Women and PH: Unique Aspects
The Scientific Leadership Council of the Pulmonary Hypertension Association

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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 revision of the World Health Organization Classification serves 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. In addition, a special section in selected issues entitled “Profiles in Pulmonary Hypertension” recognizes major contributors to the field and serves as an inspiring reminder of the rich and collegial history of dedication to advancing the field.

- **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.
  - Recognize and preserve the rich history of individuals who have made major contributions to the field via dedication to patient care, innovative research, and furthering the mission of the PH community to cure pulmonary hypertension.
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Advances in Pulmonary Hypertension: Author Guidelines

General Information

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned experts with the oversight of the Association’s Scientific Leadership Council. Its mission is to help physicians in their clinical decision making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in the peer-reviewed literature. Each article is reviewed and approved by members of the Editorial Advisory Board.

While most articles are invited by the editorial board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the editorial board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision making.

Manuscript Preparation and Submission Process

Submissions should be sent via e-mail as an attached Word document to the Editor-in-Chief, Erika Berman Rosenzweig, MD, at esb14@columbia.edu. Manuscripts should be double-spaced and follow AMA style. Full-length manuscripts should not exceed 4,000 words including references. References should be limited to 50 entries. No more than 5 figures should accompany the manuscript. Accepted file formats are .gif, .tif, and .jpg. Each figure should be a separate file and figure legends should appear at the end of the manuscript. Each figure should be cited by number in the manuscript. Tables should be self-explanatory and details of the table should not be repeated in the manuscript. Tables should be prepared as part of the Word document. No more than 3 tables should be included with the manuscript. References should conform to AMA style and be numbered consecutively in the text. Reference numbers should be placed in parentheses at the end of the relevant sentence.

Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with AMA style.

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Conflict of Interest Disclosures

A statement of any and all grant, contract, and industrial support or proprietary interests of the author(s) related to the subject matter must be submitted with the manuscript.

Checklist

Authors should be certain to include the following with the manuscript:

1. Title page listing all authors with their academic degree(s) and affiliations.
2. Corresponding author contact information including e-mail and phone number.
3. Copyright release form signed by all authors.
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.

Cover Image: Women with pulmonary arterial hypertension face additional concerns regarding routine as well as reproductive health issues.
The Uneasy Conversation

The conversation never comes easily as I counsel a young woman with newly-diagnosed pulmonary arterial hypertension (PAH) about the extreme risks of pregnancy. In that moment, I know I’ve shattered a life-long dream. Despite the many medical advances in the field of pulmonary hypertension, pregnancy and PAH remain a lethal combination. And, in a disease that affects more women than men, most experts believe that hormonal influences play a key role in the pathophysiology of the disease; however the exact mechanisms remain unclear. In this issue of Advances, guest editors Drs Kelly Chin and Deborah Levine call on authors to address this delicate topic. Dr Dianne Zwicke’s article provides readers with a review of the normal physiology of pregnancy and highlights the pathophysiological derangements that make pregnancy so dangerous for women with Group 1 PAH. Given the risks of pregnancy to both mother and fetus, including potential teratogenic effects of some of the targeted PH agents, Dr Patricia Santiago-Munoz also provides a comprehensive review of contraceptive options for women with PAH. In Dr Eric Austin’s article about sex hormones and PAH, the reader can learn about potential mechanisms of hormonal influences in PH. Finally, in the roundtable discussion, experts discuss controversies surrounding the topic of pregnancy and PH. All acknowledged that while pregnancy can be fatal and should be avoided in women with PAH, management guidelines should still be developed for practitioners who find themselves caring for a woman presenting with PAH during pregnancy. Another key message that emerged from this discussion was that the management requires a multidisciplinary team of experts with experience taking care of PH patients at a major medical center, as these patients require meticulous monitoring through all stages of pregnancy including the early post-partum period for sudden cardiovascular collapse. One can only hope that in the future we will have a better understanding of these hormonal influences, which may uncover potential therapeutic targets, and that we may be able to counsel women with PAH differently. Until then, despite the many advances in management of PAH, the conversation remains sobering.

Erika Berman Rosenzweig, MD
Director, Pulmonary Hypertension Center
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Guest editors’ memo

Although pulmonary hypertension is not a uniquely female problem, women living with pulmonary hypertension often have female-specific concerns; such as, whether they should get pregnant; what types of contraception are safe and effective in PH; and whether routine health-maintenance care and exams are necessary. Separately, the increased incidence and prevalence of pulmonary hypertension in women vs men has led to considerable discussion over the years as to the role for sex hormones in the pulmonary vasculature and in the development of pulmonary hypertension.

It is, therefore, with great pleasure that we present this issue of Advances in Pulmonary Hypertension in which “Women’s Issues” are discussed from both perspectives. Dr Austin’s article, “Gender, Sex Hormones, and Pulmonary Arterial Hypertension” starts off with a comparison of the female: male gender ratios in pulmonary hypertension as shown in large observational studies such as the REVEAL registry. He follows this with a presentation of the evidence for and against a connection between sex hormones and pulmonary hypertension, ending with an overview of his own very interesting work looking at whether certain estrogen metabolites are associated with familial forms of PH.

Dr Munoz-Santiago, a maternal-fetal medicine specialist, writes on “Contraceptive Options for the Patient with Pulmonary Arterial Hypertension.” Her review reminds us of the highly concerning maternal and fetal morbidity and mortality that are seen even in recent pulmonary hypertension case series, and provides a strong rationale for encouraging the use of highly-effective birth control in all women with pulmonary hypertension.

Next, because some patients with pulmonary hypertension may become pregnant despite medical advice, or present during pregnancy, our last article focuses on cardiopulmonary physiology during a normal pregnancy and the changes seen in PH. This is then followed by a roundtable discussion on the care for patients with PAH during a pregnancy.

Finally, so as not to ignore the men completely in this issue, Dr Williamson discusses two “Men’s Issues” in his guest coverage of the Ask the Expert column.

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Director, Pulmonary Hypertension Program; UT Southwestern Medical Center; Dallas, Texas
Ventavis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration. Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue disease (23%).

