochrome P450 (CYP) and P-glycoprotein/breast cancer resistance protein (P-gp/BCRP) inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (for example, ritonavir). Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors *[see Warnings and Precautions (5.3), Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

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)]*. It is recommended to monitor for signs and symptoms of hypotension on initiation.
- Discontinue Adempas at least 24 hours prior to administering a PDE5-inhibitor *[see Dosage and Administration (2.1), Contraindications (4.3), and Drug Interactions (7)]*. It is recommended to monitor for signs and symptoms of hypotension on initiation.

3 DOSAGE FORMS AND STRENGTHS

Tablets: film-coated, round, bi-convex:

- 0.5 mg, white, with “BAYER” cross on one side and “0.5” and “R” on the other side
- 1 mg, pale-yellow, with “BAYER” cross on one side and “1” and “R” on the other side
- 1.5 mg, yellow-orange, with “BAYER” cross on one side and “1.5” and “R” on the other side
- 2 mg, pale orange, with “BAYER” cross on one side and “2” and “R” on the other side
- 2.5 mg, red-orange, with “BAYER” cross on one side and “2.5” and “R” on the other side

4 CONTRAINDICATIONS

4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

4.3 Phosphodiesterase Inhibitors

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

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5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program *[see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)]*.

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program *[see Warnings and Precautions (5.1)]*.

Important requirements of the Adempas REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

5.5 Pulmonary Veno-Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Bleeding *[see Warnings and Precautions (5.4)]*

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6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years *[see Clinical Studies (14.1, 14.2)]*.

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse reactions in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo (Pooled from CHEST-1 and PATENT-1)

Adverse Reactions	Adempas % (n=490)	Placebo % (n=214)
Headache	27	18
Dyspepsia and Gastritis	21	8
Dizziness	20	13
Nausea	14	11
Diarrhea	12	8
Hypotension	10	4
Vomiting	10	7
Anemia (including laboratory parameters)	7	2
Gastroesophageal reflux disease	5	2
Constipation	5	1

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

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 within 48 hours after tadalafil *[see Dosage and Administration (2.6)]*. Clinical experience with co-administration of Adempas and other phosphodiesterase inhibitors

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