Pulmonary hypertension is a serious and life-threatening condition that is caused by increased pressure on the pulmonary arteries. The World Health Organization (WHO) has divided pulmonary hypertension into 5 subgroups, including pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), based on the causes and treatment options.

PAH occurs when the blood pressure in the pulmonary arteries is high. Abnormal constriction of the pulmonary arteries impairs oxygen delivery to the body and exacerbates heart function. Over time, PAH progresses and can become life-threatening.

PAH is a rare disease affecting 1 in 100,000 to 1 million people of all ages and ethnic backgrounds. The condition is more common in women than in men. The symptoms of PAH can be nonspecific, similar to those of other heart and lung problems. Common complaints of patients with PAH include chest pain, dizziness, fainting, fatigue, leg swelling, and weakness, as well as light-headedness and shortness of breath during physical activity.

Although there is no cure for PAH, several treatment options are available, including medications and surgery, as well as lifestyle changes. The primary goals of PAH treatment are to reduce symptoms, slow disease progression, and improve quality of life. The medications used to manage PAH include endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors, prostacyclins, anticoagulants, calcium channel blockers, diuretics, digoxin, and inhaled oxygen.

Treatment decisions are based on multiple factors, including functional status severity, which ranks a patient’s ability to complete everyday tasks and ranges from class I (ie, no limitations) to class IV (ie, inability to perform any physical activity).

Since their introduction, targeted therapies have improved survival, exercise capacity, functional capacity, and hemodynamics in patients with PAH. However, current treatments remain inadequate: mortality continues to be high (approximately 1.5%), and functional and hemodynamic impairment can remain significant for many patients with PAH.

A recent study regarding the cost burden of PAH among privately insured Americans has demonstrated that PAH is a costly condition. In this 2011 study, patients with PAH incurred significantly higher costs as a result of their disease and the comorbidities associated with PAH. The average monthly direct costs were more than $2000 in patients with PAH compared with approximately $500 for patients without PAH. For patients with PAH, almost half (45%) of their monthly direct costs were associated with inpatient services, 38% were for outpatient and other services, and 15% were for prescription medications.

CTEPH is a serious condition and is one of the leading causes of severe pulmonary hypertension. CTEPH occurs in 2% to 4% of patients who have had an acute pulmonary embolism (PE), and is characterized by mean pulmonary artery pressure of >25 mm Hg that continues for 6 months after a diagnosis of PE. Risk factors for CTEPH include thyroid disease, thrombophilia, and genetics.

In CTEPH, pulmonary endarterectomy is the only option for cure. However, some patients are unable to undergo or decline surgery, whereas others are unable to access specialty centers.

Adempas: A Novel Approach to Managing Pulmonary Hypertension

On October 8, 2013, the US Food and Drug Administration (FDA) approved riociguat (Adempas, Bayer Healthcare) for the treatment of (1) adults with persistent and recurrent CTEPH (WHO group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class, and (2) for patients with PAH (WHO group 1) of unknown causes, inherited PAH, or PAH associated with connective tissue disease, to improve their exercise capacity, improve WHO functional class, and to delay the clinical worsening of PAH.

Riociguat is the first agent approved by the FDA in a drug class known as soluble guanylate cyclase (sGC) stimulators. sGC helps arteries relax to increase blood flow and to decrease blood pressure. Norman Stockbridge, MD, PhD, Director, Division of Cardiovascular and Renal Drug Products in the FDA’s Center for Drug Evaluation and Research, recently discussed riociguat’s
novelty, stating, “Adempas is the first in its drug class approved to treat pulmonary hypertension and the first drug of any class to be shown to be effective for patients with CTEPH.” The FDA approved riociguat under its priority review, which is an expedited 6-month process to enable access to drugs that may offer major advances in treatment.7

The FDA approval of riociguat for patients with CTEPH or PAH was based on demonstration of safety and efficacy in 2 phase 3 clinical trials known as the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1) and the Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (PATENT-1).6,7,9 The primary efficacy measure in both studies was change in 6-minute walk distance.6,9 When discussing the PATENT-1 study findings, principal investigator Hossein-Ardeschir Ghofrani, MD, Department of Internal Medicine, University Hospital Giessen and Marburg, Germany, stated, “The six-minute walk test is a key indicator for improved outcomes in patients with PAH and, therefore, the positive results of the PATENT-1 trial are encouraging.”10