**The inhaled PAH therapy that delivered a spectrum of PAH efficacy at week 12**

- **Significant clinical improvement through a combined endpoint (p=0.0033)**
  - 19% Ventavis vs 4% placebo
- **Significant functional class improvement (p=0.03)**
  - 25% Ventavis vs 8% placebo
- **Significant hemodynamic improvement for 3 key parameters (PVR, CO, and mPAP) (p<0.001)**
  - 32% decrease in PVR*
  - 20% increase in CO*
  - 9% decrease in mPAP*
  - 3% increase (p(NS)) in SVO₂ from baseline at week 12 postinhalation
- **Significant 6MWD improvement (p<0.01)**
  - All PAH: 40-meter increase*1
  - IPAH: 59-meter increase*2

**Ventavis 20 mcg/mL: Higher concentration to give appropriate patients shorter treatment times**

**The 20 mcg/mL concentration is intended for patients who are maintained at the 5 mcg dose and who have repeatedly experienced extended treatment times which could result in incomplete dosing. Ventavis 10 mcg/mL ampules are still available. Ventavis should be taken 6 to 9 times daily during waking hours, at least 2 hours apart.**

**IMPORTANT SAFETY INFORMATION:** Hypotension leading to syncope has been observed; Ventavis should therefore not be initiated in patients with systolic blood pressure less than 85 mmHg. Stop Ventavis immediately if signs of pulmonary edema occur; this may be a sign of pulmonary venous hypertension. Ventavis inhalation may cause bronchospasm and patients with a history of hyperreactive airway disease may be more sensitive. Serious adverse events reported at a rate of less than 3% included congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, and kidney failure. Vital signs should be monitored while initiating Ventavis. In clinical studies, the most common adverse events occurring more often (≥6%) in Ventavis-treated patients than in patients taking placebo included vasodilation (flushing) (27% vs 9%), cough (39% vs 26%), headache (30% vs 20%), trismus (12% vs 3%), and insomnia (8% vs 2%). Ventavis has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents. Ventavis also has the potential to increase risk of bleeding, particularly in patients maintained on anticoagulants.

Please see brief summary of full prescribing information on adjacent page.
VENTAVIS is intended to be inhaled using either of two pulmonary drug delivery devices: the I-neb AAD System or the Prodose AAD System. The first inhaler dose should be 2.5 mg as delivered at the mouthpiece. If this dose is well tolerated, dosing should be increased to 5 mg and maintained at that dose; otherwise maintain the dose at 2.5 mg. Ventavis should be taken at least 6 minutes per day, no more than once every 2 hours during waking hours, according to individual need and tolerability. The maximum daily dose evaluated in clinical studies was 45 mg (5 mg 9 times per day). Direct mixing of Ventavis with other medications in the I-neb AAD System or the Prodose AAD System has not been evaluated; do not mix with other medications. To avoid potential interruptions in drug delivery due to equipment malfunction, the patient should have access to a back-up I-neb AAD System or Prodose AAD System.

Ventavis is supplied in 1 mL ampules in two concentrations: 10 mcg/mL and 20 mcg/mL.

Dosage and Administration

Recommended Dosing

Ventavis is intended to be inhaled using either of two pulmonary drug delivery devices: the I-neb AAD System or the Prodose AAD System.

Table 1: Adverse Events in Phase 3 Clinical Trial

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo</th>
<th>Placebo subtracted %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Vomitus</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Allergic events</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Tongue pain</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Palpitations</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

In a small clinical trial (the STEP trial), safety trends in patients receiving concomitant bosentan and Ventavis were consistent with those observed in the larger experience of the Phase 3 study in patients receiving only Ventavis or bosentan.

Adverse Events with Higher Doses

In a study in healthy subjects (n=180), inhaled doses of iloprost solution were given every 2 hours, beginning with 5 mcg and increasing up to 20 mcg for a total of 6 doses inhalations (total cumulative dose of 70 mg or up to the highest dose distributed in a group of 40 subjects. There were 13 subjects (12% who failed to reach the highest schedule dose (120 mcg). We were unable to increase the dose because of (i) lack of moderate transient chest pain/discomfort/lightness, usually accompanied by headache, nausea, and dizziness. The remaining 8 subjects discontinued for other reasons.

Postmarketing Experience

The following adverse reactions have been identified during the postapproval use of Ventavis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Drug Interactions

During clinical trials, iloprost was used concurrently with anticoagulants, diuretics, corticosteroids, and calcium channel blockers, antiarrhythmics, nonsteroidal anti-inflammatory drugs, corticosteroids, and other medications. Inhaled iloprost had no effect on the pharmacokinetics of dapsone, acetaminophen, and acyclovir. However, it has been shown to increase the bioavailability of acetaminophen.

Antihypertensives and Vasodilators

In studies in normal subjects, there was no pharmacodynamic interaction between inhaled iloprost and either nitroprusside, diltiazem, or captopril. However, Ventavis has the potential to increase the hypertension effect of vasodilators and antihypertensive agents.

Anticoagulants and Platelet Inhibitors

Since Ventavis and other antiplatelet agents are often used concomitantly, there is a potential for increased risk of bleeding, particularly in patients maintained on anticoagulants or platelet inhibitors.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C.

Ventavis has been shown to be teratogenic in an intravenous iloprost study in pregnant rats. There are no adequate and well-controlled studies in pregnant women. Ventavis should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In developmental toxicity studies in pregnant Han-Wistar rats, continuous intravenous administration of iloprost at a dosage of 0.01 mg/kg/day (mean serum levels not to be exceeded by 1.5 hours of the thoracic extremity in fetuses and pups. In comparable studies in pregnant Sprague-Dawley rats which received iloprost clathrate (13% iloprost by weight) orally at dosages of up to 50 mg/kg/day (i.e., 40 mg/kg/day in pregnant rabbits at intravenous dosages of up to 0.5 mg/kg/day, i.e., 96 mg/kg/day in pregnant monkeys at dosages of up to 0.4 mg/kg/day (serum levels of 1 ng/mL), no such lesions or anomalies or other growth retardation occurred in the fetuses/pups. However, in gravid Sprague-Dawley rats, iloprost clathrate (13% iloprost) significantly increased the number of non-viable fetuses at a maternally toxic oral dosage of 250 mg/kg/day and in Han-Wistar rats was found to be embryolethal in 15 of 44 intravenous dosage of 1 mg/kg/day.

Nursing Mothers

It is not known whether Ventavis is excreted in human milk. In studies with Han-Wistar rats, higher mortality was observed in pups of lactating dams receiving iloprost intravenously at 1 mg/kg daily. In Sprague-Dawley rats, higher mortality was also observed in nursing pups at a maternally toxic oral dosage of 250 mg/kg/day of iloprost clathrate (13% iloprost by weight).

It is not known whether iloprost is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Clinical studies of Ventavis did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects. Other clinical studies of iloprost have included differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range, and in the absence of pharmacokinetic data for the elderly patient, increasing the dosage in small increments, usually in one-week increments, and carefully observing the patient for adverse reactions. Other clinical studies of iloprost indicate that no relevant inhibition of drug metabolism is expected in the elderly.

Hepatic Impairment

Ventavis has not been evaluated in patients with impaired hepatic function. However, an intravenous iloprost study in patients with liver cirrhosis showed the mean clearance in Child Pugh Class B subjects (n=8) was approximately 10 mL/min/kg (half that of healthy subjects). Following oral administration, the mean clearance in healthy subjects was approximately 75 mL/min/kg.

OVERDOSAGE

In clinical trials of Ventavis, no case of overdose was reported. Symptoms and signs to be anticipated are extensions of the dose-limiting pharmacological effects of iloprost including hypotension, headache, nausea, vomiting, and diarrhea. A specific antidote is not known. Information on the inhibition of the cardiac system, monitoring, and symptomatic measures are recommended.

