Advances in Pulmonary Hypertension

The Fifth World Symposium on Pulmonary Hypertension: Application to Practice

The Fifth World Symposium on Pulmonary Hypertension and Robyn J. Barst, MD
C. Gregory Elliott, MD

Classification of Pulmonary Hypertension
Rogerio Souza, MD; Gerald Simonneau, MD

Pulmonary Arterial Hypertension: Epidemiology and Registries
Michael D. McGoon, MD; Marc Humbert, MD, PhD

Definitions and Diagnosis of Pulmonary Hypertension
Fernando Torres, MD

A Treatment Algorithm for Pulmonary Arterial Hypertension
Nazzareno Galiè, MD

Ask the Expert: How Might Adherence to the Treatment Recommendations of the 2013 Fifth World Symposium on Pulmonary Hypertension Improve Long-Term Outcomes?
Sean Studer, MD, MSc, FCCP

Implementation of the PHA Pulmonary Hypertension Care Center Accreditation Program
Joel A. Wirth, MD, CM; Abby Poms, RRT, RCP

PHPN: The Many Faces of the Pulmonary Hypertension Professional Network
Traci Stewart, RN, MSN, CHFN;
Melisa Wilson, ARNP, ACNP-BC
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Program Description
The mission of Advances in Pulmonary Hypertension is to serve as the premier forum for state of the art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension. The 2008 Dana Point meeting of the World Health Organization Classification servies as a guide to categories of pulmonary hypertension addressed in Advances in Pulmonary Hypertension. While focusing on WHO Group 1 PAH, the other categories (Group 2, pulmonary venous hypertension; Group 3, associated with chronic lung disease and/or hypoxemia; Group 4, pulmonary embolic hypertension; Group 5, miscellaneous) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives
Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension.
Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

The mission of the Scientific Leadership Council is to provide medical and scientific guidance and support to the PHA for:
Advocating for patients with pulmonary hypertension.
Increasing involvement of basic and clinical researchers and practitioners.

For more information on PHA; Scientific Leadership Committee and council members can be found at www.PHAAssociation.org/SLC/
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4. Conflict of Interest forms for all authors
5. List of approximately 5 key words for indexing purposes
6. Summary of the paper not exceeding 250 words in the format of Background; Objectives; Summary/Conclusions

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Advances in Pulmonary Hypertension is circulated to cardiologists, pulmonologists, rheumatologists, and other selected healthcare professionals by the Pulmonary Hypertension Association. The contents of the articles are independently determined by the Editor-in-Chief and the Editorial Advisory Board.

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EDITOR’S MEMO

The 5th WSPH: Advancing the Field of Pulmonary Hypertension – A Global Effort

The 5th World Symposium on Pulmonary Hypertension, held in Nice, France, in April was a gathering of 1138 delegates from 57 countries converging with one common goal: to advance the field of pulmonary hypertension. To carry out this mission, 129 members representing 21 countries comprising 12 task forces assessed the current state of understanding that has evolved since the previous World Symposium. They were charged with reviewing the body of literature that has emerged during the past 5 years and assessing the impact on current practice, and to set forth recommendations for needed changes and future directions. Indeed, the 3 days of presentations, deliberations, stated points and counterpoints — all aimed at trying to derive a consensus based on published data and expert opinions — embodied the work from the PH community worldwide. The global impact of PH was highlighted by emerging data characterizing this disease from parts of Asia and South America, the findings truly emphasizing that PH does not have any boundaries and affects people of all racial and ethnic backgrounds. Indeed, the focused energy and dedication of the PH community represented in this gathering emphasized the commitment that we are all in this together.

Thus, it is with my sincere pleasure to present to you this issue featuring some of the highlights from the 5th WSPH. I am grateful to our guest editor Dr. Sean Gaine for all his efforts in bringing together the key members of 4 task forces in presenting the focal points of the meeting. My sincere thanks to all our authors – Drs. Nazzareno Galie, Marc Humbert, Michael McGoon, Gerald Simonneau, Rogerio Souza, and Fernando Torres – for their insights on the emerging data and controversies on the topics of epidemiology, PH registries, classifications, treatments, definitions, and diagnosis. This issue also brings you Part 2 of the Pulmonary Hypertension Clinical Centers initiative by Dr. Joel Wirth and Ms. Abby Poms focusing on the implementation of the program, the opportunities of the PHPN organization by Ms. Traci Stewart and Melisa Wilson, and a thought-provoking discussion on our collective approach to treating our patients and assessing long-term outcome by Dr. Sean Studer. As well, we are very pleased to introduce a new section titled “Pulmonary Hypertension Grand Rounds”, a forum for fellows and junior faculty members to contribute to our Journal.

And finally, it is my sincere privilege to present to you a personal tribute to Dr. Robyn Barst by Dr. Greg Elliott. This was the first World Symposium without Dr. Barst in the “thick of the discussion,” voicing her thoughts, sharing her experiences and wisdom, giving us a greater perspective and, in turn, asking us to reach higher and do better. Her presence, however, was deeply felt during all the presentations and discussion, a true testimony to her everlasting contribution to the field of pulmonary hypertension.

Myung H. Park, MD
Associate Professor of Medicine
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University of Maryland School of Medicine

GUEST EDITOR’S MEMO

The World Cup, Olympic Games and PH World Symposium

Many major International sporting events take place every 4 years. Whether one is an avid sports enthusiast or not, one cannot but be touched in some way by the global reach of the events. Perhaps more important than the actual games themselves is the way they mark the passing of time and the link with important other events in our lives. The Atlanta Olympic Games in 1996 might have occurred during one’s college years or be remembered for occurring the same year as a new arrival in the family. The World Symposiums in Pulmonary Hypertension have a similar link in the lives of the broad PH community. From the diverse locations (Evian, Venice, Dana Point, and Nice), to their International collegiality and 5-year cycle, there is an air of the Championship about the meetings.

The first World Symposium of the current era in Evian, France in 1998 was memorable. Perhaps for the first time, all the great names in PH research were present in one room and the genuine sense of international camaraderie was truly inspiring. The Evian meeting marked the drafting of a new treatment-based classification of PH that ultimately resulted in increased interest in PAH as a target for new drugs and to the subsequent development of many of the therapies we have today. The Venice meeting in 2003 heralded a fresh new treatment algorithm, with the introduction of first oral therapy for PAH. In 2008 the meeting moved to Dana Point in California. The classification was further rationalized and the treatment algorithm was updated to include guidelines on combination therapy.

The World Symposium moved back to Europe last year and Nice witnessed a significant increase in the number of delegates. While the event takes place over three days, there is tremendous preparation during the preceding year. In all, 12 task forces were assembled with 129 PH experts from around the world. Work was done via emails and teleconferences to ultimately produce working (Continued on page 16)
WARNING: EMBRYO-FETAL TOXICITY
Do not administer Adempas (riociguat) tablets to a pregnant female because it may cause fetal harm.
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.
For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

INDICATIONS
• Adempas (riociguat) tablets are 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.
• 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 predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).†
†Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD and persistent worsening of WHO functional class.

* Soluble Guanylate Cyclase

It means different things to different people.
For Mary, it means going from the garage to the garden

Proven in PAH (WHO Group 1):

**36m** improvement in 6-minute walk distance (6MWD) over placebo at Week 12
(95% Confidence Interval (CI): 20m-52m; p<0.0001)

Contraindications

Adempas is contraindicated in:

- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. 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.

- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.

- Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

Warnings and Precautions

**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.

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.
See where you can take your patients

Proven in CTEPH* (WHO Group 4):

46m improvement in 6MWD over placebo at Week 16
(95% CI: 25m-67m; p<0.0001)

6MWD over 16 weeks (mean change)

**CHEST-1**: 261 CTEPH patients were studied (Adempas n=173, placebo n=88).

Baseline characteristics:
- Mean age: 59 years (range: 18-80).
- Mean 6MWD was 347m.
- Concomitant medications: Stable dosages of oral anticoagulants, diuretics, digitals, calcium channel blockers, and oxygen were allowed, but not NO donors, ERAs, PCAs, specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil), and nonspecific PDE inhibitors (for example, dipyridamole or theophylline), or nonspecific PDE inhibitors (for example, dipyridamole or theophylline).

Patient population was: 72% inoperable by pulmonary endarterectomy (PEA) (pulmonary vascular resistance [PVR] >300 dyne·sec·cm⁻⁵ and PAP mean >25 mm Hg measured at least 90 days after the start of full anticoagulation); 28% recurrent or persisting PH following PEA (PVR >300 dyn·sec·cm⁻¹ measured at least 180 days following PEA). The majority of patients were WHO FC II (31%) or III (64%) at baseline. Patients with SBP <95 mm Hg were excluded.

**Warnings and Precautions**

**Adempas REMS Program.** Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

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.
- 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 1-855-4ADEMPAS.
First-in-class sGC stimulator

Adempas targets sGC via a dual mode of action, regardless of nitric oxide (NO) level. It sensitizes sGC to endogenous NO by stabilizing NO-sGC binding. Adempas also directly stimulates sGC via a different binding site, independently of NO.

The first drug proven in both PAH and CTEPH

- **For PAH:** 50% more patients improved WHO Functional Class (21% Adempas vs 14% placebo at 12 weeks)
- **For CTEPH:** More than twice as many patients improved WHO Functional Class (33% Adempas vs 15% placebo at 16 weeks)
- Adempas is indicated to treat adults with PAH (WHO Group 1) and persistent/recurrent CTEPH (WHO Group 4) after surgery, or inoperable CTEPH. In studies establishing effectiveness, most patients were in WHO Functional Class II and III.

Warnings and Precautions

**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. Consider a dose reduction if patient develops signs or symptoms of hypotension.

**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.

**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.

Most Common Adverse Reactions

- The most common adverse reactions occurring more frequently (≥3%) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs. 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 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.

For important risk and use information, please see the Brief Summary of the full Prescribing Information, including Boxed Warning, on the next page.

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

BRIEF SUMMARY OF PRESCRIBING INFORMATION
For additional information, please see the full Prescribing Information at www.adempas-us.com.

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)

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–IV treated with either oral or injectable PAH (61%) or PAH associated with connective tissue diseases (25%) [see Clinical Studies (14.2)].

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 during treatment, monthly during treatment, and 1 month after treatment, it should be discontinued. Prevent pregnancy during treatment and for 1 month after treatment with Adempas. (4.1, 5.1, 8.1)

4.2 Nitrates and Nitric Oxide Donors
Co-administration of Adempas with nitrates or nitric oxide donors (such as dipyridamole or theophylline) is contraindicated because of hypotension. Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as amyl nitrite) in any form is contraindicated because of hypotension. (4.1, 4.2, 5.1, 5.2, 8.6)

4.3 Phosphodiesterase Inhibitors
Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated [see Drug Interactions (7.1) and Clinical Pharmacology (12.2)].

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 female animals, 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 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.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)].
- Pharmacists 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 1-833-4-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, the 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 (5.4)]
- Bleeding [see Warnings and Precautions (5.4)]

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)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Adempas % (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>4</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>

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpititations, 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 (4.1) and Clinical Pharmacology (12.3)].

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 [see Contraindications (4.3) and Clinical Pharmacology (12.3)]. Clinical experience with co-administration of Adempas and
other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

7.2 Pharmacokinetic Interactions with Adempas

Smoking. Adempas concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antifungics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat [see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

Strong CYP3A inducers: Strong inducers of CYP3A (for example, ritafmin, phenytoin, carbamazepine, phenobarbital or St. John’s Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered [see Clinical Pharmacology (12.3)].

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and should be avoided during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus [see Boxed Warning and Contraindications (4.1)].

Animal Data

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC) for unbound drug in rat and humans. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while plasma exposure at the mid-dose (5 mg/kg/day) is approximately 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 4 times and 13 times, respectively, the human exposure at the MRHD.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established [see Nonclinical Toxicology (13.2)].

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 33% were 65 and over, and 6% were 75 and over [see Clinical Studies (14)]. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas [see Clinical Pharmacology (12.3)].

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, and may during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1)].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas. Patients may choose one highly effective form of contraception (intratrueine devices [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner’s vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see Boxed Warning].

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis [see Clinical Pharmacology (12.3)].

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]. Instruct females of reproductive potential to use effective contraception and to contact their physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program [see Warnings and Precautions (5.2)]. Male patients are not enrolled in the Adempas REMS Program.

Inform female patients (and their guardians, if applicable) of the following important requirements:

• All female patients must sign an enrollment form.
• Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)].
• Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
• Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

• Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
• Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
• Instruct patients on the dosing, titration, and maintenance of Adempas.
• Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Patients should report all current medications and new medications to their physician.
• Advise patients that antacids should not be taken within 1 hour of taking Adempas.
• Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines [see Adverse Reactions (6.1)]. They should be aware of how they react to Adempas, before driving or operating machinery and if needed, consult their physician.

Manufactured for:

Bayer HealthCare

Bayer HealthCare Pharmaceuticals Inc.

Whippany, NJ 07981

Manufactured in Germany

Issued May 2014

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Debuting in Volume 13, No 3 in the Fall of 2014 a new section will appear in Advances in Pulmonary Hypertension dedicated to inspiring new thoughts and providing instruction through case reports and reviews. This section will focus on submissions from trainees and junior faculty interested in pulmonary hypertension (PH). It will emulate Grand Rounds and will highlight clinical cases that describe an interesting or thought-provoking entity, mechanism, presentation, or outcome in patients with PH. The cases will include reviews of topics that provide insights and education for clinicians. Interesting cases with associated teaching points and discussion that the case highlights are encouraged. Mentoring comments from a member of the editorial board will be included with each of the cases.

The Advances editorial board encourages program directors and attendings to promote this opportunity to trainees and junior faculty as an opportunity to share their observations and to obtain valuable comments from leaders in the field. It’s a great way to become involved with other clinicians and researchers.

Potential authors should submit a brief summary for consideration by the editorial board. Selected authors will be notified to prepare the complete case.

**Author Instructions**

- Each case study should be submitted double-spaced in Word. Digital files of illustrations are acceptable as long as they reproduce well.
- Abstract: 150 words in narrative format
- Text: Maximum 1000 words
- Tables and illustrations: Total of 3; color allowed
- References: Maximum of 8. Do not include any reference management software.

**Format:**

- Introduction and case presentation
- History
- Clinical features
- Clinical evaluation
- Laboratory and study results (to include imaging if possible, waveforms, etc)
- Management and therapeutics
- Outcomes
- Discussion: Review of the literature
- Recommendations and comments
- Mentoring comments from an editorial board member

Case reports that have been presented at meetings are acceptable as long as the meeting information is disclosed on the title page. IRB approval is not required; nevertheless, authors must preserve patient privacy when writing up the case. On acceptance, written patient permission will be requested as a condition of publication.

Cases will be chosen for publication by members of the Advances in Pulmonary Hypertension editorial board.

Submit a brief summary for consideration to: advancesgrandrounds@PHAssociation.org

**Section editor:**

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Important Safety Information

CONTRAINDICATIONS

• **Nitrates**: ADCIRCA should not be used in patients taking medicines that contain nitrates, as the combination could cause a sudden, unsafe drop in blood pressure

• **Hypersensitivity Reactions**: Patients with a known serious hypersensitivity to tadalafil should not take ADCIRCA

WARNINGS AND PRECAUTIONS

• **Cardiovascular**: Patients who experience anginal chest pain after taking ADCIRCA should seek immediate medical attention

• **Cardiovascular**: Phosphodiesterase 5 inhibitors (PDE-5is), including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Before prescribing ADCIRCA, physicians should carefully consider whether their patients with underlying cardiovascular disease could be adversely affected by such actions. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of ADCIRCA to these patients is not recommended

• **Cardiovascular**: The use of ADCIRCA with alpha blockers, blood pressure medications, or alcohol may lower blood pressure significantly and may lead to symptomatic hypotension (light-headedness or fainting)

• **Potential Drug Interactions**: Tadalafil is metabolized predominately by CYP3A in the liver. Use of ADCIRCA with potent CYP3A inhibitors, such as ketoconazole and itraconazole, should be avoided. For patients on ADCIRCA therapy that require treatment with ritonavir, ADCIRCA should be discontinued at least 24 hours prior to starting ritonavir. For patients on ritonavir therapy that require treatment with ADCIRCA, start ADCIRCA at 20 mg once a day. Use of ADCIRCA with potent inducers of CYP3A, such as rifampin, should be avoided

• **Special Populations**: The use of ADCIRCA is not recommended for patients with severe renal or hepatic impairment. Please see Full Prescribing Information for dosing recommendations for patients with mild to moderate renal or hepatic impairment

• **Potential Drug Interactions**: ADCIRCA contains the same ingredient (tadalafil) as Cialis®, which is used to treat erectile dysfunction (ED) and the signs and symptoms of benign prostatic hyperplasia (BPH). The safety and efficacy of combinations of ADCIRCA with Cialis or other PDE-5is have not been studied. Therefore, the use of such combinations is not recommended

• **Vision/Hearing**: Patients who experience a sudden loss of vision in one or both eyes, which could be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), or sudden decrease or loss of hearing after taking ADCIRCA should seek immediate medical attention.
A diagnosis of pulmonary arterial hypertension (PAH) CAN STOP A PATIENT IN THEIR TRACKS

Take the first step forward to a solid foundation with ADCIRCA® (tadalafil), a first-line therapy for PAH.