**Mechanism of Action**

sGC is an enzyme in the cardiopulmonary system. When nitric oxide (NO) binds to sGC, cyclic guanosine monophosphate (cGMP) is synthesized. In turn, cGMP, a signaling molecule, regulates intracellular processes that affect vascular tone, proliferation, fibrosis, and inflammation.8

Endothelial dysfunction, impaired synthesis of NO, and insufficient stimulation of the NO-sGC-cGMP pathway are associated with pulmonary hypertension.8

Riociguat has a dual mode of action. By stabilizing NO-sGC binding, riociguat sensitizes sGC to endogenous NO. Via a binding site that is independent of NO, riociguat also directly stimulates sGC. By stimulating the NO-sGC-cGMP pathway, riociguat increases the generation of cGMP and vasodilation.8

**Dosing and Administration**

The initial dose of riociguat is 1 mg 3 times daily.8 Patients who cannot tolerate riociguat’s hypotensive effect can be started at a dose of 0.5 mg 3 times daily.8 Riociguat doses can be increased by 0.5 mg at 2-week intervals and up to a maximum dose of 2.5 mg 3 times daily, depending on the blood pressure level.8

**Key Clinical Trials**

**PATENT-1: Phase 3 Trial in PAH**

In this 12-week, phase 3, double-blind, clinical trial, investigators randomly assigned 443 patients with symptomatic PAH to receive placebo, riociguat in individually adjusted doses of up to 2.5 mg 3 times daily (2.5-mg maximum group), or riociguat in individually adjusted doses that were capped at 1.5 mg 3 times daily (1.5-mg maximum group).8 Patients eligible for this protocol received no other treatment for PAH or were receiving ERAs or prostanoids at doses that had been stable for at least 90 days. Patients with PAH who were receiving PDE-5 inhibitors were excluded from the study.9

The primary end point of the PATENT-1 trial was change from baseline to the end of week 12 in distance walked in 6 minutes.9 The secondary efficacy end points measured changes from baseline to the end of week 12 in pulmonary vascular resistance, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, WHO functional class, time to clinical worsening, Borg dyspnea score, quality of life using scores from 2 questionnaires, and safety.9

**Patient population.** Baseline characteristics of patients enrolled in PATENT-1 were well balanced among the 3 arms of the study. The majority of the patients (median age, 51 years) had idiopathic PAH and were WHO functional class II (42%) or III (53%).9

Overall, 44% of the patients were receiving ERAs, 6% were receiving prostanoid therapy, and 50% were receiving no other treatment for PAH.9 A total of 38 patients withdrew from the study before week 12 for various reasons.9

**Efficacy.** At the end of week 12, 6-minute walk distance for patients in the riociguat 2.5-mg maximum group increased from baseline by an average of 30 m compared with an average decrease of 6 m in the placebo group.9 This mean improvement of 36 m between the 2 study arms was statistically significant (95% confidence interval, 20-52; P < .001).9 Figure 1 compares the mean changes from baseline in the 6-minute walk distance with riociguat versus placebo in PATENT-1.8

Significant improvements were also observed with riociguat in secondary end points, including pulmonary vascular resistance, NT-proBNP levels, WHO functional class, time to clinical worsening, Borg dyspnea score, and quality-of-life variables.9

**Safety.** Frequently occurring serious adverse events (AEs) during the PATENT-1 study included syncope (1% of patients in the riociguat 2.5-mg maximum group vs 4% in the placebo group), worsening pulmonary hypertension (<1% vs 2%, respectively), chest pain (1% in both groups), and right ventricular failure (1% in both groups).9

In the riociguat 2.5-mg maximum group, drug-related serious AEs included 3 (1%) episodes of syncope and 1 case each of increased hepatic enzyme levels, dizziness, presyncope, acute renal failure, and hypotension (a total of 0.4% of patients).9 In the placebo group, single cases of diarrhea, presyncope, syncope, dyspnea, and worsen-
ing pulmonary hypertension were reported (a total of 1% of patients).⁹