OTC MANAGEMENT

Patients receiving Ventavis should be advised to use the drug only as prescribed with either of two pulmonary drug delivery devices: the I-neb AAD System or the Prodose AAD System, following the manufacturer’s instructions (see DOSAGE AND ADMINISTRATION). Patients should be trained in proper administration techniques, including breathing frequency, airway maintenance, and equipment cleaning.

Advisory patients that they may have a fall in blood pressure with Ventavis, so they may become dizzy or even faint. They should stand up slowly when they get out of bed or chair. If standing makes you dizzy, patients should consult their physicians about dose adjustment.

Advisory patients that they should be advised whether or not they are taking other medications that may cause changes in blood pressure. Patients may want to adjust times of administration to cover planned activities.

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The Pulmonary Hypertension Association’s International PH Conference is the largest educational and networking gathering for medical professionals, pulmonary hypertension patients and family members in the world.

It includes a full day of Scientific Sessions on topics covering the genetics of PH and a new track for clinicians.

Medical professional education will take place Thursday, June 21 - Sunday, June 24, 2012

www.PHAssociation.org/Conference
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SUBMISSION DEADLINE: MARCH 10, 2012

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Although PHA encourages the submission of original abstracts, abstracts submitted to PHA do not need to be based on original work. Submit your abstract to Abstract@PHAssociation.org.

FOR MORE INFORMATION
Visit www.PHAssociation.org/Conference
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**Important safety information**

Because of the risks of liver injury and birth defects, Tracleer may be prescribed and dispensed only through the Tracleer Access Program (T.A.P.), a restricted distribution program, by calling 1-866-228-3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P.

**Liver injury**

Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer. In a setting of close monitoring, rare cases of liver failure and unexplained hepatic cirrhosis were observed after prolonged treatment. In general, avoid using Tracleer in patients with elevated aminotransferases (>3 × ULN). Measure liver aminotransferases prior to initiation of treatment and then monthly. Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

**Teratogenicity**

Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy. Exclude pregnancy before and during treatment. To prevent pregnancy, females of childbearing potential must use 2 reliable forms of contraception during treatment and for 1 month after stopping Tracleer unless the patient has a tubal sterilization or Copper T 380A IUD or LNG-20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should be obtained.

**Contraindications**

Tracleer is contraindicated with cyclosporine A, glyburide, in females who are or may become pregnant, or in patients who are hypersensitive to bosentan or any component of Tracleer.

**Warnings and precautions**

In clinical trials, Tracleer caused ALT/AST elevations (>3 × ULN) in 11% of patients accompanied by elevated bilirubin in a few cases. The combination of hepatocellular injury (increases in aminotransferases of >3 × ULN) and increases in total bilirubin (≥3 × ULN) is a marker for potential serious liver injury. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Avoid using Tracleer in patients with moderate or severe liver impairment or elevated ALT/AST >3 × ULN.

If clinically significant fluid retention develops, with or without associated weight gain, the cause, such as Tracleer or underlying heart failure, must be determined. Patients may require treatment or Tracleer therapy may need to be discontinued.

Preclinical data and an open-label safety study (N=25) showed a decline in sperm count of ≥50% in 25% of Tracleer-treated patients after 3 or 6 months. After 6 months, sperm count remained in normal range, with no changes in sperm morphology or motility, or hormone levels. Endothelin receptor antagonists such as Tracleer may adversely affect spermatogenesis.

Treatment with Tracleer can cause a dose-related decrease in hemoglobin (Hgb) and hematocrit. Hgb should be checked after 1 and 3 months, and then every 3 months. Upon marked decrease in Hgb, determine the cause and need for specific treatment.

If signs of pulmonary edema occur, the possibility of associated pulmonary veno-occlusive disease should be considered. Tracleer should be discontinued.

**Adverse events**

In Tracleer pivotal trials, the most common adverse events occurring more often in Tracleer-treated patients than in patients taking placebo (≥2%) were respiratory tract infection, edema, hypotension, sinusitis, arthralgia, liver function test abnormal, palpitations, and anemia.
Indication

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO class II patients, which may preclude future use as their disease progresses.

Please see accompanying brief summary of prescribing information, including BOXED WARNING about liver injury and pregnancy, on following pages.

*Patients ineligible for the Tracleer Patient Coupon Program include any patients whose prescriptions are paid for by the government, Medicare, Medicaid, VA/DOD (Tricare), or Indian Health Service, patients in Massachusetts and Puerto Rico, or where prohibited by law.
Tracleer [see ] is available only through a special co-administration of Tracleer in these circumstances. 

**Dosage and Administration**

**Recommended Dosing**

Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of liver injury. Tablets should be administered morning and evening with or without food.

**Dosage Adjustments for Patients Developing Aminotransferase Elevations**

The table below summarizes the dosage adjustment and monitoring recommendations for patients who develop aminotransferase elevations >3 X ULN during treatment with Tracleer. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin > 2 X ULN, treatment with Tracleer should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances.

<table>
<thead>
<tr>
<th>ALT/AST levels</th>
<th>Treatment and monitoring recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3 and ≤ 5 X ULN</td>
<td>Confirm by another aminotransferase test; if confirmed, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).</td>
</tr>
<tr>
<td>&gt; 5 and ≤ 8 X ULN</td>
<td>Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).</td>
</tr>
<tr>
<td>&gt; 8 X ULN</td>
<td>Treatment should be stopped and re-introduction of Tracleer should not be considered. There is no experience with re-introduction of Tracleer in these circumstances.</td>
</tr>
</tbody>
</table>

If Tracleer is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above.

**Use in Females of Childbearing Potential**

Initiate treatment in females of child-bearing potential only after a negative pregnancy test and only in females who are using two reliable methods of contraception. Females who have had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUS inserted do not require other forms of contraception. Effective contraception must be practiced throughout treatment and for one month after stopping Tracleer. Females should seek contraceptive advice as needed from a gynecologist or other expert. Urine or serum pregnancy tests should be obtained monthly in females of childbearing potential taking Tracleer [see Boxed Warning, Contraindications, Drug Interactions].

**Use in Patients with Pre-existing Hepatic Impairment**

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If stable aminotransferase levels are found, treatment can be re-introduced. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury or increases in bilirubin > 2 X ULN, treatment with Tracleer should be stopped. There is no experience with re-introduction of Tracleer in these circumstances [see Dosage and Administration].

**Patients with Pre-existing Hepatic Impairment**

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly.

**Fluid Retention**

Periadrenal edema is a known clinical consequence of PAH and worsening PAH and is also a known effect of other endothelin receptor antagonists. In PAH clinical trials with Tracleer, combined adverse events of fluid retention or edema were reported in 1.7 percent (placebo-corrected) of patients [see Clinical Studies].

In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension occurring within weeks after starting Tracleer. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.
If clinically significant fluid retention develops, with or without associated weight gain, further evaluation and implementation to determine the cause, such as Tracleer or underlying heart failure, and the possible need for treatment or discontinuation of Tracleer therapy.