ADCIRCA® (tadalafil) tablets is a phosphodiesterase 5 inhibitor (PDE-5i) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

- Prolonged Erection: In rare instances, men taking PDE-5is (including tadalafil) for ED reported an erection lasting more than four hours. Male patients who experience a prolonged erection should seek immediate medical attention

ADVERSE REACTIONS

- Adverse Reactions: The most common adverse event with ADCIRCA is headache (42% ADCIRCA vs 15% placebo). Other common adverse events (reported by ≥9% of patients on ADCIRCA and more frequent than placebo by 2%) include myalgia (14% vs 4%), nasopharyngitis (13% vs 7%), flushing (13% vs 2%), respiratory tract infection (13% vs 6%), extremity pain (11% vs 2%), nausea (11% vs 6%), back pain (10% vs 6%), dyspepsia (10% vs 2%), and nasal congestion (9% vs 1%)

Help your patients move forward with ADCIRCA—one step at a time.


#1 prescribed branded phosphodiesterase 5 inhibitor for PAH*

Every Step Matters

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*Includes patients on monotherapy and background bosentan therapy.1,2
*Clinical worsening is defined as death, lung transplantation, atrial septostomy, hospitalization because of worsening PAH, initiation of new PAH therapy (prostacyclin or analog, endothelin receptor antagonist, PDE-5 inhibitor), or worsening WHO functional class.1
*Patients must meet certain eligibility criteria to qualify for assistance. Patients receiving reimbursement under Medicare, Medicaid, VA, DoD (TRICARE), Indian Health Services, or similar federal or state programs, may not be eligible for some assistance. Some portion of this patient assistance may be administered by Caring Voice Coalition (CVC), an independent national nonprofit organization.

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ADIRCA® (tadalafil) tablets

BRIEF SUMMARY

The following is a brief summary of the Full Prescribing Information on ADIRCA (tadalafil). Please review the Full Prescribing Information prior to prescribing ADIRCA.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension: ADIRCA is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients 18 years of age and older. Studies establishing effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (33%).

CONTRAINDICATIONS

Co-administered Strong Nitrates: Do not use ADIRCA in patients who are using any form of organic nitrate, either regularly or intermittently. ADIRCA potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and ADIRCA on the nitric oxide/cGMP pathway. Hyperosmolarity Reactions: ADIRCA is contraindicated in patients with a known serious hypersensitivity to tadalafil (ADIRCA or Cialis). Hyperosmolarity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

WARNINGS AND PRECAUTIONS

Cardiovascular Effects: Discuss with patients the appropriate action to take in the event that they experience anginal chest pain following initiation of ADIRCA. At least 48 hours should elapse after the last dose of ADIRCA before taking nitrates. If a patient has taken ADIRCA within 48 hours, administer nitrates under close medical supervision with careful hemodynamic monitoring. Patients who experience anginal chest pain after taking ADIRCA should seek immediate medical attention. PDE5 Inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing ADIRCA, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors. Pulmonary vasodilators may already be in use for the treatment of pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of ADIRCA to patients with PVOD or veno-occlusive disease, administration of ADIRCA to such patients is not recommended. Should signs of pulmonary edema occur when ADIRCA is administered, the possibility of associated PVOD should be considered. There is a lack of data on safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:

- Patients with clinically significant aortic and mitral valve disease
- Patients with pericardial constriction
- Patients with restrictive or congestive cardiomyopathy
- Patients with significant left ventricular dysfunction
- Patients with life-threatening arrhythmias
- Patients with symptomatic coronary artery disease
- Patients with hypertension (>90/50 mm Hg) or uncontrolled hypertension

Use of Alpha Blockers and Antihypertensives — PDE5 inhibitors, including ADIRCA, and alpha-adrenergic blocking agents are vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, the concomitant use of these two drug classes can lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors and alpha blockers may be affected by other variables, including intravascular volume depletion and use of other antihypertensive drugs.

Use with Alcohol — Both alcohol and tadalafil are mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects are increased.

Use with Potent CYP3A Inhibitors or Inducers:

- Co-administration of ADIRCA in Patients on Ritonavir — In patients receiving ritonavir for at least one week, start ADIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.
- Co-administration of Ritonavir in Patients on ADIRCA — Avoid use of ADIRCA during the initiation of ritonavir. Stop ADIRCA at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume ADIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.
- Other Potent Inhibitors of CYP3A — Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole and itraconazole, avoid use of ADIRCA. Potent Inducers of CYP3A — For patients clinically taking potent inducers of CYP3A, such as rifampin, avoid use of ADIRCA.

Use in Renal Impairment: In patients with mild or moderate renal impairment — Start dosing at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. In patients with severe renal impairment — Avoid use of ADIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

Use in Hepatic Impairment: In patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) — Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, a starting dose of 20 mg once daily ADIRCA in patients with severe hepatic cirrhosis has not been studied. Avoid use of ADIRCA.

Visual Loss: Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported postmarketing in temporal association with the use of all PDE5 inhibitors. An observational study evaluated whether recent episodic use of PDE5 inhibitors, as a class, typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximate 2-fold increase in the risk of NAION within 1 to 4 days of PDE5 inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also warn patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors. Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

Hearing Impairment: Physicians should advise patients to seek immediate medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including ADIRCA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors.

Combination with Other PDE5 Inhibitors: Tadalafil is also marketed as Cialis. The safety and efficacy of taking ADIRCA together with Cialis or PDE5 inhibitors have not been studied. Inform patients taking ADIRCA not to take Cialis or other PDE5 inhibitors.

Prolonged Erection: There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek medical emergency medical attention. ADIRCA should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukaemia), or in patients with anatomic deformation of the penis (such as angulation, penile curvature, or Peyronie’s disease).

Effects on Bleeding: ADIRCA is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADIRCA has not been administered to patients with bleeding disorders or significant active ulceration. Although ADIRCA has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active ulceration should be based upon a careful risk-benefit assessment.

ADVERSE REACTIONS

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

- Hypotension
- Visual loss
- Hearing loss
- Priapism

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. Tadalafil was administered to 396 patients with PAH during clinical trials worldwide. In trials of ADIRCA, a total of 311 and 251 subjects have been treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 8% for ADIRCA 40 mg and 15% for placebo. The rates of discontinuation because of AEs, other than those related to worsening of PAH, in patients treated with ADIRCA 40 mg was 4% compared to 5% in placebo-treated patients. In the placebo-controlled study, the majority of AEs were generally transient and mild to moderate in intensity. Table 1 presents treatment-emergent adverse events reported by ≥2% of patients in the ADIRCA 40 mg group and occurring more frequently than with placebo.

TABLE 1: Treatment-Emergent Adverse Events Reported by ≥2% of Patients in ADIRCA and More Frequent than Placebo by 2%

<table>
<thead>
<tr>
<th>Event</th>
<th>ADIRCA 40 mg (%)</th>
<th>Placebo by 2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Flushing</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory Tract Infection (Upper and Lower)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nasal Congestion (Including sinus congestion)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of tadalafil. These events have been chosen for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The following list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section.

Cardiovascular and Cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient’s underlying cardiovascular disease, to a combination of these factors, or to other factors.

Body as a whole — Hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis. Nervous — Migraine, seizure and seizure recurrence, and transient global amnesia.

Ophthalmologic — Visual field defect, retinal vein occlusion, and retinal artery occlusion. Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a
combination of these factors, or to other factors. 

OTILOGIC — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient’s underlying risk factors for hearing loss, a combination of these factors, or to other factors.

UNEXPECTED — Priapism.

DRUG INTERACTIONS

Potential for Pharmacodynamic Interactions: If using any form of organic nitrate. In clinical pharmacology studies ADCIRCA potentiated the hypotensive effect of nitrates. In a patient who has taken ADCIRCA, where nitrates administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrates administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring.

Alpha-Blockers — PDE5 inhibitors, including ADCIRCA, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, alfuzosin, and tamsulosin.

Antihypertensives — PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluamide, furosemide, methyldopa). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo.

Alcohol — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increased heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Potential for Other Drugs to Affect ADCIRCA:

Ritonavir — Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir.

Other Potent Inhibitors of CYP3A — Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and triacazone, avoid use of ADCIRCA.

Potent Inducers of CYP3A — For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA. Potential for ADCIRCA to Affect Other Drugs:

Cytochrome P450 Substrates — Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan). Aspirin — Tadalafil (10 mg and 20 mg once daily) does not potentiate the increased in bleeding time caused by aspirin.

P—lycoprotein (e.g., digoxin) — Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category B — Animal reproduction studies in rats and mice revealed no evidence of fetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed.

Non—steroidal anti-inflammatory drugs — Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

Nursing Mothers: It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excrated into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of ADCIRCA in pediatric patients have not been established.

Geriatric Use: Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered.

Renal Impairment: For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based on individual tolerability. In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

Hepatic Impairment: Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients.

OVERDOSAGE

Single doses up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with pulmonary arterial hypertension. In cases of overdose, standard supportive measures should be adopted as needed. Hemodialysis contributes negligibly to tadalafil elimination.

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- New Concepts and Clinical Controversies in PAH
- Highlights of the 5th World Symposium on PH
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The Fifth World Symposium on Pulmonary Hypertension and Robyn J. Barst, MD

C. Gregory Elliott, MD
University of Utah School of Medicine
Murray, Utah

“Stars of the first magnitude are rare, but that such a one will arise among women physicians, I have not the slightest doubt.”
William Osler, MD

The Fifth World Symposium (5th WSPH) on Pulmonary Hypertension was held in Nice, France, from February 27 to March 1, 2013, almost 40 years after the first symposium was convened to develop an understanding of a rare disorder made visible by an epidemic of primary pulmonary hypertension (PH) caused by the prescription of Aminorex.

Nazzareno Galie, MD, and Gerald Simonneau, MD, organizers of the 5th WSPH, dedicated the symposium to the memory of Robyn J. Barst, MD.1 Drs Galie and Simonneau appropriately called attention to Dr Barst’s broad influence on the field. Indeed, the impact of Robyn’s many contributions can be found throughout the 13 state-of-the-art papers published in December 2013 as a supplement to the Journal of the American College of Cardiology.

Robyn’s career spanned an era of dramatic advances in the diagnosis and management of PH. During her career, primary PH (as it was called years ago) was transformed from a poorly understood disorder for which there was no effective treatment and little hope, to a well-defined disorder, diagnosed and treated by expert physicians like Robyn with an expanded armamentarium of medications and life-saving procedures such as lung transplantation.

I first met Robyn at a meeting of the National Institutes of Health (NIH) Primary Pulmonary Hypertension Registry investigators. I have never forgotten her bright eyes and her energy and enthusiasm for the work that we were about to undertake. We forged a close relationship that was built not only on our shared interest in PH, but also our love of medicine, family, and life in general. We both enjoyed early morning walks before the many meetings that we attended. I will forever picture Robyn at 5 in the morning, dressed in sneakers and walking shorts, ready for one of those walks during which we discussed anything and everything.

Robyn was no passive observer; rather, she was always at the center of the advances in the understanding and treatment of PH. As a young pediatric cardiologist Robyn contributed to the NIH Primary Pulmonary Hypertension Registry (NIH PPH Registry, 1981-1987), and as a senior clinician-investigator she served on the steering committee of the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL, 2006-2013). Both of these registries provided key epidemiologic data, and allowed the derivation of important prediction rules for survival. The 5th WSPH task force on pulmonary arterial hypertension (PAH) epidemiology and registries reported the changing demographics and survival of patients diagnosed with PAH based on registry data that Robyn influenced.

Robyn also contributed to important advances in our understanding of the genetic predisposition to PAH. Robyn collaborated closely with a team of scientists, including the late Jane Morse, MD, who discovered that mutations in the gene that codes for BMPR2 caused a heritable form of PAH. This discovery, reported almost simultaneously by 2 scientific teams, led to an entirely new understanding of heritable PH. The 5th WSPH task force on genetics and genomics of PAH reports some of the new discoveries, expanding the original contributions of many scientists, including Robyn Barst.

Robyn was also at the epicenter of the dramatic revision of the clinical classification of PH, made by a task force at the Evian meeting in 1998. She had lived through the era during which clinicians differentiated primary PH from secondary PH, and, like most of us, recognized that this classification no longer accommodated our evolving understanding of PH. The revised clinical classification, proposed first at Evian, has become widely accepted and has provided a cornerstone for global communication among PH experts. As such, it was a centerpiece of Robyn’s daily practice. She participated in each of the subsequent world symposia as clinicians and scientists refined the Evian clinical classification. However, nowhere was her influence more obvious than in the 5th WSPH updated clinical classification of PH. Key changes were made to embrace children and the field of pediatric PH, where persistent PH of the newborn was withdrawn from diagnostic Group 1 PAH; and, in agreement with the first task force on pediatric PH, a shared comprehensive classification for adults and children was created. Of course, Robyn was a driving force behind this particular committee.

The working group on definitions and
diagnosis of PH wrestled with some of the most critical issues faced by PH experts: how should we define PH? Should the pulmonary circulation be challenged with intravenous fluids or exercise? How do we differentiate pre-capillary from postcapillary PH? As a cardiologist who performed diagnostic pulmonary artery catheterizations, Robyn possessed intimate knowledge of these critical issues, even though she could not participate in the discussions.

Not surprisingly, Robyn’s contributions to the treatment of PAH, sustained over her long and distinguished career, emerge as her greatest influence on the field. Drs Galie and Simonneau again fittingly highlighted Robyn’s pivotal report, which demonstrated the efficacy of continuous intravenous epoprostenol for the treatment of primary PH. This landmark clinical trial, conducted by many pioneers in the field, changed the landscape of PH forever and enabled subsequent therapeutic advances. Of course, the epoprostenol breakthrough was only the beginning. Robyn continued to work tirelessly with others to explore new therapeutic advances. Like many of us, she had seen the devastation of PAH and was determined to overcome this disorder for her patients and their families.

Robyn was a principal investigator for pivotal clinical trials demonstrating the efficacy of endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, as well as trials to expand the routes of delivery of prostanoids and trials on combinations of therapeutic agents. Even after Robyn was diagnosed with cancer, she organized a trial of inhaled nitric oxide with the hope that this potent agent would prove to be yet another effective treatment for PAH. The 5th WPHS state-of-the-art task force statements on the updated treatment algorithm of PAH and the exploration of treatment goals of PH underscore her legacy as a clinician-investigator who, along with others, transformed the face of PAH forever. As Drs Galie and Simonneau observed, the kingdom of the near dead will never be the same because of Robyn Barst.

Robyn’s talent, passion, and dedication—known to all of us—shine brightly within the accomplishments of the 5th WSPH. I believe that Dr William Osler had Robyn J. Barst, MD, in mind when he predicted the appearance of a star of the first magnitude.

Reference
Classification of Pulmonary Hypertension

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Classification of pulmonary hypertension groups patients with similar pathological findings, hemodynamic profiles, and management strategies. Minor modifications have been made to the current classification system, particularly within Group 1 pulmonary arterial hypertension. This article summarizes the published conclusions of the Fifth World Symposium of Pulmonary Hypertension task force that addressed the updated clinical classification of pulmonary hypertension.

During the last few decades, awareness of pulmonary hypertension (PH) has improved significantly. The Fifth World Symposium on Pulmonary Hypertension, held in 2013, highlighted the advances made in the last 40 years since the first international conference in 1973, sponsored by the World Health Organization (WHO). The following symposiums (Evian, France, 1998; Venice, Italy, 2003; and Dana Point, US, 2008) were clearly reflective of the significant achievements that have been made in the field, in terms of understanding the pathophysiology and clinical behavior, as well as development of new treatment modalities.

The first classification of PH was described in 1973, and categorized patients as having “primary” or “secondary” hypertension according to the presence or absence of an identifiable cause for the disease. The limitations of such classifications became more evident as more associated conditions were identified. During the Second World Symposium on PH in 1998, the basis for the current classification system was proposed. The concept supporting the classification is to group patients with similar pathological findings, hemodynamic profiles, and management. Five different categories were then established: pulmonary arterial hypertension (PAH); PH due to left heart disease; PH due to chronic lung disease and/or hypoxia; chronic thromboembolic PH (CTEPH); and PH due to unclear multifactorial mechanisms (previously called “miscellaneous”). Although minor modifications have been made during the last decade, the concept of the current classification remains the same. The updated classification for PH, derived from the last world symposium, is presented in Table 1.

For the current classification, Group 1 PAH is the condition with the most significant changes and will be the focus of this review. PAH encompasses a group of clinical conditions that present precapillary PH, defined by the presence of mean pulmonary artery pressure (mPAP) ≥25 mm Hg with normal pulmonary artery occlusion pressure (<15 mm Hg), and share similar pathological and/or clinical findings. IPAH corresponds to sporadic disease in which no family history of PAH or an identified risk factor is present; therefore, an extensive investigation is needed to rule out alternative diagnoses.

Since the last world symposium, heritable PAH has gained significant attention. Heritable forms of PAH include those with identified gene mutations and familial cases with or without identified mutations. Up to 80% of familial cases of PAH have been linked to germline mutations in the gene coding for the bone morphogenetic protein receptor 2 (BMPR2), a member of the transforming growth factor beta (TGF-β) signaling family. Other mutations in genes from the TGF-β family have also been detected in a significant proportion of apparently idioopathic cases without familial history. Other mutations in genes from the TGF-β family were already known to be associated with particular PAH cases: ALK1, endoglin, and SMAD9.

However, new genes not closely related to the TGF-β family have recently been described: CAV1 and KCNK3. The importance of these genes is that they might provide different insights in terms of pathophysiological mechanisms of the disease and may even lead to new therapeutic targets.