A total of 8 (3%) patients in the riociguat 2.5-mg maximum group and 9 (7%) patients in the placebo group withdrew from the study as a result of AEs.⁹ Of the 5 deaths that occurred during the PATENT-1 study (2 in the riociguat 2.5-mg maximum group, 3 in the placebo group), none were believed to be related to the study drug.⁹

**PATENT-2 Study**

The results from PATENT-2, a long-term extension study of PATENT-1, further supported the findings of the initial study regarding the efficacy of riociguat for patients with PAH. Among 215 patients who received up to 2.5 mg of riociguat 3 times daily, a mean (± standard deviation [SD]) increase of 53 m (± 62 m) compared with the baseline distance in PATENT-1 was observed after the first 12 weeks of PATENT-2.⁹

**CHEST-1: Phase 3 Clinical Trial in CTEPH**

In this 16-week, phase 3, multicenter, double-blind, placebo-controlled study, investigators randomly assigned 261 patients with inoperable CTEPH or persistent or recurrent pulmonary hypertension after pulmonary endarterectomy to placebo or to riociguat.⁶ Patients were excluded from the study if they had received an ERA, prostacyclin analog, PDE-5 inhibitors, or NO donor (such as amyl nitrite) within 3 months before the study.⁶

Riociguat was titrated over 8 weeks in 0.5-mg increments from 1 mg 3 times daily to a maximum of 2.5 mg 3 times daily. After titration to the appropriate dose, riociguat was maintained at that dose for another 8 weeks.⁶ At week 16, 77% of patients who remained in the study were taking the maximum (2.5 mg 3 times daily) riociguat dose.⁶

The primary end point in CHEST-1 was change in distance walked in 6 minutes from baseline to the end of week 16.⁶ Secondary end points included pulmonary vascular resistance, NT-proBNP levels, WHO functional class, time to clinical worsening, Borg dyspnea score, and scores from 2 quality-of-life questionnaires.⁶

**Patient population.** Baseline characteristics were well balanced between the placebo and riociguat groups.⁶ The median age of patients was 59 years, 66% were female, and 71% were Caucasian.⁶ The majority of patients were WHO functional class II (31%) or III (64%), and had inoperable CTEPH (72% of total patients).⁶ A total of 18 patients withdrew from the study before week 16.⁶

**Efficacy.** After 16 weeks of treatment, patients receiving riociguat demonstrated a significant mean improvement in 6-minute walk distance of 39 m.⁶ Patients receiving placebo showed a mean decrease in 6-minute walk distance of 6 m.⁶ In addition, riociguat showed significant improvements in secondary end point parameters, including pulmonary vascular resistance, NT-proBNP levels, WHO functional class, and quality of life.⁶ Figure 2 compares mean changes from baseline in the 6-minute walk distance for the riociguat group with changes seen in the placebo group in CHEST-1.⁶

A total of 237 patients in CHEST-1 entered a long-term extension study, CHEST-2.⁶ Study assignments were concealed for the first 8 weeks followed by open-label treatment. Of the 237 patients, 182 received treat-
ment for a median of 336 days. Exploratory analysis of the first 12 weeks of CHEST-2 showed additional increases in the 6-minute walk distance among patients who received riociguat in CHEST-1. A mean (± SD) increase of 63 m (± 64 m) over the baseline distance in CHEST-1 for these 129 patients was observed at week 12 of CHEST-2.

Safety. The most frequently occurring serious AEs in CHEST-1 included right ventricular failure (3% of patients in each group), syncope (2% and 3% in the riociguat and placebo groups, respectively), and hemoptysis (2% of patients receiving riociguat).

Drug-related serious AEs in the riociguat group included syncope in 3 patients, and gastritis, acute renal failure, and hypotension in 1 patient each. In the placebo group, syncope and trauma occurred in 1 patient each. Of the 7 patients who discontinued the study as a result of AEs, 5 patients were from the riociguat group and 2 were from the placebo group.