Decreased Sperm Counts

An open-label, single-arm, multicenter, safety study evaluated the effect on testicular function of Tracleer 125 mg twice daily for 4 weeks, followed by 125 mg twice daily for 5 months. In the try-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to treatment discontinuation. There was a decrease in sperm count of at least 50% in 25% of the patients during the first 6 months of treatment with Tracleer. Sperm count remained within the normal range in all 22 patients with data after 6 months and no changes in sperm morphology, sperm motility, or hormone levels were observed. One patient discontinued marked oligospermia at 6 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Tracleer was discontinued and after two months the sperm count had returned to baseline levels. Based on these findings and preclinical data from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis.

Decreases in Hemoglobin and Hematocrit Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment. The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease in hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4–12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin (>15% decrease from baseline resulting in values <11 g/dL) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. In patients with PAH treated with doses of 125 and 250 mg twice daily, marked decreases in hemoglobin occurred in 3% compared to 1% in placebo-treated patients. A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of bosentan-treated patients as compared to 25% of placebo-treated patients. In 80% of those patients whose hemoglobin decreased based on the decrease occurred during the first 6 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained within normal limits in 8% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis.

Pulmonary Veno-Occlusive Disease

Should there be a pulmonary veno-occlusive disease occur when Tracleer is administered, the possibility of associated pulmonary veno-occlusive disease should be considered and Tracleer should be discontinued.

Prescribing and Distribution Program for Tracleer Because of the risks of liver injury and birth defects, Tracleer is available only through special restricted distribution program called the Tracleer Access Program (T.A.P.). Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. Information about Tracleer and T.A.P. can be obtained by calling 1-866-228-3546.

To enroll in T.A.P., prescribers must complete the T.A.P. Tracleer (bosentan) Enrolment and Renewal Form (see T.A.P. Tracleer (bosentan) Enrolment and Renewal Form for full prescribing physician agreement) indicating agreement to:

• Read and understand the communication and educational materials for prescribers regarding the risks of Tracleer.
• Review and discuss the Tracleer Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with every patient prior to prescribing Tracleer.
• Review the function tests (ALT/AST/Alb and bilirubin) and, for females of childbearing potential, confirm that the patient is not pregnant.
• Agree to order and monitor monthly liver function tests and, for females of childbearing potential, pregnancy tests.
• Enroll all patients in T.A.P. and renew patients’ enrollment annually thereafter.
• Educate and counsel females of childbearing potential to use reliable contraception, as defined on the Tracleer Enrollment and Renewal Form, during treatment with Tracleer and for one month after treatment discontinuation.
• Counsel patients to comply with the program requirements.
• Notify Actelion Pharmaceuticals US, Inc. of any adverse events, including liver injury, and report any pregnancy during Tracleer treatment.

Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNG 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer.

ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in the labeling:

• Hypersensitivity [see Boxed Warning, Contraindications]
• Acute failure [see Boxed Warning]
• Hepatotoxicity [see Contraindications]
• Thrombocytoopenia
• Rash
• Jaundice
• Anemia requiring transfusion
• Neutropenia and leukopenia

DRUG INTERACTIONS

Cytochrome P450 Summary Bosentan is metabolized by CYP2C9 and CYP3A. Inhibition of these enzymes may increase the plasma concentration of bosentan (see ketonazole). Concomitant administration of both a CYP2C9 inhibitor and a strong CYP3A inhibitor (such as fluconazole or amiodarone) and a strong CYP3A inhibitor (e.g., ketoconazole or itraconazole) or a moderate CYP3A inhibitor (e.g., amphotericin or erythromycin, fluconazole, diltiazem) with bosentan will likely lead to large increases in plasma concentrations of bosentan. Co-administration of such combinations of a CYP2C9 inhibitor plus a strong or moderate CYP3A inhibitor with Tracleer is not recommended.

Bosentan is an inducer of CYP3A and CYP2C9. Consequently plasma concentrations of drugs metabolized by these two isozymes will be decreased when Tracleer is co-administered. Bosentan may have a potent inhibitory effect on any CYP isozyme in vitro (CYP1A2, CYP2C8, CYP2C9, CYP2D6, CYP3A4). Consequently, Tracleer is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

Hormonal Contraceptives

Hormonal contraceptives, including oral, injectable, transdermal, and implantable, forms may not be reliable when Tracleer is co-administered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking Tracleer [see Boxed Warning, Contraindications].

An interaction study demonstrated that co-administration of bosentan and a combination oral hormonal contraceptive produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects.

Cyclosporine A

The concomitant administration of bosentan and cyclosporine A is contraindicated [see Contraindications].

During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. Steady-state bosentan plasma concentrations of bosentan were also decreased by approximately 30%. Bosnia was also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A. The possibility of worsened glucose control in patients using these agents should be considered.

Adverse events occurring in 35% of patients treated with bosentan 125-250 mg twice daily and more common on bosentan in placebo-controlled studies in pulmonary arterial hypertension

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Bosentan N=258</th>
<th>Placebo N=172</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. % No. %</td>
<td>No. % No. %</td>
<td>No. % No. %</td>
</tr>
<tr>
<td>Respiratory Tract Infection</td>
<td>56 22%</td>
<td>30 17%</td>
</tr>
<tr>
<td>Headache</td>
<td>39 15%</td>
<td>25 14%</td>
</tr>
<tr>
<td>Edema</td>
<td>28 11%</td>
<td>16 9%</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>13 5%</td>
<td>6 5%</td>
</tr>
<tr>
<td>Syncope</td>
<td>12 5%</td>
<td>7 4%</td>
</tr>
<tr>
<td>Flushing</td>
<td>10 4%</td>
<td>5 3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 4%</td>
<td>3 2%</td>
</tr>
<tr>
<td>Smurfits</td>
<td>9 4%</td>
<td>3 2%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>9 4%</td>
<td>3 2%</td>
</tr>
<tr>
<td>Liver Function Test Abnormal</td>
<td>9 4%</td>
<td>3 2%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>9 4%</td>
<td>3 2%</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 3%</td>
<td>3 2%</td>
</tr>
</tbody>
</table>

*Note: only AEs with onset from start of treatment to 1 calendar day after end of treatment are included. All reported events (at least 2%) are included except those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

Combined data from Study-351, BREATHE-1 and EARLY Postmarketing Experience There have been several post-marketing reports of angioedema associated with the use of bosentan. The onset of the reported cases occurred within a range of 0 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their signs of angioedema resolved without discontinuing Tracleer. The following additional adverse reactions have been reported during the post approval use of Tracleer. Because these adverse reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Tracleer exposure:

• Unexplained hepatic cirrhosis [see Boxed Warning]
• Acute failure [see Boxed Warning]
• Hepatotoxicity [see Contraindications]
• Thrombocytopenia
• Rash
• Jaundice
• Anemia requiring transfusion
• Neutropenia and leukopenia
Lopinavir/Ritonavir or Other Ritonavir-containing HIV Regimens

In vitro data indicate that bosentan is a substrate of the Organic Anion Transport Protein (OATP), CYP3A and CYP2C9. Ritonavir inhibits OATP and inhibits and induces CYP3A. However, the impact of ritonavir on the pharmacokinetics of bosentan may largely result from its effect on OATP.