Besides genetic predisposition, there are a number of risk factors associated with the development of PAH. Ami-nox, a potent appetite suppressant, was the first drug to drive the attention to the possible link of its use and pulmonary vascular disease. Its use in the 1960s led to an outbreak of rapidly progressive PAH in Switzerland, Austria, and Germany. More than 20 years after the aminorex epidemics, fenfluramine and dexfenfluramine have been marketed as appetite suppressants, leading to a new outbreak of drug-induced PAH in the 1980s-1990s. PAH cases in patients exposed to fenfluramine derivatives share clinical, functional, hemodynamic, and genetic features with IPAH.

More recently, benfluorex, a benzoate
ester that shares structural and pharmacologic characteristics with dexfenfluramine and fenfluramine, has been linked to the development of PAH. The active and common metabolite of each of these molecules is norfenfluramine, which itself has a chemical structure similar to that of the amphetamines. Given its pharmacological properties, benfluorex would be expected to have similar toxic effects to the fenfluramine derivatives.\textsuperscript{15,16} An outbreak of valvular heart diseases and/or PAH induced by benfluorex use has been uncovered in France in the 2000s. Eighty-five cases of PH associated with benfluorex exposure were identified by the French PH network from June 1999 to March 2011. The analysis of these cases caused benfluorex to be withdrawn from the French market in 2009.\textsuperscript{17}

Other classes of drugs have also been linked to the development of PAH. Cases of precapillary PH fulfilling the criteria of drug-induced PAH have been reported in chronic myelogenous leukemia patients treated with the tyrosine kinase inhibitor dasatinib. Clinical, functional, and hemodynamic improvements were observed within a few months of dasatinib discontinuation in most patients, although the majority failed to demonstrate complete clinical remission.\textsuperscript{18}

The presence of genetic abnormalities and risk factors (such as specific drug exposures) reinforces the “multiple hit” concept for the development of PH\textsuperscript{19} and emphasizes the importance of active investigation of PH in any symptomatic individual with known exposure to any risk factor. The list of the recognized risk factors potentially related to the development of PH is presented in Table 2.

Connective tissue disease (CTD) is one of the most important forms of PAH, accounting for about 15% of all cases in the French registry.\textsuperscript{20} The prognosis of these patients remains worse compared with other forms of PAH.\textsuperscript{21,22} Recently, it has been suggested that implementation of a systematic screening program that allows the use of specific therapies in a less symptomatic phase of the disease might result in better long-term outcomes for this subgroup of PAH patients.\textsuperscript{23}

Patients with HIV are another group with increased risk of developing PAH. The prevalence of PAH in such group is estimated at 0.5%, with clinical and

---

### Table 1. Clinical Classification of PH

| 1. PAH |
| 1.1. Idiopathic PAH (IPAH) |
| 1.2. Heritable PAH |
| • 1.2.1. BMPR2 |
| • 1.2.2. ALK1, ENG, SMAD9, CAV1, KCNK3 |
| • 1.2.3. Unknown |
| 1.3. Drug- and toxin-induced |
| 1.4. Associated with: |
| • 1.4.1. Connective tissue diseases |
| • 1.4.2. HIV infection |
| • 1.4.3. Portal hypertension |
| • 1.4.4. Congenital heart diseases |
| • 1.4.5. Schistosomiasis |
| 1’ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis |
| 1” Persistent PH of the newborn |
| 2. PH owing to left heart disease |
| • 2.1. Left ventricular systolic dysfunction |
| • 2.2. Left ventricular diastolic dysfunction |
| • 2.3. Valvular disease |
| • 2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies |
| 3. PH owing to lung diseases and/or hypoxia |
| • 3.1. Chronic obstructive pulmonary disease |
| • 3.2. Interstitial lung disease |
| • 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern |
| • 3.4. Sleep-disordered breathing |
| • 3.5. Alveolar hypoventilation disorders |
| • 3.6. Chronic exposure to high altitude |
| • 3.7. Developmental lung diseases |
| 4. CTEPH |
| 5. PH with unclear multifactorial mechanisms |
| • 5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy |
| • 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis |
| • 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders |
| • 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH |

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### Table 2. Updated Classification for Drug- and Toxin-Induced PAH* |

<table>
<thead>
<tr>
<th>Definite</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminorex</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>Phenytoinolamine</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>Toxic rapeseed oil</td>
<td>Chemotherapeutic agents</td>
</tr>
<tr>
<td>Benfluorex</td>
<td>Interferon α and β</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Amphetamine-like drugs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Likely</th>
<th>Unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>D-Tryptophan</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Cigarette smoking</td>
</tr>
</tbody>
</table>

*Nice 2013. | Selective serotonin reuptake inhibitor (SSRIs) have been demonstrated as a risk factor for the development of persistent pulmonary hypertension in the newborn (PPHN) in pregnant women exposed to SSRIs (especially after 20 weeks of gestation). PPHN does not strictly belong to Group 1 (pulmonary arterial hypertension [PAH]) but to a separated Group 1. Major modification to the previous Danapoint classification are in bold.

hemodynamic presentation very similar to IPAH. Prognosis of this particular subgroup of PAH has improved in recent years; in the REVEAL registry, the mortality of HIV-PAH patients was 93% and 75% at 1 and 3 years, respectively.

PAH associated with portal hypertension is another important subgroup of PAH patients, since about 6% of patients with portal hypertension might develop PAH independently of the severity of the liver disease; nevertheless, long-term prognosis of these patients is determined by both the severity of PH and of liver disease. Portopulmonary hypertension (POPH) represents an important problem for liver transplantation programs since its presence is related to increased mortality during the procedure. The prognosis in POPH is worse than in IPAH; recent reported data suggest a 3-year survival of 40%.

Due to the improvement in the management of congenital heart diseases (CHD), more children survive to adulthood and about 10% of these adults develop PAH. According to findings from the last world symposium, patients with CHD-PAH (except those with more complex congenital heart defects) should be subclassified into 4 different subgroups (Table 3) to facilitate disease management. Nevertheless, absolute criteria to determine whenever a small cardiac defect is a cause or just a concomitant factor as the operability criteria for such defects are still missing, with most of the therapeutic approach based on expert consensus.

Schistosomiasis is an infectious disease affecting more than 200 million people worldwide. PAH represents one of the most severe complications of chronic schistosomiasis, with a 4.6% prevalence among patients diagnosed with hepatosplenic schistosomiasis mansoni. Schistosomiasis-associated PAH has a clinical profile similar to IPAH and a similar targeted treatment response, but with better clinical course (3-year mortality of about 15%).

One of the key changes in the current classification is related to chronic hemolytic anemia. Previously classified into Group 1, it was shifted to Group 5 for a number of reasons. Recent cohorts on PH might be present in up to 10% of patients with hemolytic anemias. The hemodynamic profile of this patient is quite peculiar as a consequence of high cardiac output, with elevated pulmonary pressures and low pulmonary vascular resistance. Also, available data on the pathological findings were inconsistent with the presence of many confounding factors. Together with the absence of robust data regarding the use of targeted therapies in this particular subform of PH, it was changed to Group 5 until more evidence to support otherwise is generated.

Another important step in the current classification was related to pediatric PH. During the last world symposium it was determined that a single classification should be used for children and adults to facilitate the transition of children now surviving to adulthood from pediatric to adult medical services. To make this possible, a number of pediatric disorders/specificities were highlighted in the single classification, as the separation of persistence of PH of the newborn from Group 1 and the addition of left heart inflow and outflow obstruction in Group 2.

It is important to emphasize that since the 5-group classification of PH was established, a number of benefits resulted: clinical trials were designed in less heterogeneous subgroups, allowing the registration of all available therapies; pathophysiological studies were also carried out according to the known subgroups, gathering more knowledge about each of the subforms of PH. While the system seems to remain robust, it does carry some important limitations. The main one might be related to the prevalence of the different forms of PH. Much of the focus has been on PAH, although PH due to left heart disease (Group 2), lung disease (Group 3), or chronic thromboembolic disease (Group 4) might be much more prevalent. Perhaps future classification should also reflect the importance of each one of the groups and subgroups of PH, also taking their prevalence into account.

In summary, the current classification...
of PH parallels the improved understanding about PH gleaned in the last decades. Its concept is intended to provide pathophysiological and prognostic information as diagnosis and management guidelines: hence the importance of revisiting its structure occasionally, according to the best available knowledge about all forms of PH.

References
Registries of pulmonary arterial hypertension (PAH) are important means by which to characterize the presentation and outcome of patients and to provide a basis for predicting the course of the disease. This article summarizes the published conclusions of the World Symposium of Pulmonary Hypertension task force that addressed registries and epidemiology of PAH.

Collection of patient information into registry databases enables characterization of pulmonary arterial hypertension (PAH) in terms of demographics, clinical presentations, and outcomes. Because this type of information provides the foundation for recognizing PAH and assessing the utilization of treatment strategies, the Fifth World Symposium for Pulmonary Hypertension included a task force to summarize what has been learned from PAH registries, to outline appropriate interpretation of registry data, and to recommend how registries ought to be pursued for optimal acquisition of useful knowledge in the future. This article will summarize some of the major conclusions of that effort that have been published previously.1

The common denominator of all PAH registries is to provide a description of patients with PAH, to determine the impact of the disease (outcome), to elucidate how the outcome is determined by patient characteristics (risk), and to document how outcome may be broadly altered by therapy.

The task force described at the outset what sort of information could be included in registries and what factors must be considered in meaningfully analyzing that data. All PAH registries considered by the task force sought to be as comprehensive as possible in assimilating variables while simultaneously recognizing the limitations imposed by available resources required to collect the data. Thus, a registry must: (i) wisely confine its methodology to addressing carefully constructed and clearly articulated questions, (ii) understand and transparently describe limitations, and (iii) identify potential biases imposed by the methodology. All major registries have been observational and descriptive. Therefore, conclusions emerge about how PAH is identified and handled in “the real world” rather than within a framework of “ideal” management as advised by consensus guidelines. Moreover, registries have varied with respect to the exact selection criteria, which in turn may predetermine the nature of some conclusions. Some of the specific ways in which registries have differed from one another include the clinical and hemodynamic definitions used to identify the types of patients enrolled in the studies, the use of newly diagnosed and/or previously diagnosed patients, the specific data collected, and the frequency and duration of follow-up.

The determination of patient eligibility depends to a large extent on the goal of the particular registry. Registries that intend to evaluate a previously well-specified population are carefully designed to include only patients who meet the accepted definition of disease. Thus, these PAH registries enroll patients in whom other types of pulmonary hypertension (PH) have been conscientiously excluded by clinical and hemodynamic criteria. The strength of these types of registries is that they describe the behavior of a well-circumscribed disease entity, which can be compared to similar populations from other eras or geographic locales. An example of this type of registry is the French registry.2 Other registries may be more interested in identifying the characteristics of a more loosely circumscribed population to uncover the limits that define post-hoc a cohesive group that could be considered to have PAH, without recourse to a precise, pre-specified consensus definition. This approach is exemplified by the REVEAL registry, in which a pulmonary arterial wedge pressure up to 18 mm Hg was permitted and the clinical diagnosis of PAH was based only on the opinion of the treating physician.3,4

Inclusion of patients with “nonconforming” high wedge pressures (pulmonary artery wedge pressure ranging from 16 to 18 mm Hg) allows for these patients to be excluded or included in individual analyses so that similarities and differences between groups may be evaluated.5

Likewise, some registries focus on describing the course of disease exclusively from the time of its first documentation by right heart catheterization (so-called incident patients) to unambiguously understand the “full” natural history of PAH from the time of diagnosis. Others emphasize trying to understand the course of disease from any time point in its trajectory, and therefore include both incident and previously diagnosed (“prevalent”) patients to compare these 2 groups and attempt to identify predictors of survival (risk factors) independent of time of diag-
nosis. Survival studies emerging from the UK\textsuperscript{6} and REVEAL registries,\textsuperscript{7} respectively, are representative of these 2 approaches. Of course, in a registry that enrolls both types of patients, analyses can be performed on either subpopulation or on both together, depending on the specific question being asked. Some investigators favor restricting survival analyses to incident patients,\textsuperscript{6} while others point out that risk stratification or a delayed entry model accounting for left truncation is preferable to excluding prevalent patients from PAH registries.\textsuperscript{8} A population is considered left truncated if patients may have been excluded from a cohort due to events that occurred prior to the study. Patients who die prior to study initiation are excluded, while patients who survive to study initiation are included from the point in their survival at which they were enrolled. An approach to analyzing survival from diagnosis, utilizing both newly diagnosed and previously diagnosed patients, was used in the US-REVEAL protocol, as well as in the French registry. Survival from time of diagnosis, utilizing data from both incident and prevalent patients, is comparable to survival estimates that are restricted to incident patients.\textsuperscript{2,3,9}

The key to interpreting registries using different study populations is clearly understanding the broad population to whom the results can be generalized. For example, using an outcome measure (ie, survival) derived from a prevalent population as a basis for comparing outcome in newly diagnosed patients is inappropriate, whereas generalizing it to the population of patients with previously diagnosed disease is legitimate. Additionally, survival estimates from one incident cohort may not be generalizable to another incident cohort if diagnosis method or time from symptom onset to diagnosis differs.

<table>
<thead>
<tr>
<th>Study cohort</th>
<th>Study design and time period</th>
<th>Centers</th>
<th>Patients No.</th>
<th>Incidence/prevalence</th>
<th>Predominant etiologies of PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-NIH\textsuperscript{12,13}</td>
<td>IPAH Prospective, 1981-1985</td>
<td>32</td>
<td>187</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>US-PHC\textsuperscript{29}</td>
<td>Group 1 PH and CTEPH Age &gt;18 yrs</td>
<td>Prospective, 1982-2004</td>
<td>3</td>
<td>578</td>
<td>NA</td>
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<tr>
<td>Scottish-SMR\textsuperscript{30}</td>
<td>Group 1 PH (IPAH, CTD-PAH, and CHD-PAH) Age between 16-65 yrs</td>
<td>Retrospective, 1986-2001</td>
<td>NA</td>
<td>374</td>
<td>PAH 7.6/26 cases/MAI IPAH 2.6/9 cases/MAI</td>
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<tr>
<td>French\textsuperscript{2,24,31}</td>
<td>Group 1 PH Age &gt;18 yrs</td>
<td>Prospective, 2002-2003</td>
<td>17</td>
<td>674</td>
<td>PAH 2.4/15 cases/MAI IPAH 1.0/5.9 cases/MAI</td>
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<td>Chinese\textsuperscript{16}</td>
<td>IPAH and HPAH Prospective, 1999-2004</td>
<td>1</td>
<td>72</td>
<td>NA</td>
<td>NA</td>
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<td>US-REVEAL\textsuperscript{4,7,32,40}</td>
<td>Group 1 PH</td>
<td>Prospective, 2006-2009</td>
<td>55</td>
<td>3515 (Age &gt;3 months)</td>
<td>PAH 2.0/10.6 cases/MAI IPAH 0.9 cases/MAI</td>
</tr>
<tr>
<td>Spanish\textsuperscript{41}</td>
<td>Group 1 PH and CTEPH Age &gt;14 yrs</td>
<td>Retrospective, 1998-2006</td>
<td>31</td>
<td>PAH 866 CTEPH 162</td>
<td>PAH 3.2/16 cases/MAI IPAH 1.2/4.6 cases/MAI</td>
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<td>UK\textsuperscript{5,42}</td>
<td>IPAH, HPAH, and anorexigen-associated PAH</td>
<td>Prospective, 2001-2009</td>
<td>8</td>
<td>482</td>
<td>1.1/6.6 cases/MI</td>
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<td>New Chinese Registry\textsuperscript{43,44}</td>
<td>Group 1 PH Age &gt;18 yrs</td>
<td>Prospective, 2008-2011</td>
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<td>Mayo\textsuperscript{91}</td>
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<td>Prospective, 1995-2004</td>
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</tr>
<tr>
<td>Compera\textsuperscript{14}</td>
<td>IPAH Age &gt;18 yrs</td>
<td>Prospective, 2007-2011</td>
<td>28</td>
<td>587</td>
<td>NA</td>
</tr>
</tbody>
</table>

between cohorts. The task force recognized that it is not appropriate to define an at-risk period that includes time during which patients were not on study. Doing so leads to immortal time bias because patients are guaranteed to have survived the prestudy period.

The use of registry data for comparative effectiveness is difficult and controversial,\textsuperscript{10,11} since aggressive treatments will generally be applied to the sickest patients, the worst outcomes will occur frequently among these patients, thereby confounding assessment of efficacy. A variety of methods exist to adjust for confounding. Matching, multivariable risk-adjusted models of outcomes, and propensity scores can be effective if all confounding variables have been identified and measured. In PAH, it is plausible that most (but not all) important potential confounders have been successfully identified.

Finally, a source of potential bias is the means of funding for a registry. Registries are expensive. Costs include funding for site coordinators, project management, in-person meetings, data management, and statistical analysis. When studies receive industry sponsorship, the relationship of the sponsor and advisors must be clearly delineated, and it is similarly important for data ownership and data access rules to be specified contractually. Disclosing conflict of interest is critical, but there are many important scientific objectives where the interests of industry, patients, and the scientific community are fully aligned.

The task force summarized characteristics of 11 major registries in which 6 countries were represented. All registries enrolled patients with idiopathic and heritable PAH, 7 included other PAH patients, and 1 also included chronic thromboembolic PH (CTEPH, PH Group 4) (Table 1). The number of patients in each registry ranged from 72 to 3515, and participating centers ranged from 1 to 55. Table 2 provides the basic presenting characteristics of patients enrolled in each registry.