Overall, 2 patients in the riociguat group died as a result of AEs: acute renal failure (which was deemed related to the study drug) and heart failure. In the placebo group, 3 patients died as a result of respiratory insufficiency, circulatory arrest, and cardiac arrest.

The Table summarizes adverse reactions that occurred more frequently with riociguat compared with placebo using pooled data from CHEST-1 and PATENT-1.

### Contraindications
The use of riociguat is contraindicated concomitant with any PDE inhibitors, including the specific PDE-5 inhibitors sildenafil, tadafal, and vardenafil, and non-specific PDE inhibitors, including dipyridamole and theophylline. Riociguat use is also contraindicated concomitant with nitrates (including NO donors, such as amyl nitrite) in any form.

### Warnings and Precautions
**Boxed warning.** Riociguat carries a boxed warning indicating that the drug can harm a developing fetus and should not be used in pregnant women. Female patients using riociguat and prescribers of the drug must enroll in the Adempas Risk Evaluation and Mitigation Strategies program. Women taking riociguat must comply with pregnancy testing requirements and be counseled regarding the importance of contraception use while taking the medication. Pharmacies must be certified to dispense riociguat to eligible patients.

**Hypotension.** Because riociguat reduces blood pressure, hypotension and ischemia may occur in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, and those who take concomitant anti-hypertensive or strong cytochrome P and P-glycoprotein/breast cancer resistance protein inhibitors.

**Bleeding.** During clinical trials of riociguat, serious bleeding occurred in 2.4% of patients in the riociguat group and in none of the patients in the placebo group. Serious hemoptysis was observed in 5 (1%) patients taking riociguat and in none of the patients receiving placebo, with 1 event resulting in death. Other serious hemorrhagic events included 2 patients with vaginal hemorrhage, 2 patients with catheter-site hemorrhage, and 1 patient each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

**Pulmonary veno-occlusive disease.** Because vasodilators, including riociguat, can exacerbate symptoms of pulmonary veno-occlusive disease (PVOD), its use is not recommended for patients with this condition. If signs of pulmonary edema are noted and a diagnosis of PVOD is confirmed, treatment with riociguat should be discontinued.

### Use in Specific Populations

**Pregnancy.** Riociguat is contraindicated in pregnant women. Patients who are using riociguat during pregnancy or become pregnant while using riociguat should be counseled about the potential risks to the fetus.

**Nursing mothers.** Although it is not known whether riociguat is present in human milk, nursing or use of riociguat should be stopped, because of the potential for serious adverse reactions from riociguat in nursing infants.

**Pediatric use.** The safety and efficacy of riociguat have not been established in pediatric patients.

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### Table

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Riociguat, % (N = 490)</th>
<th>Placebo, % (N = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Dyspepsia and gastritis</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Anemia (including laboratory parameters)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: Adempas (riociguat) tablets prescribing information; 2013.
Geriatric use. Clinical studies have demonstrated that there was no difference between the safety and efficacy of riociguat in patients aged ≥65 years and the safety and efficacy of riociguat in younger patients. However, the possibility of greater sensitivity of some older individuals cannot be dismissed.8

Females and males of reproductive age. Female patients of reproductive age should have a negative pregnancy test before starting treatment with riociguat, monthly during treatment, and 1 month after stopping treatment. Patients should contact their health provider if they become pregnant during treatment or suspect they may be pregnant. In addition, patients should be counseled about the potential hazards to the fetus.8

Female patients of reproductive potential must use contraception during treatment with riociguat and 1 month after treatment. A hormone or barrier method must be used in combination with a partner’s vasectomy. Healthcare providers should discuss pregnancy planning and prevention with their patients.8

Renal and hepatic impairment. The safety and efficacy of riociguat in patients with creatinine clearance of <15 mL/min or in patients on dialysis have not been demonstrated.8

The safety and efficacy of riociguat have not been demonstrated in patients with severe hepatic impairment.8

Conclusion
Riociguat is the first in the novel drug class of sGC stimulators to demonstrate efficacy in 2 forms of pulmonary hypertension—CTEPH and PAH. It is the first pharmacologic therapy ever approved by the FDA for CTEPH, for which standard treatment until now has been pulmonary endarterectomy surgery.8

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References