In normal volunteer administration of Tracleer 125 mg twice daily and lopinavir 400/100 mg twice daily increased the trough concentrations of bosentan on Days 4 and 10 approximately 48-fold and 5-fold, respectively, compared with those measured after Tracleer administered alone. Therefore, adjust the dose of Tracleer when initiating lopinavir/ritonavir (see Dosage and Administration).

Co-administration of Tracleer 125 mg twice daily had no substantial impact on the pharmacokinetics of lopinavir/ritonavir 400/100 mg twice daily.

Simvastatin and Other Statins

Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A substrate), and its active β-hydroxy acid metabolite, by approximately 50%. The plasma concentrations of simvastatin were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that are significantly metabolized by CYP3A, such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A-metabolized statins should have cholesterol levels monitored after Tracleer is initiated to see whether the statin dose needs adjustment.

Rifampin

Co-administration of bosentan and rifampin in normal volunteers resulted in a mean 6-fold increase in bosentan trough levels after the first concomitant dose (likely due to inhibition of OATP by rifampcin), but about a 60% decrease in bosentan levels at steady-state. The effect of bosentan on rifampin levels has not been assessed. When consideration of the potential benefits and known and unknown risks leads to concomitant use, measure liver function weekly for the first 4 weeks before reverting to normal monitoring.

Tacrolimus

Co-administration of tacrolimus and bosentan has not been studied in humans. Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals. Caution should be exercised if tacrolimus and bosentan are used together.

Ketocanazole

Co-administration of bosentan 125 mg twice daily and ketoconazole, a potent CYP3A inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold in normal volunteers. No dose-adjustment of bosentan is necessary, but increased effects of bosentan should be considered.

Warfarin

Co-administration of bosentan 500 mg twice daily for 6 days in normal volunteers, decreased the plasma concentrations of both S-warfarin [a CYP2C9 substrate] and R-warfarin [a CYP3A substrate] by 29% and 38%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baselines vs. end of the clinical studies), and the need to change the warfarin dose during trials that changed INR or due to adverse events was similar among bosentan- and placebo-treated patients.

Digoxin, Nimodipine, and Losartan

Bosentan may have significant pharmacokinetic interactions with digoxin and nimodipine, and losartan has no significant effect on plasma levels of bosentan in animals.

Sildenafil

In normal volunteers, co-administration of multiple doses of 125 mg twice daily bosentan and 80 mg three times daily sildenafil resulted in a reduction of sildenafil plasma concentrations by 60% and increased bosentan plasma concentrations by 50%. The changes in plasma concentrations were not considered clinically relevant and dose adjustments are not necessary. This recommendation holds true even when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

Iloprost

In a small, randomized, double-blind, placebo-controlled study, 34 patients treated with bosentan 125 mg twice daily for at least 16 weeks tolerated the addition of iloprost (up to 5 mcg to 9 times per day during waking hours). The mean daily inhaled dose was 27 mcg and the mean number of inhalations/day was 18.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X: Teratogenic Effects [see Contraindications]

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no available data on the effects of bosentan in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. Bosentan caused teratogenic effects in animals including malformations of the head, mouth, face, and large blood vessels. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Females of childbearing potential should have a negative pregnancy test before starting treatment with Tracleer. The prescriber should not dispense a prescription for Tracleer without documenting a negative urine or serum pregnancy test performed during the first 5 days of a normal menstrual period.

Important Information

• Monitoring of serum aminotransferases

The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases.

• Pregnancy testing and avoidance of pregnancy

Patients should be advised that Tracleer is likely to cause birth defects based on animal studies. Tracleer treatment should only be initiated in females of childbearing potential following a negative pregnancy test. Females of childbearing potential must have monthly pregnancy tests and need to use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. Females who have a tubal ligation or a Copper T 380A IUD or LNG 20 IUS can use these contraceptive methods alone. The physician should be informed if they suspect they may be pregnant and should seek contraceptive advice from a gynecologist or other expert as needed.

• Drug Interactions

The physician should discuss with the patient the possible drug interactions with Tracleer, and which medications should not be taken with Tracleer. The physician should discuss the importance of disclosing all concomitant or new medications.

Important Information

Advice patients to consult the Medication Guide on the safe use of Tracleer.

Nursing mothers

It is not known whether Tracleer is excreted into human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Tracleer, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

Safety and efficacy in pediatric patients have not been established.

Geriatric use

Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between elderly and younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

Hepatic Impairment

Because there is in vivo and in vitro evidence that the main route of excretion of bosentan is biliary, any impairment could be expected to reduce Tracleer exposure (C0, AUC and M) of bosentan. Mild liver impairment was shown not to impact the pharmacokinetics of bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of Tracleer has not been evaluated. There are no specific data to guide dosing in hepatatically impaired patients; caution should be exercised in patients with mildly impaired liver function. Tracleer should generally be avoided in patients with moderate or severe liver impairment [see Dosage and Administration, Warnings and Precautions].

Renal Impairment

The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dose adjustment.

Nonclinical Weight [see Dosage and Administration]

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatic adenomas and carcinomas in males at doses as low as 400 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 125 mg twice daily, on a mg/m2 basis). In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenoma in males and females, and in rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of in vitro and in vivo genotoxicity assays, including the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay and an in vivo mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Reproductive and Developmental Toxicology

Bosentan was teratogenic in rats given oral doses >400 mg/kg/day. In an early-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 300 and 600 mg/kg/day. Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. Postnatal fertility of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs.

The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents. Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m2 basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the more severe duration fertility studies in which males had been exposed for 18 months.

An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

PATIENT COUNSELING INFORMATION

Advise patients to consult the Medication Guide on the safe use of Tracleer.

April 2011

Reference for previous pages: 1. Data on file, Actelion Pharmaceuticals US, Inc. © 2011 Actelion Pharmaceuticals US, Inc. All rights reserved.
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%).

ADCIRCA once-daily opens up possibilities

Proven PDE-5 inhibition that can help patients with PAH be more active

- The only once-daily PDE-5 inhibitor for PAH
- 33-meter placebo-adjusted mean improvement in 6MWD at 16 weeks
- A $20 co-pay for eligible patients on commercial/private insurance plans
- The most common adverse event with ADCIRCA is headache. Other common adverse events include myalgia, nasopharyngitis, flushing, respiratory tract infection, extremity pain, nausea, back pain, dyspepsia, and nasal congestion

*This assistance program is not valid for prescriptions reimbursed under Medicare, Medicaid, TRICARE, state pharmaceutical assistance programs, or other federal or state programs. This assistance program is not valid for patients in the state of Massachusetts with prescription drug coverage.