In general, survival in registry populations has improved as treatment options increase (Table 3). Data from the US-REVEAL registry suggest that current median survival is 7 years for patients with PAH\textsuperscript{p} compared to 2.8 years for patients with primary PH (PPH, now referred to as idiopathic/heritable PAH [IPAH/IPAH]) in the US-National Institutes of Health (NIH) registry.\textsuperscript{12} Considerable changes in the PAH phenotype have been observed over time. These include substantial changes in age, gender, comorbidities, and survival (Tables 2 and 4). While the mean age of patients with IPAH in the first registry created in 1981 (US-NIH registry) was 36 ± 15 years,\textsuperscript{13} PAH is now more frequently diagnosed in elderly patients, resulting in a mean age at diagnosis between 50 ± 14 and 65 ± 15 years in current registries (Table 2). Furthermore, the female predominance is quite variable among registries and may not be present in elderly patients.\textsuperscript{14} A potential explanation for the change in phenotype may be the increased awareness of PAH in the modern management era as effective therapies become available. For example, since PPH was considered a rare disease that affected young women at the time of the initial US-NIH registry, it is likely that older patients and men were often not considered for the diagnosis at that time. Other factors contributing to biased enrollment include lack of awareness of this registry among nonexperts in the community and unavailability of widespread screening tools such as Doppler echocardiography. Since PAH may be detected more frequently in elderly patients, one should also be cautious about possible misconstruals.

### Table 2. Demographic, Clinical, and Hemodynamic Characteristics of PAH Registries From Different Countries and Time Periods

<table>
<thead>
<tr>
<th>Registry</th>
<th>Age, yrs</th>
<th>Female, %</th>
<th>WHO 3/4, %</th>
<th>6MWD, m</th>
<th>RAP, mm Hg</th>
<th>mPAP, mm Hg</th>
<th>PVRI, U·m(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-NIH</td>
<td>36 ± 15</td>
<td>NA 63</td>
<td>NA 75</td>
<td>NA NA</td>
<td>NA 10 ± 6</td>
<td>NA 60 ± 18</td>
<td>NA 26 ± 14</td>
</tr>
<tr>
<td>US-PHC</td>
<td>48 ± 14</td>
<td>45 ± 14</td>
<td>77 75 80 80</td>
<td>NA NA</td>
<td>11 ± 7 11 ± 7</td>
<td>52 ± 14 56 ± 13</td>
<td>NA NA</td>
</tr>
<tr>
<td>Scottish-SMR</td>
<td>52 ± 12</td>
<td>49 ± 11</td>
<td>70 62 NA NA</td>
<td>NA NA</td>
<td>NA NA NA</td>
<td>NA NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>French</td>
<td>50 ± 15</td>
<td>52 ± 15</td>
<td>65 62 75 81</td>
<td>329 ± 109 328 ± 112</td>
<td>8 ± 5 9 ± 5 55 ± 15 56 ± 14</td>
<td>21 ± 10 23 ± 10</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>36 ± 12</td>
<td>NA 71</td>
<td>NA 61 NA NA</td>
<td>NA NA</td>
<td>NA 13 ± 6</td>
<td>NA 69 ± 19</td>
<td>NA NA</td>
</tr>
<tr>
<td>US-REVEAL</td>
<td>50 ± 14</td>
<td>50 ± 15</td>
<td>80 83 56 55</td>
<td>366 ± 126 374 ± 129</td>
<td>9 ± 6 10 ± 6 51 ± 14 52 ± 13 21 ± 13 23 ± 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spanish</td>
<td>45 ± 17</td>
<td>46 ± 18</td>
<td>71 73 69 70</td>
<td>363 ± 120 382 ± 117</td>
<td>9 ± 5 8 ± 5 54 ± 16 55 ± 15</td>
<td>NA NA</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>NA 50 ± 16</td>
<td>NA 70</td>
<td>NA 84 NA NA</td>
<td>292 ± 123 NA 10 ± 6</td>
<td>NA 54 ± 14 23 ± 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Chinese Registry</td>
<td>36 ± 13</td>
<td>38 ± 13</td>
<td>70 70 54 66</td>
<td>378 ± 125 353 ± 127</td>
<td>8 ± 5 8 ± 6 63 ± 20 63 ± 15 25 ± 14 27 ± 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayo</td>
<td>52 ± 15</td>
<td>52 ± 15</td>
<td>75 76 55 56</td>
<td>329 ± 125 344 ± 125</td>
<td>13 ± 6 13 ± 6 53 ± 15 55 ± 12</td>
<td>NA NA</td>
<td></td>
</tr>
<tr>
<td>Compera</td>
<td>NA 65 ± 15</td>
<td>NA 60 91</td>
<td>293 ± 126 NA 8 ± 5</td>
<td>NA 44 ± 12 27 ± 14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as frequency (female, WHO functional class) and means ± SD (age, 6MWD, and hemodynamic variables).

Comparisons between PAH and non-PAH PH (particularly postcapillary PH due to heart failure with preserved ejection fraction, HFpEF), which may occur particularly in elderly patients as a consequence of uncertainties in the current definitions and difficulties in the measurement of the pulmonary arterial wedge pressure.

Registries from China and other developing countries demonstrate similar demographics and characteristics to the early studies of the US-NIH registry, suggesting that some differences in phenotype might be related to the health care environment rather than to different expressions of the disease. Nonetheless, specific sources of systematic bias in PAH registries include: (i) changes in the classification of PH, which have led to inclusion of a varying spectrum of patients in modern registries; (ii) changing interest in PH by academic physicians, producing more development and dissemination of information; (iii) increased awareness of PH by clinicians due to availability and marketing of efficacious therapy, with associated education from pharmaceutical representatives; (iv) easier access to medical information by patients, who may then influence their own referral to specialized care; and (v) widespread use of noninvasive techniques (Doppler echocardiography), which allow for disease detection even in the absence of prior suspicion, thereby leading to a perception of increased disease prevalence. Thus, it appears that the changing phenotype of patients with PH in modern registries is potentially influ-

### Table 3. Survival Data of PAH Registries From Different Countries and Time Periods

<table>
<thead>
<tr>
<th>Study cohort</th>
<th>1 yr, %</th>
<th>2 yrs, %</th>
<th>3 yrs, %</th>
<th>5 yrs, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAH</td>
<td>IPAH</td>
<td>PAH</td>
<td>IPAH</td>
</tr>
<tr>
<td>US-NIH</td>
<td>Inc</td>
<td>NA</td>
<td>68</td>
<td>NA</td>
</tr>
<tr>
<td>US-PHC</td>
<td>Prev and Inc</td>
<td>84</td>
<td>NA</td>
<td>67</td>
</tr>
<tr>
<td>French</td>
<td>Prev and Inc</td>
<td>Ent</td>
<td>87</td>
<td>Ent</td>
</tr>
<tr>
<td>Chinese</td>
<td>Inc</td>
<td>NA</td>
<td>68</td>
<td>NA</td>
</tr>
<tr>
<td>US-REVEAL</td>
<td>Prev and Inc</td>
<td>85</td>
<td>91</td>
<td>NA</td>
</tr>
<tr>
<td>Spanish</td>
<td>Prev and Inc</td>
<td>NA</td>
<td>89</td>
<td>NA</td>
</tr>
<tr>
<td>UK</td>
<td>Inc</td>
<td>79a</td>
<td>93</td>
<td>68a</td>
</tr>
<tr>
<td>Mayo</td>
<td>Prev and Inc</td>
<td>NA</td>
<td>81</td>
<td>NA</td>
</tr>
<tr>
<td>Compera</td>
<td>Inc</td>
<td>NA</td>
<td>Ent</td>
<td>92</td>
</tr>
</tbody>
</table>


### Table 4. Multivariate Predictors of Survival

<table>
<thead>
<tr>
<th>Category</th>
<th>Increase Risk</th>
<th>Decrease Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male) and age interaction (&gt;65 years old)</td>
<td>2-7,18,40</td>
<td></td>
</tr>
<tr>
<td>Age6,29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender2-6,7,41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology: CTD,6,7,18,29,41,44, POHP,6,18,41, HPAH,7,18 PVOD6,41</td>
<td>Higher NYHA/WHO class7,15,18,29,41,44</td>
<td>Lower NYHA/WHO class7,29</td>
</tr>
<tr>
<td>Lower 6MWD2,6,7,18</td>
<td></td>
<td>Higher 6MWD2,6,7</td>
</tr>
<tr>
<td>Laboratory and Biomarkers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher BNP or NT-proBNP7,18</td>
<td>Lower BNP or NT-proBNP7</td>
<td></td>
</tr>
<tr>
<td>Higher creatinine7,16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo: pericardial effusion7,18,24</td>
<td>Higher predicted DCO7,18</td>
<td></td>
</tr>
<tr>
<td>Lung Function Studies</td>
<td>Lower predicted DCO7,18,24,</td>
<td>Higher predicted DCO7,18</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher mRAP5,7,18,29,41</td>
<td>Higher CO or CI2-6,41</td>
<td></td>
</tr>
<tr>
<td>Lower CO or CI2-6,41</td>
<td>Higher PVR or PVRI7,18</td>
<td></td>
</tr>
<tr>
<td>Higher PVR or PVRI7,18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

enced by factors that are independent of the disease itself.

An important asset of registries is the capability of identifying patient characteristics that predict outcome. The US-NIH registry was the first to develop a prognostic equation. Use of this equation in the current treatment era has limitations, as it provides information only on the natural history of untreated PPH rather than on Group 1 PH (PAH). More recent registries have identified predictors of outcome (Table 4) that show substantial homology between studies, including disease etiology, patient gender, and factors reflective of right heart function. Four registries (US-REVEAL, US-PHC, French, and UK) employed multivariable analyses to develop prognostic equations (US-REVEAL, US-PHC, French) or calculators (US-REVEAL, UK). Despite the US-REVEAL equation’s derivation in a combined incident and prevalent cohort at the time of enrollment, the US-REVEAL equation’s derivation was from the Scottish registry (derivation was from the Scottish registry only). Both the French and US-REVEAL equations have shown strong predictive power when cross-validated in matched patients from the US-REVEAL and French registries, respectively. It appears that concerns about the relative contribution to mortality risk of “newly” and “previously” diagnosed patients is minimized and overshadowed by the overall contribution of individual risk profiles in each of these populations, respectively. In other words, a newly diagnosed patient is not “independently” at risk of dying by the mere fact of being “newly diagnosed,” but rather because they have a larger proportion of “at-risk” factors than those previously diagnosed.

The task force discussed about how future registry databases could be expanded to better understand broad PH populations. Although patients belonging to Group 2 (PH due to left heart disease) and Group 3 (PH due to chronic lung diseases and/or hypoxia) represent an increasing part of the clinical practice, there is little information about the demographics and clinical course of this segment of the PH population, suggesting that registry database methodology may be useful for these groups. However, the structure of registries incorporating “non-PAH” PH is problematic. A single registry could include all patients with any type of PH from which defined subgroups (ie, PH associated with interstitial lung disease, chronic obstructive pulmonary disease [COPD], left ventricular systolic dysfunction, or left ventricular HFpEF) could be extracted for analyses. An advantage of this model is that all patients would be enrolled from the same sites and would permit direct comparisons between cohorts with minimal adjustment for differences in enrollment patterns, location, or follow-up. Disadvantages are that many patients would need to be enrolled to provide sufficient cohort size for characterization of all groups and a single case report form (CRF) may not be appropriate for all cohorts. The ASPIRE registry has attempted to assess the spectrum of PH across the 5 PH groups encountered in a single specialist referral center, allowing specific descriptions of PH patients with associated diseases such as COPD and other comorbidities. An alternative model would be to develop separate registries around specific disease entities of interest, using focused CRFs at less anticipated cost. This has been successfully proposed for CTEPH.

The task force recognized that unless all patients who have PH within a population are enrolled in a registry, estimates of incidence or prevalence of disease in a prespecified population are not possible. To understand the chances of PH developing in a population requires that the population at risk be observed systematically over time in order to detect the occurrence of PH. Examples of populations of interest in whom the risk of developing PH makes systematic data collection likely to yield clinically useful information include patients with known BMPR2 mutations, with 2 or more family members with PH, with systemic sclerosis, with cirrhosis and portal hypertension, with past or present methamphetamine use, with mean pulmonary artery pressure of 20-25 mm Hg, or with PH observed only during exercise.

Since not all factors that may be determinants of outcome can be anticipated, registries must be designed to accommodate and explore future advances in knowledge as they develop. This requires CRFs to be fluid enough to allow changes in coding variables over time, but more importantly mandates that blood and tissue of participants be collected and stored so that biomarker and genetic correlates to clinical phenotypic expression can be examined both in the present and the future.

The profile of PH varies throughout the world, and comparison between environments, population demographics, and health care delivery systems may permit the development of hypotheses about how PH is best diagnosed and managed under different conditions. Accordingly, systematic acquisition of clinical data in registries worldwide represents a desirable objective.

Collaborative efforts among registries have been useful in creating hypotheses about these observations, but have been hampered to an extent by differences in study design, patient ascertainment, entry criteria, and follow-up. More uniformly designed and orchestrated registry data acquisition and analysis will likely yield more coherent observations and conclusions.

The overriding question is not so much whether a global approach to PH registry data is desirable, but how it could be achieved. Several models can be considered: (i) a single global registry with a unified funding source under the direction of a single steering committee; (ii) a variety of national or regional registries, each with distinct funding sources and separate steering committees, but using a common (or overlapping) CRF and comparable enrollment principles; (iii) independently developed and operated databases using separate CRFs, which can be compared using adjustments for differences to the extent possible during post-hoc collaborations. Of these, (ii) seems to be the best compromise between collaboration and feasibility.
References
During the Fifth World Symposium on Pulmonary Hypertension, the working group on diagnosis and assessment was charged with evaluating the definition of pulmonary arterial hypertension (PAH) as it was established at the Fourth World Symposium. The group also covered related topics such as “borderline PAH,” exercise-induced PAH, and issues surrounding the measurement of pulmonary capillary wedge pressure (PCWP). The working group’s discussion specifically addressed the following questions:

1. Should pulmonary hypertension (PH) continue to be defined by a resting mean pulmonary artery pressure (MPAP) ≥25 mm Hg, and should the term “borderline PH” be introduced?
2. Should exercise-induced PH be included as a subset of PH?
3. Should pulmonary vascular resistance (PVR) be reintroduced in the definition of PAH?
4. Is pulmonary artery wedge pressure (PAWP) of 15 mm Hg adequate to distinguish between pre- and post-capillary PH, and how should it be measured?
5. Should fluid or exercise challenge be used to distinguish patients with PAH from pulmonary venous hypertension (PVH)?
6. Should exercise hemodynamics be used to unmask left sided heart failure?

The task force met for 2 consecutive days to address these 6 questions. The group spent many hours reviewing research and communicating with experts in the specific fields, and was able to successfully provide evidence-based, expert opinion surrounding these issues. Specific recommendations for each of the 6 issues are summarized in this article.

The first question concerned the definition of PH. The controversial issue at hand is considering the value of 25 mm Hg of mean pulmonary artery pressure (MPAP) as the cutoff to define PH. A normal MPAP has been described as less than 20 mm Hg; however, the value 25 mm Hg has historically been used as the lowest pressure to define PH. This value comes from data on 1187 healthy volunteers from 47 studies in 13 countries. The MPAP at rest was 14.0 ± 3.3 mm Hg, independent of gender and ethnicity. Age did not seem to change this value either (<30 years: 12.8 ± 3.1 mm Hg; 30-50 years: 12.9 ± 3.0 mm Hg; ≥50 years: 14.7 ± 4.0 mm Hg). All multicenter clinical trials have used 25 mm Hg as part of the definition to define PAH, and this pressure is now well established in the PH community. Furthermore, patients with significant PH generally have MPAP well above 25 mm Hg. The controversy involves those patients with MPAP 21-24 mm Hg who in fact have an elevated MPAP, but no “diagnosis.” Thus, the committee considered use of the term “borderline PH” for this subset of patients. The group agreed that this population does have an abnormal MPAP, but had concerns regarding the implications of labeling it as PH.

There is some evidence showing that patients with scleroderma-spectrum PAH who have MPAP between 21 and 24 are at risk for developing PAH. The PHAROS registry was a multicenter, prospective, longitudinal cohort of patients with scleroderma “at risk” for or recently diagnosed with resting PH on right heart catheterization. Using the PHAROS registry, out of 206 patients who underwent right heart catheterization, 28 patients were found to have borderline MPAP. Of the patients with borderline PH, 55% developed resting PH in the following 25.7 months. Little is known about the implications of these pressures in other diseases associated with PH. One concern involves the group of patients with heart failure with preserved ejection fraction (HFpEF) who may be mistakenly classified as having PAH and then be exposed to medications that have shown no clear benefit. In the HFpEF population, the term “borderline PH” as discussed in the current context does not apply. Thus, after multiple discussions the group determined that the creation of this category would be a disservice to patients. The final recommendations
were to continue close monitoring of patients at high risk of developing PH if they had MPAP 21–24 mm Hg, as they could progress to PAH.

The second question addressed by the work force related to the controversial term “exercise-induced PH.” This term was introduced before the Fourth World Symposium. There are patients who develop a “significant” elevation of their MPAP with exercise—the definition of exercise-induced PH. This term has been used to describe an increase of the MPAP ≥30 mm Hg for patients during exercise. However, the workload level, type, or position of exercise has not been standardized. Furthermore, the MPAP seems to increase with age, especially in patients over age 50. During the review of the literature, subjects >50 years of age had MPAP 29.4 ± 8.4 mm Hg during exercise. This was statistically higher (P<0.001) than the younger patients, whose MPAP increased to 19.4 ± 4.8 mm Hg during exercise.1

One of the purposes to define “exercise-induced PH” is the ability to determine prognostic values and therapeutic implications during exercise. Currently, we do not have definitive data on either of these measures. Active studies are being conducted among the patients with scleroderma-spectrum disease and exercise-induced PH.

During a 24-week study, patients exercised in a supine position on a lower extremity cycle ergometer. At baseline, they all had normal resting hemodynamics, but with exercise MPAP >30 mm Hg and transpulmonary gradient of >15 mm Hg. After 24 weeks of treatment with ambrisentan, there were improvements in MPAP: -4.1 mm Hg (P=0.02), PVR -1.0 Wood units (P=0.003), and cardiac output (CO) 1.4 L/min (P=0.006).3 Tolle et al described the cardiopulmonary exercise test of patients with “exercise-induced PH,” identifying 78 patients with the condition. These patients were compared to 15 resting PAH and 16 normal subjects. All subjects did the cardiopulmonary exercise test with a PA catheter in place. The VO2 max 55.8% ± 20.3% vs 66.5% ± 16.3% vs 91.7% ± 13.7% predicted was lowest in the resting PAH, “exercise-induced PH,” and normal groups respectively. The MPAP at exercise was 48.4 ± 11.1 vs 36.6 ± 5.7 vs 27.4 ± 3.7 mm Hg respectively.4 Studies on exercising patients, attempting to better define this population, are increasing in number. But despite the available data, the final recommendation was to not incorporate the term “exercise-induced PH” as part of the formal PH definition until further studies have been performed.

The third issue discussed was the need to add PVR to the definition of PH and/or PAH. Much of the conversation focused on ensuring that a right side catheterization was performed to make the diagnosis of PAH in conjunction with certain conditions that increase blood flow through the pulmonary capillary bed, which can cause an elevation of the MPAP without increasing the PVR. Thus, it was considered important for the definition of PH to remain without the requirement of a specific PVR during the 4th World Symposium meeting. When the current state of hemodynamic considerations were discussed in Nice, the strong opinion of the committee was to add PVR to the definition of PAH to ensure that patients will have a cardiac output measurement as well as a PAWP measurement at the time of diagnosis of PAH and, for patients with left heart disease and PH, to incorporate PVR along with PAWP to aide in discriminating the two entities. Though the upper limit of normal for PVR is 2 Wood units, keeping a PVR >3 Wood units is important since that value is used in hemodynamics in clinical trials, and patients with PAH rarely have a lower PVR. Standardization of the units of the PVR was also part of the discussion. The group agreed on the preference of using Wood units since this measurement does not necessitate using a factor of 80 to calculate dyn·s/cm². The use of SI unit was not recommended as it is not used clinically.

The fourth subject addressed by the working group involved the use of the term PAWP rather than PCWP, and the value of keeping the definition of abnormal PAWP at >15 mm Hg. The term PCWP can be deceiving, as the pressure in the capillary bed may be different in the “ocluded” vessel than in the “nonocluded” areas. At the same time, the term “wedge” is very well established in the medical community, including countries that do not have English as their first language. Therefore, the group decided to recommend using the term pulmonary artery occlusion pressure (PAOP) or PAWP. Thus, PAWP will become the new official term for “wedge.”

Following the consensus of the term PAWP, the group discussed the normal value of PAWP and how to measure it correctly—ultimately agreeing that the standard way to measure PAWP is at the end of expiration. It is concerning that digital equipment will sometimes underestimate PAWP, as it does not always account for the breathing pattern. Measuring PAWP at end of expiration, across all ages, normal PAWP should be 9 ± 2 mm Hg. The committee acknowledged that during a small study of healthy volunteers at ages >70, the normal level appeared to be higher, but not over 15 mm Hg. Also, Prasad et al had a small group of patients well characterized as having HFpEF in which hemodynamics were performed showing that normal PAWP increased with age slightly, but usually not greater than 15 mm Hg.5 So, the group acknowledged that PAWP ≤15 mm Hg did not rule out the presence of HFpEF, therefore introducing the consideration of lowering the PAWP ≤12 mm Hg rather than the historical ≤15 mm Hg. Lowering the PAWP cutoff was favored in one regard, because it would decrease the chance of misclassifying HFpEF patients as having PAH. This was balanced with the increased sensitivity of keeping the PAWP ≤15 mm Hg and identifying more PAH patients. The committee recognized that there is no single PAWP that enables correct classification of all patients. Abraham et al implanted hemodynamic monitoring devices on 500 patients with left heart failure, and noticed that it is possible to at least temporarily lower the PAWP below 15 mm Hg with diuretics and medications for treatment of left heart failure.6 Ultimately the group decided it was more important not to risk mistakenly missing presence of PAH by lowering the PAWP to 12 mm Hg, and recom-
mended the PAWP \(\leq 15\) mm Hg remain as the cutoff for the definition of PAH.

The fifth question of performing fluid challenges was very interesting, as it was evident that most of the group had been performing fluid challenges during right side catheterization to increase the sensitivity of identifying patients with HFpEF when their wedge is normal in patients with clinical scenario of HFpEF rather than PAH. Data from Bush et al described marked increase in PAWP in normal volunteers when a large volume of fluid was given. Infusion of 1 L normal saline over 6-8 minutes. The subjects had an increase in PAWP by 3 mm Hg, but not above 11 mm Hg. Other data from Fujimoto et al described marked increase in PAWP in normal volunteers when a large volume of fluid was given. Infusion of 1 L normal saline at 100-200 cc/min to healthy volunteers increased the PAWP from 10 to 20 mm Hg. In addition, females >50 years of age demonstrated a steeper increase in PAWP at 20 mm Hg compared to males. Subjects with HFpEF showed a greater increase in PAWP at 25 mm Hg. Thus, the group determined that there is no optimal standardized fluid challenge procedure, and the response to fluid challenge may differ depending on gender and age. Furthermore, there were not enough safety data on patients with severe PH or HFpEF to determine definitively regarding fluid challenge testing. However, based on collective experience in the absence of formal guidelines, 500 cc over 5 to 10 minutes would be considered enough to distinguish PAH from HFpEF.

The last topic addressed by the committee related to the use of exercise hemodynamics to unmask left heart failure. This was a nonstarter early in the discussion. During exercise, the pleural pressures and airway pressures change, making it very difficult to assess PAWP. Further complicating the issue, there are multiple reports about normal volunteer athletes with PAWP over 20 mm Hg during exercise. It is understood that patients with presumed HFpEF and normal resting PAWP levels at rest would increase their PAWP \(>30\) mm Hg with exercise. It is also known that...
patients with left heart disease have higher PAWP than PAH scleroderma patients. Thus, the committee acknowledged some value to the exercise hemodynamics. But, given the difficulty of doing the procedure during exercise, with no standardization and lack of normal values at different ages, the group could not endorse this practice until further studies are completed.

The committee recognized a need to reinforce some of the previous recommendations regarding right heart catheterizations, as inaccurately measuring hemodynamics could have significant consequences. Thus, the group discussed the necessity of measuring the right atrium (RA), right ventricle, MPAP, PAWP, CO, and mixed venous saturations on all right side catheterizations. The Fick method was deemed the gold standard test for measuring CO, but the group determined that its difficulty and limited availability are not enough to endorse it as the preferred method. The indirect Fick measure is considered too unreliable. Thus, the group feels that thermodilution CO is the preferred CO measurement during right catheterization. The committee was also careful to remind physicians of the importance of making the zero level of the pressure transducer at the RA level, and also discussed that pulmonary arteriogram (if it was to be performed) should be done after the full set of hemodynamics have been collected.

The committee remains concerned about the delay in diagnosis of this lethal disorder, and highlighted some of the advances and recommendations to improve early diagnosis of PAH. The group discussed the challenge of using genetic markers on patients with hereditary PAH (HPAH). In the sporadic cases of idiopathic PAH, 20% have a BMPR2 gene mutation, while 70% of HPAH have the mutation. The low penetrance of the mutation makes the genetic testing difficult to justify, as it will cause significant psychological distress on a patient who may never develop the disorder. Thus, it is still the recommendation that if genetic testing is ordered, expert counseling must be provided to the patient. Screening protocols on other at-risk populations have not changed, except for patients with the scleroderma spectrum of disease.

The DETECT (evidence-based detection of PAH in systemic sclerosis) study is a 2-step method to screen patients for PAH. The first step is to look for telangiectasia, anti-centromere antibodies, right axis deviation on ECG, and low diffusion lung capacity for carbon monoxide (DLCO) (<60%) and biomarkers. This gave a 97% sensitivity for PAH. Step 2 included doing an echocardiogram and then right side catheterization. The DETECT algorithm has not been validated for DLCO >60%. Finally, the committee made a diagnostic algorithm for PH (Figure 1) modified from the 2009 European guidelines.

In summary, the working group reviewed new published data attempting to better understand PH. Significant advances have been made in the scleroderma-spectrum disease, clarifying hemodynamics in this population and making guidelines on how to screen for PAH in this population. But still more is needed in other types of PAH patients. The HFpEF population continues to present a challenge for the PH community, and progress is underway in identifying these patients and understanding their hemodynamics on exercise and with fluid challenges. Still, the correct use of right side catheterization to diagnose this disease—the most critical aspect in determining the presence, type, and severity of PH—is not at 100%, and the committee hopes that this article helps expand its use.

References
The complexity of the treatment algorithm for pulmonary arterial hypertension (PAH) has progressively increased since the Second World Symposium on Pulmonary Hypertension (WSPH) in Evian, France, in 1998 when, apart from calcium channel blockers (CCBs) for vasoreactive patients, the only approved therapy was epoprostenol administered by continuous intravenous infusion. Currently 10 drugs from 3 main pharmacological groups (addressing 3 pathways) and 4 different routes of administration (oral, inhaled, subcutaneous, and intravenous) have been officially approved for PAH patients. Although this progress in pharmacotherapy has been associated in different meta-analyses with a reduction of morbidity and mortality observed, limiting symptoms and poor outcome still characterize patients with PAH.

The current treatment algorithm, as proposed during the Fifth World Symposium on Pulmonary Hypertension is divided into 3 main sections. The first includes general measures (rehabilitation/exercise and exercise training, psychosocial support, pregnancy, vaccinations), supportive therapy (anticoagulants, diuretics, digitalis, oxygen), the roles of referral centers, acute vasoreactivity testing, and chronic CCB therapy. The second provides information about the initial therapy and includes drugs approved in PAH in at least one country, according to the World Health Organization functional class (WHO-FC) of the patients and the grade of recommendation and level of evidence of each individual compound. The third section provides indications according to the clinical response to the initial therapy and in case of inadequate results, combination drug therapy and additional interventional procedures such as balloon atrial septostomy (BAS) and lung transplantation are recommended. The European Society of Cardiology grades of recommendation and levels of evidence are adopted to score the proposed treatments. The treatment algorithm is shown in Figure 1.

**GENERAL MEASURES**

**Pregnancy**

Pregnancy is associated with a substantial mortality rate in PAH. A recent report over a 3-year period documented 26 pregnancies. Three women (12%) died and one (4%) developed right heart failure requiring urgent heart-lung transplantation. These data must be confirmed by larger series before the general recommendation to avoid pregnancy in all patients with PAH is reconsidered (grade of recommendation I, level of evidence C).

**Rehabilitation and Exercise Training**

Supervised exercise rehabilitation may improve exercise and functional capacity and quality of life in patients with pulmonary hypertension (PH). The limitations of this method are based on the gaps in knowledge of the optimal method, intensity, and duration of the training; of the characteristics of the supervision; and of the practical organization in the real world. Despite this, a grade of recommendation class I with a level of evidence A has been granted.

**Supportive Therapy**

No changes have been proposed for anticoagulants, diuretics, digitalis, and oxygen. Long-term oxygen therapy is suggested to maintain arterial blood oxygen pressure ≥8 kPa (60 mm Hg).

**Referral Centers and Vasoreactivity Testing**

The recommendation to refer patients to expert centers after PAH diagnosis is maintained, and acute vasoreactivity testing remains mandatory in patients with idiopathic PAH to identify subjects that will respond favorably to long-term treatment with high doses of CCBs. Inhaled nitric oxide (iNO) is the compound of choice for the acute test.

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**Key Words**— endothelin receptor antagonists, guanylate cyclase stimulators, lung transplantation, phosphodiesterase type-5 inhibitors, prostanoids, pulmonary hypertension

Disclosure: Dr Galie reports having served on advisory boards for Eli Lilly and Company, Actelion, Pfizer, Bayer-Schering, GlaxoSmithKline, and Novartis; he has received payment for lectures for Eli Lilly and Company, Pfizer, Bayer-Schering, and GlaxoSmithKline. He reports that his institution has received grant support from Actelion, Pfizer, Bayer-Schering, GlaxoSmithKline, and Novartis.
INITIAL THERAPY WITH APPROVED PAH DRUGS

Therapy with approved PAH drugs needs to be initiated in PAH patients who are not vasoreactive, or are vasoreactive but not responding appropriately to CCBs (Figure 1). For the initial therapy, drugs are classified according to the grade of recommendation and the level of evidence based on published randomized controlled trials (RCTs). In addition, initial drug therapies are stratified according to WHO-FC.

INDIVIDUAL COMPONDS

Pharmacological classes and drugs are listed in alphabetical order. Only compounds approved for PAH are included in the treatment algorithm and are listed in alphabetical order (Figure 1).

Endothelin Pathway

Activation of the endothelin system has been demonstrated in both plasma and lung tissue of PAH patients, and these data support a prominent role for the endothelin system in the pathogenesis of PAH. Endothelin exerts vasoconstrictor and mitogenic effects.

Endothelin Receptor Antagonists

Ambrisentan. Ambrisentan is a nonsulfonylamide, propanoic acid-class, endothelin receptor antagonist (ERA) that is selective for the endothelin-A receptor. Ambrisentan has been evaluated in different studies that have demonstrated efficacy on symptoms, exercise capacity, hemodynamics, and time to clinical worsening of patients with idiopathic PAH and PAH associated with connective tissue disease (CTD) and HIV infection. Ambrisentan has been approved for the treatment of WHO-FC II and III patients. The incidence of abnormal liver function tests ranges from 0.8% to 3%, and monthly liver function assessment is not mandated in the United States. An increased incidence of peripheral edema has been reported. Ambrisentan is approved for PAH patients.

Bosentan. Bosentan is an oral active dual endothelin A- and B-receptor antagonist and has been evaluated in PAH (idiopathic, associated with CTD and Eisenmenger syndrome) in multiple RCTs, which showed improvement in exercise capacity, functional class, hemodynamics, echocardiographic and Doppler variables, and time to clinical worsening. Increases in hepatic aminotransferases occurred in approximately 10% of the subjects, and liver function testing should be performed monthly in patients receiving bosentan. Bosentan is approved for PAH patients.
Macitentan. The dual ERA macitentan was developed by modifying the structure of bosentan to increase efficacy and safety. In the event-driven SERAPHIN study\textsuperscript{25} of 742 PAH patients, macitentan significantly reduced a composite endpoint of morbidity and mortality among patients with PAH and also increased exercise capacity. Benefits were shown both for patients who had not received treatment previously and for those receiving sildenafil. While no liver toxicity was shown, reduction in blood hemoglobin ≤8 g/dl was observed in 4.3% of patients receiving 10 mg of macitentan. The drug is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for PAH patients.

Nitric Oxide Pathway
Impairment of nitric oxide (NO) synthesis and signalling through the NO–soluble guanylate cyclase–cyclic guanosine monophosphate pathway (cGMP) is involved in the pathogenesis of PH through the reduction of intracellular concentrations of cGMP, a vasodilator and antiproliferative effector.

Soluble Guanylate Cyclase Stimulators
While phosphodiesterase type-5 inhibitors (PDE-5is) such as sildenafil, tadalafil, and vardenafil enhance the NO–cGMP pathway slowing cGMP degradation, soluble guanylate cyclase (sGC) stimulators enhance cGMP production.

Riociguat. Riociguat has a dual mode of action, acting in synergy with endogenous NO and also directly stimulating sGC independent of NO availability. An RCT (PATENT-1)\textsuperscript{26} in 443 PAH patients (44% and 6% on background therapy with ERAs or prostanoids, respectively) treated with riociguat up to 2.5 mg 3 times daily has shown favorable results on exercise capacity, hemodynamics, WHO-FC, and time to clinical worsening. The most common serious adverse event in the placebo group and the 2.5 mg group was syncope (4% and 1%, respectively). Hemoptyis was more frequent with riociguat and not observed with placebo. The combination of riociguat and PDE-5i is contraindicated due to hypotension and other relevant side effects detected in the open-label phase of the PATENT-plus study.\textsuperscript{27} Riociguat is approved by the FDA and EMA for PAH patients.

Phosphodiesterase Type-5 Inhibitors
Inhibition of the PDE-5 results in vaso-dilatation and antiproliferative effects through the NO/cGMP at sites expressing this enzyme, including the pulmonary vasculature.\textsuperscript{28,29} All 3 PDE-5is approved for the treatment of erectile dysfunction—sildenafil, tadalafil, and vardenafil—cause significant pulmonary vasodilation, with maximum effects observed after 60, 75–90, and 40–45 minutes, respectively.\textsuperscript{30}

Sildenafil. Sildenafil is an orally active, potent, and selective inhibitor of PDE-5. Four RCTs in PAH patients treated with sildenafil have confirmed favorable results on exercise capacity, symptoms, and/or hemodynamics.\textsuperscript{31–34} The PACES trial addressing the effects of adding sildenafil to epoprostenol showed improvements after 12 weeks in 6-minute walk distance (6MWD) and time to clinical worsening. Of note, 7 deaths occurred in this trial, all in the placebo group.\textsuperscript{35} The approved dose of sildenafil is 20 mg tid. Most side effects of sildenafil are mild to moderate and mainly related to vasodilation (headache, flushing, epistaxis).