Important Safety Information

CONTRAINDICATIONS
- ADCIRCA should not be used in patients taking medicines that contain nitrates, as the combination could cause a sudden, unsafe drop in blood pressure
- Patients with a known serious hypersensitivity to tadalafil should not take ADCIRCA

WARNINGS AND PRECAUTIONS
- If a patient experiences anginal chest pain after taking ADCIRCA they should seek immediate medical attention
- Phosphodiesterase 5 inhibitors (PDE-5i), 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
- The use of ADCIRCA with alpha blockers, blood pressure medications, and alcohol may lower blood pressure significantly and may lead to symptomatic hypotension (fainting)
- 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
- 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
- ADCIRCA contains the same ingredient (tadalafil) as Cialis, which is used to treat erectile dysfunction (ED). The safety and efficacy of combinations of ADCIRCA with Cialis or other PDE-5 inhibitors have not been studied. Therefore, the use of such combinations is not recommended
- In rare instances, men taking PDE-5 inhibitors (including tadalafil) for ED reported a sudden decrease or loss of vision or hearing, or an erection lasting more than four hours. A patient who experiences any of these symptoms should seek immediate medical attention

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%), back pain (10% vs 6%), nausea (11% vs 6%), dyspepsia (10% vs 2%), and nasal congestion (9% vs 1%)

Please see brief summary of Full Prescribing Information on following page. Please see Full Prescribing Information and Patient Information available at www.adcirca.com, or call 1-800-545-5979.

ADCIRCA is a registered trademark of Eli Lilly and Company, 2011.
www.adcirca.com
877-UNITHER
INDICATIONS AND USAGE
BRIEF SUMMARY
of idiopathic or heritable PAH (61%) or PAH associated with CIALIS. Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

WARNING AND PRECAUTIONS
Cardiovascular Effects: Discusses with patients the appropriate action to take in the event that they experience anginal chest pain requiring nitroglycerin following intake of ADCIRCA. Administration of ADCIRCA within 48 hours of nitroglycerin intake is not recommended. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 9% for ADCIRCA 20 mg and 15% for CIALIS. The rates of discontinuation because of AEs, other than those related to worsening of PAH, in patients treated with ADCIRCA 40 mg was 4% compared to 5% in placebo-treated patients. In the placebo-controlled study, the most common AEs were angina, angioedema, and peripheral edema.

Table 1 presents treatment-emergent adverse events reported by ≥5% of patients in the ADCIRCA 40 mg group and occurring more frequently than with placebo.

Table 1. Treatment-Emergent Adverse Events Reported by ≥5% of Patients in ADCIRCA and More Frequent than Placebo by 2%

<table>
<thead>
<tr>
<th>EVENT</th>
<th>ADCIRCA (N=61)</th>
<th>Placebo (N=82)</th>
<th>ADCIRCA 20 mg (N=61)</th>
<th>Placebo (N=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16</td>
<td>10</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>6</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>2</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>2</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>5</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 establish their frequency reliably from these sources, and therefore to compensate for lack of precise frequency estimates, the following lists contain all reports that were received by the manufacturer. The estimates can only be used to compare safety experience with the same drug in clinical trials to the estimates from other clinical trials and the databases in postmarketing studies.

CARDIOVASCULAR SYSTEM
Hypotension: In patients receiving tadalafil for at least one week, hypertension was noted in 19% of patients receiving tadalafil 20 mg once daily, compared to 10% in placebo-treated patients. In the placebo-controlled study, the most common AEs were angina, angioedema, and peripheral edema.

Table 1 presents treatment-emergent adverse events reported by ≥5% of patients in the ADCIRCA 40 mg group and occurring more frequently than with placebo.

Table 1. Treatment-Emergent Adverse Events Reported by ≥5% of Patients in ADCIRCA and More Frequent than Placebo by 2%
Organic nitrates are 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 nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrate 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 or 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 (amiloride, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol). 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 increase in 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 plasma concentrations. Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isofunctions (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan). Amodiaquine — Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin. P. gingivalis and P. aeruginosa — Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

**AFFECT OTHER DRUGS:**

Cytochrome P450 Substrates — Coadministration of tadalafil (40 mg once daily) for 20 days did not alter plasma concentrations or bioavailability of digoxin. Tadalafil may not be expected to significantly affect the pharmacokinetics of drugs that are substrates for cytochrome P450. Sildenafil, verapamil, diltiazem, and amiodarone did not significantly decrease the pharmacokinetics of tadalafil. Coadministration of tadalafil (20 mg and 10 mg once daily) with ketoconazole, itraconazole, and erythromycin did not significantly change the pharmacokinetics of tadalafil. Tadalafil plasma concentrations were unchanged when tadalafil was coadministered with potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of ADCIRCA. Tadalafil is metabolized predominantly by CYP3A4 in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, 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) isofunctions (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan). Amodiaquine — Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin. P. gingivalis and P. aeruginosa — Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

**USING 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-teratogenic Effects — 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. 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: 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 upon 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. Marketed by Lung Rx, LLC, a wholly owned subsidiary of United Therapeutics Corporation.

Rx only April 2011 www.adcirca.com

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**DR. MICHAEL McGOON DOESN’T HAVE PH. HIS VISION IS A WORLD WHERE NO ONE ELSE DOES, EITHER.**

Michael McGoon, MD, a PH-treating physician and member of PHA’s Scientific Leadership Council and Board of Trustees, has been inspired by PHA’s work and the stories of its members. "PHA is a unique organization,” Mike says. “From a medical perspective, it’s amazing to see a group of patients, caregivers, researchers, physicians and allied health professionals all working toward a common goal. His wife, Bonnie, has been just as involved.

To read how Mike and Bonnie continue to devote their efforts to defeating PH, visit PHAssociation.org/Give/McGoon

Like the McGoon family, you can strike a blow against PH by designating PHA as a legacy beneficiary. Your contribution will help shape a brighter future for all those affected by PH. For details, call us at 301-565-3004 x767, or email giving@PHAssociation.org.

Visit our website for more information at PHAssociation.org/Give.
Preventive Health Care for Women with Pulmonary Hypertension

Mae Centeno DNP, RN, CCRN, CCNS, ACNS-BC
Program Manager/Clinical Nurse Specialist, Heart Failure Program and Advanced Lung Disease Center
Baylor University Medical Center
Houston, TX

Women with idiopathic pulmonary arterial hypertension (IPAH) are often of childbearing age and outnumber males with IPAH by a 4:1 ratio.1 All patients with PAH should have a primary care provider, but in some cases the PH provider may be the only health care professional that the PH patient is seeing on a regular basis. Therefore, while the primary focus is on the treatment of PH, routine preventive care should also be incorporated. This article will examine important preventive health care strategies for patients with PH, with a special focus on women’s issues. Topics covered include immunization; counseling on tobacco, alcohol, and drug avoidance; screening for osteoporosis, breast cancer, cervical cancer, sexually transmitted disease, and colorectal cancer; and pregnancy prevention. A summary of select U.S. Preventive Services Task Force (USPSTF) screening recommendations is listed in Table 1.