Tadalafil. Tadalafil is a once-daily, selective PDE-5i. An RCT (PHIRST) in 406 PAH patients (53% on background bosentan therapy) treated with tadalafil 2.5, 10, 20, or 40 mg has shown favorable results on exercise capacity, symptoms, hemodynamics, and time to clinical worsening at the highest dose.\textsuperscript{36} The side-effect profile was similar to that of sildenafil. Tadalafil is approved for PAH patients.

Vardenafil. Vardenafil is a twice-daily PDE-5i. An RCT (EVALUATION) in 66 treatment-naïve PAH patients treated with vardenafil 5 mg has shown favorable results on exercise capacity, hemodynamics, and time to clinical worsening.\textsuperscript{37} The side-effect profile was similar to that of sildenafil. Vardenafil is currently not approved for PAH patients.

Platelet-Derived Growth Factor Pathway
Evidence from animal models and human disease suggest that platelet-derived growth factor (PDGF) and c-KIT signalling are important in vascular smooth muscle cell proliferation and hyperplasia.

Tyrosine Kinase Inhibitors
Imatinib. Imatinib is an antiproliferative agent developed to target the BCR-abl tyrosine kinase in patients with chronic myeloid leukemia. In addition, the inhibitory effects of imatinib on PDGF receptors and c-KIT suggest that it may be efficacious in PAH. Two RCTs on PAH patients treated with imatinib (all of them on background therapy with at least 2 approved PAH drugs) have shown positive results on exercise capacity and hemodynamics (data possibly influenced by the dropout rate in the treated group), but failed to show favorable effects on time to clinical worsening.\textsuperscript{38,39} In addition, an increased incidence of subdural hematoma was observed in PAH patients treated with both imatinib and oral antiagulants. Regulatory consideration of imatinib for the PAH indication has recently been halted.

Prostacyclin Pathway
Prostacyclin is produced predominantly by endothelial cells and induces potent vasodilatation of all vascular beds, and in addition is an inhibitor of platelet aggregation and appears to have both cytoprotective and antiproliferative activities.\textsuperscript{40}

Prostanoids
Beraprost. Beraprost is the first chemically stable and orally active prostacyclin analogue. The RCT ALPHABET\textsuperscript{41} in Europe and a second study in the US\textsuperscript{42} with this compound have shown an improvement in exercise capacity, which unfortunately persists only up to 3 to 6 months. Beraprost is approved for PAH in Japan and South Korea.

Epoprostenol. Epoprostenol (synthetic prostacyclin) has a short half-life (3 to 5 minutes) and is stable at room temperature for only 8 hours requiring cooling, continuous administration by means of an infusion pump, and a permanent tun-
nelled catheter. The efficacy of continuous intravenous administration of epoprostenol has been tested in 3 unblinded RCTs in patients with idiopathic PAH and in those with PAH associated with the scleroderma spectrum of diseases. Epoprostenol improves symptoms, exercise capacity, and hemodynamics in both clinical conditions, and is the only treatment shown to reduce mortality in idiopathic PAH in a randomized study and a meta-analysis. Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction, and sepsis. Intravenous epoprostenol is approved for PAH patients. A thermostable formulation of epoprostenol is approved by the FDA and EMA.

Iloprost. Iloprost is a chemically stable prostanycin analogue available for intravenous, oral, and aerosol administration. Inhaled iloprost has been evaluated in 1 RCT (AIR) with daily repetitive iloprost inhalations (6 to 9 times). The study showed an increase in exercise capacity and improvement in symptoms, pulmonary vascular resistance (PVR), and clinical events in enrolled patients. Two additional RCTs (STEP and COMBI) of patients already treated with bosentan have shown conflicting results of the addition of inhaled iloprost. Continuous intravenous administration of iloprost appears to be as effective as epoprostenol in a small, uncontrolled series of patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH). Inhaled iloprost is approved for PAH. The intravenous formulation is approved for PAH in New Zealand.

Treprostinil. Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at ambient temperature. These characteristics allow administration of the compound intravenously, as well as subcutaneously and orally. The subcutaneous administration of treprostinil can be accomplished by a micro-infusion pump and a small, subcutaneous catheter. The effects of treprostinil in PAH were studied in an RCT and showed improvements in exercise capacity, hemodynamics, and symptoms. Infusion site pain was the most common adverse effect of subcutaneous treprostinil. An RCT was performed with intravenous treprostinil in PAH patients (TRUST), but the enrollment of this trial was closed after 45 (36%) of the planned 126 patients had been randomized because of safety considerations. The data generated from 42 (25%) survivors after the randomized phase (23 active and 8 placebo) are not considered reliable.

An RCT (TRIUMPH) with inhaled treprostinil in PAH patients on background therapy with either bosentan or sildenafil showed improvements in 6MWD by 20 m at peak dose, NT-proBNP, and quality of life measures. Oral treprostinil has been evaluated in 2 RCTs in PAH patients on background therapy with bosentan and/or sildenafil (FREEDOM C1 and C2) and in both the primary endpoint 6MWD did not reach statistical significance. An additional RCT in PAH-naïve patients showed improvement in 6MWD by 26 m at peak dose. Subcutaneous treprostinil is approved for PAH. Intravenous treprostinil is approved in the US and EU in patients with PAH who cannot tolerate the subcutaneous administration. Inhaled and oral treprostinil are approved for PAH in the US.

Prostacyclin IP-receptor Agonists
Selexipag. Selexipag is an orally available, selective prostacyclin IP receptor agonist. In a pilot RCT in PAH patients (receiving stable ERA and/or PDE-5i therapy), selexipag reduced PVR after 17 weeks. A large, event-driven Phase 3 RCT (GRIPHON) is ongoing. Sel exipag is currently not approved for PAH.

CLINICAL RESPONSE, COMBINATION THERAPY, AND INTERVENTIONAL PROCEDURES
Clinical Response
After initial therapy, the next steps are based on the clinical response, which is usually reassessed at 3 to 6 months after treatment start. The clinical response is based on the evaluation of different parameters, including WHO-FC, exercise capacity, cardiac index, right atrial pressure, NT-proBNP plasma levels, echocardiographic parameters, and perceived need for additional/change of therapy. If the clinical response is considered not adequate, combination therapy is considered.

Combination Therapy
Combination therapy—using 2 or more classes of drugs simultaneously—is an attractive option for the management of PAH, because 3 separate signalling pathways are known to be involved in the disease: the prostacyclin pathway, the endothelin pathway, and the NO pathway. A recent meta-analysis on 6 RCTs with combination therapy including 858 patients has been published: compared with the control group, combination therapy reduced the risk of clinical worsening.

The patterns to apply combination therapy may be sequential or initial (up front). Sequential combination therapy is the most widely utilized strategy both in RCTs and in clinical practice. From monotherapy there is addition of a second and then a third drug in cases of inadequate clinical results or in cases of deterioration. A structured prospective program to evaluate the adequacy of clinical results is the so-called “goal-oriented therapy,” a treatment strategy that uses known prognostic indicators as treatment targets. The therapy is considered adequate only if the targets are met. The key difference between goal-oriented therapy and nonstructured approaches is that patients are stabilized, or even those who improve slightly, can still receive additional therapy if treatment goals are not met. The goal-oriented treatment strategy has been endorsed by recent PAH guidelines proposing different targets including WHO-FC I or II and the near normalization of resting cardiac index and/or of NT-proBNP plasma levels. A recent study has confirmed a better prognosis in patients achieving these goals as compared with the patients who did not.

Sequential combination therapy has been allocated a grade of recommendation I and level of evidence A in PAH patients with inadequate clinical response to initial monotherapy. The rationale for
Initial or up-front combination therapy is based on the severity of PAH and with the attempt to “hit early and hit hard.” The evidence for this strategy is still limited. The study showed a statistically significantly greater decrease in PVR in the initial combination therapy group, but this hemodynamic benefit did not translate into a statistically significant difference in survival, or in transplant-free survival. An RCT (AMBITION) comparing first-line monotherapy with tadalafil or ambrisentan with initial combination therapy with tadalafil and ambrisentan in de novo WHO-FC II and III PAH patients has been completed recently, and results will be available very soon. In the meantime, initial combination therapy has been allocated a grade of recommendation IIb and level of evidence C in WHO-FC IV PAH patients in case of nonavailability of intravenous prostanoids.

Interventional Procedures

Lung transplantation. The advent of disease-targeted therapy for severe PAH has reduced and delayed patients’ referral to lung transplant programs. The long-term outcomes of medically treated patients remains uncertain, and transplantation should continue to be an important option for those who fail on such therapy and remain in WHO-FC III or IV. The overall 5-year survival following transplantation for PAH was considered to be 45% to 50%, with evidence of continued good quality of life. More recent data show that survival is increased to 52% to 75% at 5 years and to 45% to 66% at 10 years. Given this information, it seems reasonable to consider eligibility for lung transplantation after an inadequate clinical response to the initial monotherapy, and to refer the patient soon after the inadequate clinical response is confirmed on maximal combination therapy. Currently the vast majority of patients worldwide receive bilateral lungs as evidenced by the International Society for Heart and Lung Transplantation registry figures. Patients with Eisenmenger syndrome due to simple shunts have been treated by isolated lung transplantation and repair of the cardiac defect or by heart-lung transplantation. Recent reports indicate that venoarterial extracorporeal membrane oxygenation may be employed in awake end-stage PH patients for bridging to lung transplantation.

Balloon atrial septostomy. The creation of an interatrial right-to-left shunt can decompress the right heart chambers and increase left ventricle preload and cardiac output. In addition, this improves systemic oxygen transport despite arterial oxygen desaturation and decreases sympathetic hyperactivity. The recommended technique is graded BAS, which produces equivalent improvements in hemodynamics and symptoms, but reduced risk compared with the original blade technique. Other techniques are considered experimental. The impact of BAS on long-term survival has not been established in RCTs. BAS should be regarded as a palliative or bridging procedure to be performed only by centers with experience in the method.

TREATMENT ALGORITHM

The treatment algorithm for PAH patients is shown in Figure 1. The treatment algorithm does not apply to patients in other clinical groups, and in particular not to patients with PH associated with Group 2, left heart disease, or with Group 3, lung diseases. Only the compounds officially approved for PAH in at least one country are included. Single compounds are listed by alphabetical order according to the pharmacological name. As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be proposed. In this case, the choice of the drug may depend on a variety of factors including the approval status, the labelling, the route of administration, the side-effect profile, patients’ preferences, physician experience, and the cost. Drugs with morbidity and mortality as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined) have been highlighted.

The first algorithm section includes the adoption of the general measures, the initiation of the supportive therapy, and referral to an expert center. The acute vasoreactivity testing should be performed in patients with idiopathic PAH, heritable PAH, and PAH associated with anorexigen use. Vasoreactive patients should be treated with optimally tolerated doses of CCBs; adequate response should be confirmed after 3 to 4 months of treatment. Nonresponders to acute vasoreactivity testing who are in WHO-FC II should be treated with an oral compound; patients in WHO-FC III should be considered candidates for treatment with any of the approved PAH drugs. As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be proposed (see above) for either WHO-FC II or III patients.

Continuous intravenous epoprostenol is recommended as first-line therapy for WHO-FC IV PAH patients because of the survival benefit in this subset. In the absence of intravenous epoprostenol, all other compounds may be utilized. In WHO-FC IV patients, initial combination therapy may be considered.

In case of inadequate clinical response, sequential combination therapy should be considered. Combination therapy can either include an ERA plus a PDE-5i or a prostanoid plus an ERA or a prostanoid plus a PDE-5i. The sGC stimulator riociguat can be considered as a potential alternative to PDE-5i in the different types of double combinations. The combination of riociguat and PDE-5i is contraindicated.

In case of inadequate clinical response with double combination therapy, triple combination therapy should be attempted. It seems reasonable to consider eligibility for lung transplantation soon after the inadequate clinical response is confirmed on maximal combination therapy. BAS should be regarded as a palliative or bridging procedure in patients deteriorating despite maximal medical therapy.

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ASK THE EXPERT

How Might Adherence to the Treatment Recommendations of the 2013 Fifth World Symposium on Pulmonary Hypertension Improve Long-Term Outcomes?

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A significant expansion in knowledge regarding the diagnosis and treatment of pulmonary arterial hypertension (PAH) within the past 2 decades has transformed a very high-mortality disease without specific therapy for the majority of patients to one with 10 drugs as very effective therapeutic choices. Yet despite these advances, data from various worldwide registries indicate a sobering 5-year survival between 21% and 68%. While ongoing pulmonary vascular research holds the promise of future novel treatment modalities for PAH, the more immediate impact of the Fifth World Symposium on Pulmonary Hypertension (WSPH) on disease treatment may be the intensifying focus on goal-oriented therapy.

Whether the term is “goal-oriented therapy,” “treat-to-target strategies,” or “goal-directed therapy,” the treatment approach to PAH is evolving in a manner similar to that of other diseases such as diabetes and sepsis. The treat-to-target trial, published in 2003, reported the results of using different insulin types added to oral diabetic therapy as a combination treatment approach in meeting a specific target hemoglobin A1c. The results demonstrated that insulin could be safely added to oral therapy, more effectively achieving the recommended targets of diabetes care. In 2001, when an acceptable treatment goal for PAH may have been any functional improvement or even disease stability, an approach to early goal-directed therapy for severe sepsis and septic shock was published. This sepsis treatment algorithm monitored cardiovascular parameters including central venous pressure, mean arterial pressure, and mixed venous oxygenation, and responded with directed therapies to meet specific goals. The goal-directed therapy group had nearly half the mortality due to sudden cardiovascular collapse compared with the standard-therapy group in that trial. Both of these studies contain parallels to evolving PAH care: the diabetes trial for its promulgation of an earlier combination therapeutic approach to improve care, and the sepsis trial for its use of well-established treatments to achieve goals and not relying on a newly developed drug or device in their algorithm. The diabetes trial, however, benefited from a single, well-accepted marker of disease treatment in the hemoglobin A1c, while the sepsis trial may be more relevant to PAH as it relied on a combination of cardiovascular parameters to describe its treatment targets.

Defining a set of treatment targets for guiding PAH therapy was becoming established by 2005 with the publication of Hoeper and colleagues, who described their clinical practice of progressive therapeutic interventions aimed at achieving a 6-minute walk distance greater than 380 meters, peak oxygen uptake during exercise testing of greater than 10.4 mL/min/kg, and peak systolic blood pressure greater than 120 mm Hg during exercise. These authors observed a significant improvement in actual survival compared to expected survival and that of historical controls, as well as reduced requirement for initiation of intravenous prostacyclin and referral for lung transplantation. Subsequently, in 2010, Sitbon and Galie reviewed additional prognostic data in PAH and stressed the importance of using multiple goals to assess the adequacy of response to therapy in individual patients. The European Society of Cardiology/European Respiratory Society guidelines for pulmonary hypertension are cited in that review, which (similarly to the American College of Cardiology/American Heart Association 2009 expert consensus document on pulmonary hypertension) recommend clinical evidence of right ventricular (RV) failure, rate of symptom progression, syncope, World Health Organization functional class, B-type natriuretic peptide (BNP)/N-terminal BNP, echocardiographic findings, and hemodynamics as additional determinants of prognosis to incorporate when assessing treatment strategies.

The Fifth WSPH report on treatment goals of pulmonary hypertension builds on these previous guidelines and appropriately promotes identification of clinically relevant treatment goals that correlate with long-term outcome as a top priority. While incorporating previously defined treatment goals, the WSPH report also emphasizes our evolving approach to set more aggressive

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targets for patients to achieve in terms of exercise capacity and right heart function, as these are known to be important correlates of long-term outcome (Table 1). Right heart function as assessed by cardiac magnetic resonance imaging and echocardiographic parameters other than estimated RV systolic pressure, such as tricuspid annular plane systolic excursion (TAPSE), RV strain, RV area, and pericardial effusion expand on those cardiac parameters emphasized in previous publications. Importantly, this workforce on treatment goals also reaffirmed that published studies have consistently shown that composite treatment goals are more predictive of long-term outcomes than any single test.

In summary, our overall aim of maximizing survival and function in PAH may best be achieved by utilizing a goal-oriented approach in clinical practice, as was shown to significantly benefit outcomes in illnesses such as diabetes and sepsis. Unlike diabetes, however, PAH clinicians must utilize a multifaceted assessment, as in PAH we are lacking a single reliable test equivalent to the hemoglobin A1c. We need to rely on composite treatment targets, which have proven successful in the early goal-directed treatment of sepsis. Ultimately, we realize that our patients face multiple challenges during their journey with PAH. If we pursue the updated PAH treatment algorithm as our roadmap for optimal use of currently available therapy, then the goal-oriented parameters for follow-up assessment may serve as our signposts to help keep our patients on course.

References
Implementation of the PHA Pulmonary Hypertension Care Center Accreditation Program

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In the previous issue of Advances in Pulmonary Hypertension, Dr Studer discussed the emerging evidence suggesting that patients with pulmonary hypertension (PH) managed by specialized centers have improved outcomes compared with those without access to comprehensive PH care. He also summarized some of the anticipated benefits of referral to and collaboration with specialized treatment centers for PH.¹ In 2011, the Pulmonary Hypertension Association (PHA) Pulmonary Hypertension Care Center (PHCC) Committee began to explore a process for formal accreditation of PH programs in the United States.