Standard screening tests, performed at specified intervals, can be a cost-effective way to identify and treat potential health problems before they develop or worsen.2 However, while many of the usually recommended assessments apply, the presence of PH leads to modifications in some cases. For example, pneumococcal vaccination is recommended at age 65 or with "chronic disease," and thus all patients with PH should receive the pneumococcal vaccine. Additionally, if the first pneumococcal vaccination is received before the age of 65, then a second dose should be given at or after age 65. Other vaccination recommendations include annual influenza vaccination and a one-time zoster vaccination for patients 60 years and over.

Similarly, colorectal screening should probably only be considered in patients with very stable PAH, as current recommendations are for screening only in patients age 50 to 75 with a life expectancy greater than 10 years.3 Screening options include fecal occult blood testing, sigmoidoscopy, and colonoscopy, all of which have demonstrated a mortality benefit in other patient populations.3 The type of screening should also be carefully considered: colonoscopy is typically a preferred test in the general population, but it requires significant sedation which can pose a risk for PH patients. In addition to the other screening options above, CT-colonography is now also a recommended option that requires bowel preparation but no sedation.3 Therefore, while the lack of sedation makes this option attractive, the tolerability of the large amount of oral fluid needed for bowel preparation needs to be considered.

Preventive care recommendations that should be given to all patients with PAH include counseling on tobacco, alcohol, and drug use avoidance.4 Patients should also be screened for depression, and if present, referred for treatment. Several depression screening tools are available and easy to use; or alternatively, asking two simple questions may be as effective as longer questionnaires: “Over the past two weeks, have you felt down, depressed, or hopeless?” and “Over the past two weeks, have you felt little interest or pleasure in doing things?”5

Women with PH also need routine well-woman screening. After menopause, women are at increased risk of developing osteoporosis.6 Some women with PAH associated with connective tissue disease may be taking prednisone, which is also a risk factor for the development of osteoporosis. Bone mineral density measurement using dual-energy x-ray absorptiometry (DXA) of the hip and lumbar spine and quantitative ultrasonography of the calcaneus (a noninvasive test) can help identify early manifestations of the disease. This test is recommended for anyone age 65 or older and those at risk for developing osteoporosis.6 A healthy diet with adequate amounts of calcium and vitamin D can help prevent osteoporosis. Experts recommend premenopausal women consume at least 1000 mg of calcium and 400 to 600 international units of vitamin D per day. Postmenopausal women should have an intake of 1200 mg of calcium and 800 international units of vitamin D daily.7

The American College of Physicians (ACP) and the USPSTF recommend screening mammography be conducted biennially in women ages 50 to 74 years, and recommend mammography be considered in women ages 40-49 years, after discussing the risks and benefits.8 The benefit of screening mammography in patients under age 50 is a potential decrease in breast cancer mortality of approximately 15%, but at the cost of potentially false-positive results, need for biopsies, and radiation exposure.9

The lack of evidence to support annual cervical screening has led to changes in testing frequency. The American Congress of Obstetricians and Gynecologists (ACOG) recommend women have their first cervical cancer screening at age 21 and once every 2 years until age 30, though women at increased risk due to immunosuppression, prior cervical cancer, or prior abnormal cytology results may need more frequent screening.10 Women older than 30 years of age with...
pelvic inflammatory disease.11 This sexually transmitted disease that can lead to Chlamydia trachomatis, a common sex partner's screening for women who have new or multiple sexual partners should also be screened as well. Studies have shown that encouragement all patients to establish good primary care as well. The physiological, cardiovascular, and pulmonary changes that occur during pregnancy have been associated with high maternal mortality in PAH, and thus pregnancy avoidance and use of adequate contraception are important.12,13 Additionally, one of the most common categories of medications to treat PAH, the endothelin receptor antagonists (ERAs), are category X in pregnancy, as they caused severe birth defects in animal studies.14 Pregnancy must be excluded prior to initiating therapy and women must be educated about the risks, required monthly pregnancy testing, and need for adequate contraception (Table 2; see also Pregnancy article and Contraception in PH article for additional details).15,16 Women should be advised to notify their health care professional of any delay in onset of menses or any other reason to suspect pregnancy, so that immediate pregnancy testing can be performed and the ERA discontinued.15,16

Finally, although we began this article with the suggestion that the PH provider might consider tackling some or all of the patient’s preventive health care needs, in reality, the large number of preventive care items required is a strong argument for encouraging all patients to establish good primary care as well. Studies have shown that patients with a primary care physician are more likely to receive appropriate preventive care and may have improved survival.17

3 consecutive negative cervical cytology results may have screening either Pap test or liquid-based cytology every 3 years.10 Routine cervical screening should be discontinued in women who have had a total hysterectomy for noncancerous causes regardless of age, and discontinuation can also be considered in women over age 65 who have had 3 consecutive negative cytology results and no abnormal results in the last 10 years.10 These guidelines also apply to women who have been vaccinated against the human papillomavirus.10 Women ages 25 years or younger and all women who have new or multiple sex partners should also be screened for Chlamydia trachomatis, a common sexually transmitted disease that can lead to pelvic inflammatory disease.11 This screening process also provides an opportunity to counsel patients on safe sex practices.

Table 1: Summary of UPSTF Recommendations That Commonly Apply to PH Patients

<table>
<thead>
<tr>
<th>Screening for breast cancer</th>
<th>Women age 50 and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening for cervical cancer with Pap smear</td>
<td>Women age 21 to 65 who are sexually active and have a cervix</td>
</tr>
<tr>
<td>Screening for Chlamydia</td>
<td>Women age ≥25 or at increased risk</td>
</tr>
<tr>
<td>Screening for colorectal cancer</td>
<td>Adults age 50 to 75; generally discontinue when life expectancy &lt;10 years and avoid screening when life expectancy &lt;5 years.</td>
</tr>
<tr>
<td>Screening for osteoporosis</td>
<td>Adults age &gt;65 or at increased risk.</td>
</tr>
<tr>
<td>Screening for tobacco, alcohol, and drug use</td>
<td>All adults: even brief counseling increases quit rates for tobacco and reduces alcohol consumption</td>
</tr>
<tr>
<td>Depression</td>
<td>All adults: screening plus referral for therapy reduces the burden of suffering from depression</td>
</tr>
<tr>
<td>Immunizations</td>
<td>Influenza, varicella or zoster, tetanus/diphtheria and pneumovax are recommended</td>
</tr>
</tbody>
</table>

Table 2: Acceptable Methods of Contraception for Patients on ERAs

<table>
<thead>
<tr>
<th>Methods to Use Alone</th>
<th>Combination Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone Methods</td>
<td>Barrier Methods</td>
</tr>
<tr>
<td>Choose one and use with a barrier method</td>
<td>Use both OR choose one and use with a hormone method</td>
</tr>
<tr>
<td>Intrauterine devices (IUDs)</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>● Copper T 380A IUD</td>
<td>Transdermal patch</td>
</tr>
<tr>
<td>● LNG 20 IUS (progesterone IUD)</td>
<td>Vaginal ring</td>
</tr>
<tr>
<td>Tubal sterilization</td>
<td>Progesterone only</td>
</tr>
<tr>
<td>● Injection</td>
<td>● Diaphragm with spermicide</td>
</tr>
<tr>
<td>● Implant</td>
<td>OR</td>
</tr>
</tbody>
</table>

A partner’s vasectomy still requires 1 additional method of contraception

References


The Gender/Estrogen Paradox and the Right Ventricle in Pulmonary Vascular Disease

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The Clinical Trials Update highlights new and ongoing research trials that are relevant to the diagnosis and treatment of PAH. In this issue, Corey Ventetuolo, MD, MS, describes a study on the relationships among genetic predictors of sex hormone processing, sex hormones and their metabolites, and RV measures both at baseline and longitudinally in male and female participants from the Multi-Ethnic Study of Atherosclerosis–Right Ventricle Study.