Drs Chakinala and McGoon reviewed the rationale for creating PHA’s PHCC program and initiating its early development phase.² The expressed near-term goals of the PHCC program include aligning professionals, patients, and caregivers with increased pulmonary arterial hypertension (PAH) disease awareness, improving access to expert care, increasing adherence to published diagnosis and management guidelines, fostering collaboration among centers to optimize PAH clinical management and research, and providing guidance to prospective programs desiring to become accredited. Additionally, the PHCC program aims to develop a national patient registry for the purpose of supporting PH-related quality improvement and clinical research. The eventual long-term goal is to clearly define and promote PAH standards of care to improve patient outcomes.

The above articles outline the current context in which the PHCC program was constructed and delineate how the program may contribute to the larger agenda. During the initial development phase, the PHCC Committee has sought to build interest, consensus, and support among multiple stakeholders in the PH community, including health care professionals and patients. The PHA has posted information on its Web site (www.phassociation.org/PHCareCenters), and PHCC Committee members hosted several introductory webinars for various stakeholders, published information in Pathlight for patients and caregivers, and developed a long-range strategic plan. During the past year, the PHCC Committee has attempted to operationalize the PHCC program. The PHCC Criteria Taskforce dedicated more than 12 months to defining the initial set of accreditation criteria. The PHCC Implementation and Accreditation Taskforce focused on identifying the infrastructure necessary to make the program feasible. As a result of these determinations, the governance structure of the PHCC program was designed. Two committees, the PHCC Oversight Committee (OC) and the PHCC Review Committee (RC), were established to carry out the administrative functions of the PHCC accreditation program. The OC comprises physicians, allied health professionals, a patient, a board of trustees member, an attorney, and PHA staff members. The committee is charged with analyzing and updating the PHCC accreditation criteria, program evaluation tools, and the accreditation scoring system. The OC is also responsible for establishing and governing the PHCC RC and reports to the PHA Board of Trustees. Calls for applications to serve on the OC were announced in Fall 2013, and the 7 selected members will each serve a 3-year term. The RC consists of 22 members including physicians and allied health professionals serving 2-year terms, supported by PHA PHCC staff. The responsibilities of the RC include reviewing site applications, conducting site visits, and determining accreditation status. Calls for applications to serve on the RC were made public in Winter 2013, and membership was selected.

A PHCC will be designated as a PHA-accredited “Center of Comprehensive Care” (CCC) or PHA-accredited “Regional Clinical Program” (RCP) based on the spectrum of resources available and therapies offered.
The PHCC accreditation criteria focus on the evaluation of PH patients, diagnosis of PAH, and appropriate use of therapies for Group 1 (PAH) and Group 4 (chronic thromboembolic PH [CTEPH]) patients. The criteria emphasize appropriate resources, staff, and facility; diagnostic evaluations of PH patients (based on published consensus guidelines); access to PAH-specific therapy; and experience in treating PAH. Participation in clinical research is also a focus area for PHA CCCs. Collaboration between centers is an additional objective. PHA-accredited PHCCs will be expected to deliver appropriate and effective care to PH patients.

Our goal is to implement only criteria that are replicable, core to the mission, and add value to the PHCC accreditation program. Implementation of the PHCC program is a complex undertaking that has been described as "a specified set of activities designed to put into practice an activity or program of known dimensions." The ultimate value of the PHCC program is dependent on the quality of our implementation. The PHCC program will be successful only if implemented in an effective manner.

The PHCC accreditation process has been designed to be comprehensive and includes multiple evaluation elements. We are seeking to assess the context within which each program functions, compliance with broadly accepted treatment and management guidelines, and the overall competency of care provided. Applicants are required to complete an online application and provide a roster of their PAH and CTEPH patients, obtain letters of support from ancillary program services, assemble supporting documents, and assist PHA PHCC staff in coordinating a 1-day site visit. Site visits will be performed by 2 PHCC RC members (a physician and an allied health care professional). The RC site visitors will interview key PH program faculty and staff, a PAH patient, and will review the additional supporting documentation. The PAH/CTEPH patient roster will be utilized for a focused chart review aimed at verifying PH diagnosis and management according to published guidelines. Site visitors will provide preliminary feedback to the program leadership and answer questions at the end of the day. Both CCCs and RCPs will need to substantially satisfy the established PHCC criteria. Understanding and adhering to the goals and principles underlying the criteria allows for some flexibility in evaluating how programs provide care individually and have developed resources locally. The RC as a whole will discuss the completed applications and evaluations to make accreditation decisions. Letters regarding PHA accreditation status will be distributed by the RC twice annually. Accredited programs will be required to maintain a roster of Group 1 and 4 patients in anticipation of a PHCC patient registry, currently under development. Duration of PHCC accreditation status is anticipated to be 3 years, after which renewal will be required.

Moving from program exploration to installation, we have been establishing the necessary processes, policies, and tools for the PHCC accreditation program. Program implementation entered the pilot phase in January 2014. The objectives of the PHCC pilot program include:

1. Refining the PHCC application and application instructions
2. Refining the site visit procedures and interview schedules
3. Refining the PHCC review processes and evaluation forms
4. Refining policies and procedures for the PHCC RC
5. Assessing the pilot results to help shape the grading system
6. Training PHCC RC members

The initial pilot program is currently underway and has been invaluable in helping meet these stated goals. The PHA is grateful to the pilot sites for agreeing to participate at an early stage and for providing program development contributions. Feedback from the pilot sites thus far has been quite positive. Undergoing the accreditation process has uniformly allowed program directors and coordinators to reflect on and evaluate their PH protocols, quality improvement initiatives, and ways to improve their patients' experience. They have also noted that the PHCC review process itself has improved the care they offer PH patients. Patients interviewed were overwhelmingly supportive of accrediting programs, thereby offering assurance for themselves, their families, and medical providers that designated specialty PH centers will have the ability to provide the expertise they are seeking. The PHA anticipates the beginning of the full PHCC program implementation and a call for applications in the second half of 2014.

*PHCC Committee: Murali Chakinala, MD (PHCC Chair), Associate Professor of Medicine, Washington University School of Medicine; Richard Channick, MD (SLC President), Associate Professor of Medicine, Harvard School of Medicine; Steven M. Kawut, MD, MS (Chair, Registry Taskforce), Associate Professor of Medicine and Epidemiology, Perelman School of Medicine at the University of Pennsylvania; Vallerie McLaughlin, MD (SLC Past-President), Professor of Medicine, University of Michigan School of Medicine; Ronald Oudiz, MD (Chair, Criteria Taskforce), Professor of Medicine, David Geffen School of Medicine at UCLA; Abby Poms, RRT, RCP (Co-Chair, Implementation and Accreditation Taskforce), Pulmonary Vascular Disease Center Manager, Duke University School of Medicine; Joel A. Wirth, MD (Co-Chair, Implementation and Accreditation Taskforce), Associate Clinical Professor of Medicine, Tufts University School of Medicine; Roham Zamanian, MD (Chair, Funding and Sustainability Taskforce), Assistant Professor of Medicine, Stanford University School of Medicine.

References
The Many Faces of the PH Professional Network

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Ms Stewart: A lecture topic I recall from one of my last undergraduate nursing courses was to “join a nursing organization and be active in that organization.” Why do I remember that over so many other topics many years later? The thought of creating change at an organizational level was daunting. As a new pulmonary hypertension (PH) nurse coordinator in the mid-1990s, it was hard to find information about how to care for someone with PH. Building a PH clinic required implementation of many new processes and was fraught with challenges. Connecting with others in the PH medical community was difficult and occasionally awkward. No one wants to admit to being the new person on the block. My mission became: “If something scares you, become an expert and then help others with the same challenges.” The PH Professional Network (PHPN) offered an excellent opportunity to become involved in creating change.

Ms Wilson: Since the beginning of my journey as a nurse, I have been an active participant in nursing organizations. I sought roles that would offer professional growth potential while challenging me to learn new things. However, what was most important to me was to be part of something valuable and to actively help improve it. The PHPN is that something. I think all health care professionals have unique skills. Some are more overt with these abilities, while others tend to keep them hidden like secret treasures waiting to be discovered. Our individual talents have the capacity to change the world around us. Whatever your skill is, PHPN has a place for you—a place to showcase your unique expertise to enhance the field of PH.

Ms Stewart and Ms Wilson: As chair and chair-elect of PHPN, one of our goals has been to advance a shift in the focus of the organization toward mentoring newer allied health PH providers. We are all responsible for nurturing the next generation of PH professionals to provide a seamless transition so patients remain in the hands of extremely capable providers. These providers must have knowledge of the background of PHPN and possess a desire to continue to improve outcomes. Joining PHPN provides networking opportunities to integrate providers with varying experience levels. PHPN offers many possibilities for networking, mentoring, and sharing and developing educational processes.

PHPN was established in 1999 to provide a network for allied health professionals caring for people with PH. Diversity within the PHPN membership is critical to success of the organization. The membership consists of nurses, nurse practitioners, physician assistants, respiratory therapists, pharmacists, dietitians, and social workers. There are adult and pediatric professionals from large centers, small centers, and community clinics. These multidisciplinary team members are all focused on the complex needs of the PH community.

Joining PHPN offers members the opportunity to learn and to teach others. Time for networking is reserved at the PHPN Symposium and PHA International Conference, while the PHPN mentor program offers a more formal one-on-one experience. Members have the ability to ask questions and obtain feedback on day-to-day challenges via the PHPN listserv. Access to the membership roster enables individual contact. PHPN members are actively involved in Pulmonary Hypertension Association (PHA) initiatives to deliver insight from the allied health perspective. The creation of the PH Care Centers project...
aligns with the goals of PHPN, and allows members to assure excellent care is provided to patients with PH.

Leadership in PHPN consists of executive and committee chairs working to facilitate necessary change. The PHPN committees include Education, Membership, Practice, Publication, and Symposium. Committee chairs and committee members are engaged in identifying needs of the organization, mentoring, educating, and growing the membership. Tools and resources created in the committees benefit all members. The PHPN biannual symposium, PH Pulse newsletter, and webinars are designed to disseminate strategies for managing and caring for PH patients.

We encourage you to become actively involved in PHPN, sharing your unique talents. There are many opportunities for professional growth, and an enormous amount that we can do collectively to create change in the PH community.

Building Medical Education in PH
A Partnership Initiative to Advance Medical Understanding of Pulmonary Hypertension

*Building Medical Education in PH (BME)* events are designed to foster partnerships between PHA, PH Centers and medical professionals. The program supports continuing education in the PH field through CEU/CME educational events. Participating in PHA’s BME program can benefit your educational event by providing one-time use of PHA’s medical professionals mailing list, advertising support, educational materials for distribution to attendees and more.

To partner with PHA in *Building Medical Education in PH* for your upcoming CME event, please contact 301-565-3004 x776 or BME@PHAssociation.org.

To learn more about this partnership, visit: [www.PHAssociation.org/BME](http://www.PHAssociation.org/BME)

**Upcoming BME events:**

**Pulmonary Hypertension Fellow Education Day and 10th Pulmonary Hypertension Symposium**
Wednesday, November 5, 2014
InterContinental Hotel and Bank of America Conference Center
Cleveland, OH

**6th Annual Research Triangle Pulmonary Hypertension Symposium**
Friday, November 7, 2014
Doubletree by Hilton Hotel
Durham, NC

**5th Annual Pulmonary Hypertension Symposium: Sharing Knowledge Through Case Studies with PH**
Wednesday, November 26, 2014
Advocate Christ Medical Center
Oak Lawn, IL

To view a full list of educational opportunities for medical professionals, visit: [www.PHAssociation.org](http://www.PHAssociation.org)
Once-daily OPSUMIT® (macitentan) is the first and only oral PAH therapy indicated to both delay disease progression and reduce hospitalization for PAH.

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

- Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced hospitalization for PAH.
- Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years.
  - Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
  - Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

**IMPORTANT SAFETY INFORMATION**

**BOXED WARNING: EMBRYO-FETAL TOXICITY**

- Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.
- 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.
- For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS).

**CONTRAINDICATIONS**

Pregnancy: OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus.

**WARNINGS AND PRECAUTIONS**

**Embryo-fetal Toxicity and OPSUMIT REMS Program**

Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

**Hepatotoxicity**

Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN were 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × ULN were 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.

Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.

Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).

If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT.

Notable requirements of the OPSUMIT REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.
when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

**Hemoglobin Decrease**
- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.
- Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

**Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)**
Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

**Decreased Sperm Counts**
Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

**ADVERSE REACTIONS**
Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

**DRUG INTERACTIONS**
- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

*Please see Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.*
Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), • Females of reproductive potential must comply with the pregnancy testing and contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraception [see Use in Specific Populations (Females and Males of Reproductive Potential)]. • For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) [see Warnings and Precautions (OPSUMIT REMS Program)].

INDICATIONS AND USAGE Pulmonary Arterial Hypertension OPSUMIT® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group II) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

CONTRAINDICATIONS Pregnancy OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus [see Warnings and Precautions (Embryo-fetal Toxicity) and Use in Specific Populations (Pregnancy)].

WARNINGS AND PRECAUTIONS Embryo-fetal Toxicity OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests [see Dosage and Administration section 2.2 in full Prescribing Information and Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)]. OPSUMIT is available for females through the OPSUMIT REMS Program, a restricted distribution program [see Warnings and Precautions (OPSUMIT REMS Program)].

OPSUMIT REMS Program For all females, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program, because of the risk of embryo-fetal toxicity [see Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), and Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)]. Notable requirements of the OPSUMIT 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 OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS. • Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (Females and Males of Reproductive Potential)]. • Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT. Further information is available at www.OPSUMITREMS.com or 1-866-228-3546. Information on OPSUMIT certified pharmacies or wholesale distributors is available through Actelion Pathways at 1-866-228-3546. 

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

<table>
<thead>
<tr>
<th></th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;/2 × ULN</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>&gt;/3 × ULN</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.5% for placebo. Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.

Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 12 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated [see Adverse Reactions (Clinical Trial Experience)].

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD) Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility [see Use in Specific Populations (Females and Males of Reproductive Potential) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)].

ADVERSE REACTIONS Clinically significant adverse reactions that appear in other sections of the labeling include: • Embryo-fetal Toxicity [see Warnings and Precautions (Embryo-fetal Toxicity)] • Hepatotoxicity [see Warnings and Precautions (Hepatotoxicity)] • Decrease in Hemoglobin [see Warnings and Precautions (Hemoglobin Decrease)]

Clinical Trial Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 clinical practice. Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study). The exposure to OPSUMIT in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

Table 2 presents adverse reactions more frequent on OPSUMIT than on placebo by >3%.

Table 2: Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis/pharyngitis</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>12%</td>
<td>b%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9%</td>
<td>b%</td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS Strong CYP3A4 Inducers Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see Clinical Pharmacology (Pharmacokinetics)].
OREGON™ (macitentan)

**Strong CYP3A4 Inhibitors**

Concomitant use of strong CYP3A4 inhibitors like ketocconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OREGON™ with strong CYP3A4 inhibitors [see Clinical Pharmacology (Pharmacokinetics)]. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see Clinical Pharmacology (Pharmacokinetics)].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Pregnancy Category X.

**Risk Summary**

OREGON™ may cause fetal harm when administered to a pregnant woman and is contraindicated in pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see Contraindications(Pregnancy)].

**Animal Data**

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

**Nursing Mothers**

It is not known whether OREGON™ is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue OREGON™.

**Pediatric use**

The safety and efficacy of OREGON™ in children have not been established.

**Geriatric use**

Of the total number of subjects in the clinical study of OREGON™ for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

**Females and Males of Reproductive Potential**

**Females**

**Pregnancy Testing:** Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OREGON™ and monthly pregnancy tests during treatment with OREGON™. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus [see Boxed Warning and Dosage and Administration section 2.2 in full Prescribing Information].

**Contraception:** Female patients of reproductive potential must use acceptable methods of contraception during treatment with OREGON™ and for 1 month after treatment with OREGON™. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner’s vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see Boxed Warning].

**Males**

**Testicular effects:** Like other endothelin receptor antagonists, OREGON™ may have an adverse effect on spermatogenesis [see Warnings and Precautions (Decreased Sperm Count) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)].

**OVERDOSE**

OREGON™ has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

**Special Populations**

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

**Renal impairment:** Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

**Hepatic impairment:** Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

**Drug interactions**

**In vitro studies**

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

**In vivo studies**

**Effect of other drugs on macitentan:** The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

**Figure 1**

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Macitentan</th>
<th>Active metabolite</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see Drug Interactions (Strong CYP3A4 Inhibitors)].

**Effect of macitentan on other drugs**

Warfarin: Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis:** Carcinogenicity studies of 2 years’ duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

**Mutagenesis:** Macitentan was not genotoxic in a standard battery of in vitro and in vivo assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an in vivo micronucleus test in rats.

**Impairment of Fertility:** Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

**Animal Toxicology**

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans. There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

**Manufactured for:**

Actelion Pharmaceuticals US, Inc. 5000 Shoreline Court, Ste. 200 South San Francisco, CA 94080, USA

ACT20131018

Reference: 1. OREGON™ full Prescribing Information. Actelion Pharmaceuticals US, Inc. October 2013

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The **goals** that matter to you matter to patients

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ambrisentan
5 mg and 10 mg Tablets

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Please see accompanying brief summary of full Prescribing Information, including Boxed WARNING on the risk of embryo-fetal toxicity.
Letairis® (ambrisentan) 5 mg and 10 mg Tablets, for oral use
Brief summary of full prescribing information. See full prescribing information. Rx only.

BOXED WARNING: EMBRYO-FETAL TOXICITY
Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant female, as this effect has been seen consistently when it is administered to animals [see Contraindications, Use in Specific Populations].

Exclude pregnancy before the initiation of treatment with Letaris. Females of Reproductive Potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment [see Use in Specific Populations].

Because of the risk of embryo-fetal toxicity, females can only receive Letairis through a restricted program called the Letairis REMS Program [see Warnings and Precautions].

INDICATIONS AND USAGE: Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).

DOSE AND ADMINISTRATION: Adult Dosage: Initiate treatment at 5 mg once daily, and consider increasing the dose to 10 mg once daily if 5 mg is well tolerated. Tablets may be administered with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not produced additional benefit

[see adverse reactions].

Contraindications, Warnings and Precautions, Use in Specific Populations].

Idiopathic Pulmonary Fibrosis: Letairis is contraindicated in patients with Idiopathic Pulmonary Fibrosis (IPF) including IPF patients with pulmonary hypertension (WHO Group 3) [see Clinical Studies].

WARNINGS AND PRECAUTIONS: Letairis REMS Program: For all females, Letairis is available only through a restricted program called the Letairis REMS, because of risk of embryo-fetal toxicity [see Contraindications, Warnings and Precautions, Use in Specific Populations]. Notable requirements of the Letairis REMS Program include that the Prescribers must be certified with the program by enrolling and completing training. All females, regardless of reproductive potential, must enroll in the Letairis REMS Program prior to initiating Letairis. Male patients are not enrolled in the REMS. Females of Reproductive Potential must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations]. Pharmacies that dispense Letairis must be certified with the program and must dispense to female patients who are authorized to receive Letairis. Further information is available at www.letairisrems.com or 1-866-664-5327.

Fluid Retention: Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg Letairis compared to placebo [see Adverse Reactions].

Most edema was mild to moderate in severity, and it occurred with greater frequency and severity in elderly patients. In addition, there have been post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting Letairis. Patients requiring intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure. If peripheral edema and retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Letairis or underlying heart failure, and the possible need for specific treatment or discontinuation of Letairis therapy. Pulmonary Veno-Occlusive Disease: If patients develop acute pulmonary edema during initiation of therapy with vasoactive agents, such as Letairis, the possibility of PAH must be considered, and if confirmed Letairis should be discontinued. Decreased Sperm Counts: Decreased sperm counts have been observed in human and animal studies with another endothelin receptor antagonist and in animal fertility studies with ambrisentan to 5 mg once daily when co-administered with cyclosporine approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of cyclosporine to 50 mg (AUC 3.14 h•μg/mL) and do not exceed a maximum dose of 100 mg (AUC 31.7 h•μg/mL) per day. In healthy volunteers, a significant decrease in plasma concentrations of ambrisentan to 5 mg once daily when co-administered with cyclosporine approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of cyclosporine to 50 mg (AUC 3.14 h•μg/mL) and do not exceed a maximum dose of 100 mg (AUC 31.7 h•μg/mL) per day. In healthy volunteers, a significant decrease in plasma concentrations of ambrisentan was observed when the dose of cyclosporine was increased from 50 mg to 100 mg/day (AUC 6.9 h•μg/mL) [see Drug Interactions].

DRUG INTERACTIONS: Multiple dose co-administration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of cyclosporine to 50 mg (AUC 3.14 h•μg/mL) per day. In patients receiving Letairis who were treated with Letairis and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving Letairis in the 12 week placebo-controlled studies was 0.8 (±0.5) mL. Marked decreases in hemoglobin (≥15%) from baseline resulting in a value below the lower limit of normal were observed in 7% of all patients receiving Letairis (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo. The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis. In the long-term open-label extension of the two pivotal clinical trials, mean decreases from baseline (ranging from 0.9 to 1.2 mg/dL) in mean hemoglobin concentrations persisted for up to 4 years of treatment. There have been postmarketing reports of decreases in hemoglobin concentration and hematoctit that have resulted in anemia requiring transfusion. Measure hemoglobin prior to initiation of Letairis, at one month, and periodically thereafter. Initiation of Letairis therapy is not recommended for patients with clinically significant anemia and a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing Letairis.

ADVERSE REACTIONS: Clinically significant adverse reactions that appear in other sections of the labeling include: Embryo-Fetal toxicity [see Warnings and Precautions, Use in Specific Populations]; Fluid Retention [see Warnings and Precautions]; Pulmonary Edema with PVD [see (Warnings and Precautions). Decreased Sperm Count [see Warnings and Precautions]; Hematologic changes [see Warnings and Precautions]. 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. Safety data for Letairis were obtained from 2 to 12 weeks, placebo controlled studies in patients with pulmonary arterial hypertension (PAH) (WHO Group 1-2) and four nonplacebo controlled studies in 4 to 24 weeks with PVD who were treated with doses of 11.2, 5.5, or 10 mg once daily. The mean decreases in hemoglobin in these studies ranged from 1 day to 4 years (N=418 for at least 6 months and N=343 for at least 1 year). In PAH 1-2 and PAH 1-2, a total of 261 patients received Letairis at doses of 2.5, 5 or 10 mg once daily and 132 patients received placebo. The adverse reactions that occurred in ≥5% more patients receiving Letairis than those receiving placebo are shown in the table. [see Table 1. Adverse Reactions with Placebo-Adjusted Rates].

Table 1 Adverse Reactions with Placebo-Adjusted Rates

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Placebo (N=132)</th>
<th>Letairis (N=261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>14 (11)</td>
<td>47 (17)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2 (2)</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0  (0)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (1)</td>
<td>10 (4)</td>
</tr>
</tbody>
</table>

Most adverse drug reactions were mild to moderate and only nasal congestion was dose dependent. Few notable differences in the incidence of adverse reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving Letairis (14%) vs placebo (13%; 13/104), and was greater in elderly patients (≥65 years) receiving Letairis (29%; 16/56) vs placebo (2% to 3/132 patients). The incidence of serious adverse events related to PAH for patients treated with Letairis was similar for Letairis (2%, 5/261 patients) and placebo (2% to 3/132 patients). The incidence of serious adverse events associated with PAH for patients treated with Letairis was similar for Letairis (2%, 5/261 patients) and placebo (2% to 3/132 patients). The incidence of serious adverse events associated with PAH for patients treated with Letairis was similar for Letairis (2%, 5/261 patients) and placebo (2% to 3/132 patients). The incidence of serious adverse events associated with PAH for patients treated with Letairis was similar for Letairis (2%, 5/261 patients) and placebo (2% to 3/132 patients). The incidence of serious adverse events associated with PAH for patients treated with Letairis was similar for Letairis (2%, 5/261 patients) and placebo (2% to 3/132 patients). The incidence of serious adverse events associated with PAH for patients treated with Letairis was similar for Letairis (2%, 5/261 patients) and placebo (2% to 3/132 patients). The incidence of serious adverse events associated with PAH for patients treated with Letairis was similar for Letairis (2%, 5/261 patients) and placebo (2% to 3/132 patients). The incidence of serious adverse events associated with PAH for patients treated with Letairis was similar for Letairis (2%, 5/261 patients) and placebo (2% to 3/132 patients).
Letairis is only available through a restricted program called the Letairis REMS Program. Male patients are not enrolled in the Letairis REMS Program. For female patients, Letairis is only available through a restricted program called the Letairis REMS Program. Male patients are not enrolled in the Letairis REMS Program. Inform female patients (and their guardians, if applicable) of the following notable requirements: All female patients must use acceptable methods of contraception during treatment with Letairis and for 1 month after stopping treatment with Letairis. Patients may choose one highly effective form of contraception (intrauterine devices, IUD, contraceptive implants, or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a patient’s partner’s method is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraception counseling (see Boxed Warning). Infertility: Males In a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data (see Nonclinical Toxicology) from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Letairis have an adverse effect on spermato genesis. Counsel patients about the potential effects on fertility (see Warnings and Precautions). Renal Impairment: The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan (see Clinical Pharmacology). Dose adjustment of Letairis in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment. The impact of hemodialysis on the disposition of ambrisentan has not been investigated. Hepatic Impairment: Pre-existing hepatic impairment: The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is in vitro and in vivo evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan (see Clinical Pharmacology). Letairis is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of Letairis in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients. Elevation of Liver Transaminases: Other endothelin receptor antagonists (ERAs) have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure (see Adverse Reactions). In patients who develop hepatic impairment after Letairis initiation, the cause of liver injury should be fully investigated. Discontinue Letairis if aminotransferase elevations >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded. OVERDOSAGE: There is no experience with overdosage of Letairis. The highest single dose of Letairis administered to healthy volunteers was 100 mg and the highest daily dose administered to patients with PAH was 10 mg once daily. In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Massive overdosage could potentially result in hypotension that may require intervention. PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling (Medication Guide). Embryo-Fetal toxicity: Instruct patients on the risk of fetal harm when Letairis is used in pregnancy (see Warnings and Precautions; Use in Special Populations). Female patients must enroll in the Letairis REMS Program. Instruct females of Reproductive Potential to immediately contact their physician if they suspect they may be pregnant. Letairis REMS Program: For female patients, Letairis is only available through a restricted program called the Letairis REMS Program. Inform female patients (and their guardians, if applicable) of the following notable requirements: All female patients must sign an enrollment form. Advise female patients of reproductive potential that they must comply with the pregnancy testing and contraception requirements (see Use in Specific Populations). Educate and counsel females of Reproductive Potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure. Advise pre-pubertal females to report any changes in their reproductive status immediately to their prescriber. Review the Letairis Medication Guide and REMS educational material with female patients. A limited number of pharmacies are certified to dispense Letairis. Therefore, provide patients with the telephone number and website for information on how to obtain the product. Hepatic Effects: Some members of this pharmacological class are hepatotoxic. Patients should be educated on the symptoms of potential liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) and instructed to report any of these symptoms to their physician. Hematological Change: Patients should be advised of the importance of hemoglobin testing. Administration: Patients should be advised not to split, crush, or chew tablets.
ADD MORE to your treatment strategy with Tyvaso, an inhaled prostacyclin analogue

- PAH may be progressing even if patients seem stable
- Many patients plateau on oral therapy (PDE-5 inhibitor or ERA) in as few as 12 weeks

TYVASO is the only PAH treatment studied solely as an add-on to bosentan (an ERA) or sildenafil (a PDE-5 inhibitor)

- Clinically stable patients improved median 6MWD by 20 m (P<0.001) after adding Tyvaso for 12 weeks
- 4X daily dosing with short treatment sessions (2-3 minutes) approximately every 4 hours

INDICATION
Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

In patients with low systemic arterial pressure, Tyvaso may cause significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age.

In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.

Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System.

IMPORTANT SAFETY INFORMATION
Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.

The most common adverse events seen with Tyvaso in 24% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%).

Tyvaso should be used in pregnancy only if clearly needed. Caution should be exercised when Tyvaso is administered to nursing women.

Please see brief summary of Full Prescribing Information on following page. For more information, please see Full Prescribing Information, Patient Package Insert, and the Tyvaso Inhalation System Instructions for Use Manual. These items are available at www.tyvaso.com.
TYVASO® (treprostinil) Inhation Solution

INDICATIONS AND USAGE
TYVASO® is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Patients with Pulmonary Disease or Pulmonary Infections—The safety and efficacy of TYVASO have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.

Risk of Symptomatic Hypotension—Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with TYVASO may produce symptomatic hypotension. Patients with Hepatic or Renal Insufficiency—Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function.

Risk of Bleeding—Since TYVASO inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulant therapy.

Effect of Other Drugs on Treprostinil—Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure [both Cmax and AUC] to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

ADVERSE REACTIONS
The following potential adverse reactions are described in Warnings and Precautions:

• Decrease in systemic blood pressure
• Bleeding

Adverse Reactions Identified in Clinical Trials—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. In a 12-week placebo-controlled study (TRIUMPH II) of 225 patients treated with PAH WHO Group I and nearly all NYHA Functional Class III, the most commonly reported adverse reactions to TYVASO included: cough and breath irritation; headache, gastrointestinal effects, muscle, jaw or bone pain, flushing and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with TYVASO than with placebo. The safety of TYVASO was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of 2.3 years with a maximum exposure of 5.4 years. Eighty-nine (89%) percent of patients achieved the target dose of nine breaths, four times daily. Forty-two (42%) percent achieved a dose of 12 breaths four times daily. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo-controlled trial. Adverse Events Associated with Route of Administration—Adverse events in the treated group during the double-blind and open-label phase reflecting irritation to the respiratory tract included: cough, throat irritation, pharyngeal pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 1% subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience. Adverse Reactions Identified in Post-Marketing Experience—The following adverse reaction has been identified during the postapproval use of TYVASO. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure: Angioedema

DRUG INTERACTIONS
Pharmacokinetic/pharmacodynamic interaction studies have not been conducted with inhaled treprostinil (TYVASO); however, some of such studies have been conducted with orally (treprostinil diolamine) and subcutaneously administered treprostinil (Remodulin®). Unchanged treprostinil is the major component of treprostinil plasma concentrations. Treprostinil and its metabolites are excreted mainly through the urinary route, patients with renal insufficiency may have decreased clearance of the drug and its metabolites, leading to an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency.

Concomitant use of TYVASO with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension. Anticoagulants—Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Pharmacokinetics—Antihypertensive Agents or Other Vasodilators—Concomitant administration of TYVASO with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension. Anticoagulants—Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Precautions:

• Decrease in systemic blood pressure
• Bleeding

Effect of Cytochrome P450 Inhibitors and Inducers—In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure [both Cmax and AUC] to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

Table 1: Adverse Events in ≥4% of PAH Patients Receiving TYVASO and More Frequent* than Placebo

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TYVASO n = 115</th>
<th>Treatment n (%)</th>
<th>Placebo n = 120</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>62 (54)</td>
<td>35 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>47 (43)</td>
<td>27 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Throat Irritation/Pharyngalgae Pain</td>
<td>29 (25)</td>
<td>17 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (19)</td>
<td>13 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>17 (15)</td>
<td>11 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>7 (6)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*More than 3% greater than placebo.

Pharmacokinetics of R- and S-warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

USE IN SPECIFIC POPULATIONS

Pregnancy—Pregnancy Category B—There are no adequate and well-controlled studies with TYVASO in pregnant women. Animal reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (s.c.) infusions of treprostinil sodium at infusion rates higher than the recommended human sc infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity. Animal reproduction studies are not always predictive of human response; TYVASO should be used during pregnancy only if clearly needed.

Labor and Delivery—No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether treprostinil is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when treprostinil is administered to nursing women.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established. Clinical studies of TYVASO did not include patients younger than 18 years to determine whether they respond differently from older patients.

Geriatric Use—Clinical studies of TYVASO did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

Patients with Hepatic Insufficiency—Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptake slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency.

Patients with Renal Insufficiency—No studies have been performed in patients with renal insufficiency. Since treprostinil and its metabolites are excreted mainly through the urinary route, patients with renal insufficiency may have decreased clearance of the drug and its metabolites and consequently, dose-related adverse outcomes may be more frequent.

OVERDOSAGE
In general, symptoms of overdose with TYVASO include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

Tyvaso manufactured for: United Therapeutics Corporation Research Triangle Park, NC 27709
Rx only April 2013
www.tyvaso.com
Program Description
This one-day, highly interactive program offers direct instruction and case-based discussion of state-of-the-art PAH diagnosis, initial treatment, and comprehensive long-term management of patients with PAH.

Programs run from 9:00 AM to 3:30 PM. Complimentary breakfast and luncheon are served. There is no fee for this program.

Register now at: www.regonline.com/PHApreceptorship
For more information, please visit the PHA website: www.PHAssociation.org/Preceptorship

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— JM, Ann Arbor, Preceptorship participant

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Faculty from Temple University School of Medicine/Allegheny Health Network and the University of Pittsburgh School of Medicine

Check the PHA website for an additional Preceptorship offering in 2014 in Dallas, Texas, with faculty from the University of Texas Health Sciences Center

“"We expect this, our sixth year of the PHA Preceptorship Program, to be the best one yet. Please join us as we work toward our goal of strengthening links among community specialists, primary-care clinicians, and experts from PAH centers of excellence. This collaborative approach is critical in achieving comprehensive care for our patients with PAH."”
— Stephen C. Mathai, MD, MHS Preceptorship Committee Chair
Program Announcement:

New Application Deadline: October 12, 2014
New Application Deadline: February 12, 2015
Resubmission Deadline: November 12, 2014
Resubmission Deadline: March 12, 2015

Jointly Sponsored

**Mentored Clinical Scientist Development Award (K08) &
Mentored Patient-Oriented Research Career Development Award (K23)**

**PURPOSE: K08**
- To support the development of outstanding clinician research scientists in the area of pulmonary hypertension.
- To provide specialized study for clinically trained professionals who are committed to a career in research in pulmonary hypertension and have the potential to develop into independent investigators.
- To support a 3 to 5 year period of supervised research experience that integrates didactic studies with laboratory or clinically based research.
- To support research that has both intrinsic research importance and merit as a vehicle for learning the methodology, theories, and conceptualizations necessary for a well-trained independent researcher.

**MECHANISM:**
Awards in response to the program announcement will use the National Institutes of Health (NIH) K08 or the K23 mechanism.

**FUNDING:***
The award will be funded by PHA and NHLBI and the K08 and/or the K23 will be awarded in 2013.

**PURPOSE: K23**
- To support career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.
- To support a 3 to 5 year period of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research in pulmonary hypertension.
- To support patient-oriented research, which is defined as research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects.
- To support areas of research that include: 1) mechanisms of human disease; 2) therapeutic interventions; 3) clinical trials; and 4) development of new technologies.

Learn about all of PHA’s research opportunities at [www.PHAssociation.org/MedicalProfessionals/PHAResearchProgram](http://www.PHAssociation.org/MedicalProfessionals/PHAResearchProgram)

* Restrictions apply. Please see complete announcement at the website listed above.
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