While we have long understood pulmonary arterial hypertension (PAH) to be a female-predominant disease, modern PAH registries suggest this gender bias is increasing.1 Similar trends have been observed for pulmonary hypertension (PH) and PH providers are now faced with caring for older, postmenopausal patients with complex medical comorbidities and contributors to disease.1 Right ventricular (RV) function ultimately determines outcome for our patients, but the mechanisms and determinants of RV failure are unknown. Surprisingly, despite greater disease prevalence, it appears that women have preserved RV function and survival compared to men with PAH.3 In fact, estrogen therapy has been shown to rescue both pulmonary vasculopathy and RV function in animals.8 In light of these observations, the study of sex hormone pathways and their associations with RV performance has never seemed so timely.

STUDYING THE RIGHT VENTRICLE IN HEALTH

RV structure and function reflect the afterload imposed by PH and PAH over time, and even small increments or fluctuations in loading may lead to RV sequelae. There is, however, great variability in the clinical trajectory of patients with pulmonary vascular disease. Patients often present late in disease, when RV failure has already occurred, and currently available therapies target only the pulmonary vasculature. The study of RV performance in healthy participants (or those with subclinical disease) may not only generate new hypotheses about the mechanisms of RV failure, but lead to the development of therapeutic approaches for RV dysfunction.

The Multi-Ethnic Study of Atherosclerosis (MESA) is a 10-year, NHLBI-sponsored, multicenter prospective cohort study of 6814 participants 45-84 years old without clinical cardiovascular disease at baseline. Participants were enrolled from 6 geographically diverse field centers around the country. MESA-RV is an ancillary study that has measured RV structure and function in over 4000 MESA participants by cardiac magnetic resonance imaging (MRI), representing the largest and only study of its kind. We have also completed follow-up RV measures (5 years later) in an unselected group of approximately 700 MESA participants, giving us the opportunity to study longitudinal predictors of RV morphology. In addition to the participant diversity inherent in MESA’s design, extensive clinical and genetic data are available, representing a unique opportunity to feasibly confirm/refute hypotheses about the impact of gender, sex hormones, and genetic variation in hormonal processing on RV structure and function. Given the increasing prevalence of PAH not only in females but in older individuals, and the high rate of medical comorbidities observed, the MESA cohort offers a unique opportunity to study possible mechanistic pathways in participants with demographics similar to modern PAH registries.1

GENDER, SEX HORMONES, AND THE RIGHT VENTRICLE

As has been shown for PAH patients, female MESA participants have higher RV ejection fractions (RVEF) than their male counterparts, as well as lesser volumes and end-diastolic mass.3 These morphologic associations with gender may be explained by serum sex hormone levels, and in fact study of baseline levels of estradiol (E2), testosterone, and dehydroepiandrosterone (DHEA) revealed some interesting findings.9 First, higher levels of E2 were associated with higher RVEF and lower RV end-systolic volume in postmenopausal women using hormone therapy (HT), but not in HT nonusers or men. These associations persisted after adjustment for respective left ventricular (LV) measures, suggesting that exogenous E2 was associated with RV systolic function independent of any effects on the LV. Second, higher testosterone levels were associated with greater RV mass and larger RV volumes in men (but not in women). Third, higher levels of DHEA were associated with greater RV mass and...
larger volumes in women and possibly in men. The associations seen with DHEA and the RV in women were similar to those seen with testosterone in men, suggesting a possible androgenic effect. Our observed small changes in RV function in normals could indeed translate to clinically meaningful effects in individuals at risk for (or after onset of) disease. From these data, we conclude that E2 is associated with better RV performance in women and that androgens (testosterone and DHEA) are associated with greater RV mass and volumes in both genders.

**FUTURE DIRECTIONS**

We and others have hypothesized that sex hormone-driven angiogenesis may underpin the gender/estrogen paradox in pulmonary vascular disease and RV function. Genetic variation in hormone metabolism and signaling, with resultant effects on downstream angiogenesis, may further modify an individual’s risk for disease. While certain polymorphic variants in sex hormone pathways have been associated with PAH, these and other variants have unknown impact on RV function, a key predictor of outcome in pulmonary vascular disease.10-12

We plan to investigate the relationships among genetic predictors of sex hormone processing, sex hormones and their metabolites, and RV measures both at baseline and longitudinally in male and female participants from MESA-RV. Our work will be the first to characterize these relationships and the largest genetic study of RV function available. We hope that by studying these pathways in a population-based cohort, we may gain insight into the epidemiologic trends observed in both PH and PAH, and may generate new hypotheses about the complex interplay between gender, sex hormones, and the cardiopulmonary interaction.

**References**

Program Overview
Pulmonary arterial hypertension (PAH), an incurable disease, is characterized by medial hypertrophy, intimal fibrosis, and in situ thrombi in small muscular pulmonary arteries. PAH was considered a rapidly fatal illness with a median survival of 2.8 years in the 1980s when no evidence-based therapies were available. Since then the treatment of this disease has made tremendous advances, and in the last 10 years the discovery of new medications have positively influenced the prognosis and survival of patients with PAH.

This self-study activity is based on 3 articles that review the management of pulmonary hypertension in women.

This activity is jointly sponsored by the University of Michigan Medical School and the Pulmonary Hypertension Association.

Target Audience
This self-study activity is appropriate for cardiologists, pulmonologists, rheumatologists, and other physicians who treat patients with PH.

Learning Objectives
Upon completion of this activity, participants will be able to:
1. Describe the contraceptive options available to the patient with PAH
2. Understand the physiologic changes and challenges associated with pregnancy in PAH patients
3. Discuss the influence of sex hormones in pathogenesis of PAH

Self-Assessment Examination
See pages 178 and 179 for self-assessment questions, answer key, and evaluation form.

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Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Michigan Medical School and the Pulmonary Hypertension Association. The University of Michigan is accredited by the ACCME to provide continuing medical education to physicians.

Credit Designation
The University of Michigan Medical School designates this enduring material for a maximum of 2.0 AMA PRA Category 1 Credits.™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Instructions for Earning Credit
This activity is a self-study program; a self-assessment examination is included on page 178 to help physicians review important points. A form is also included on page 179 for physicians to evaluate the CME activity. Completion of this activity involves reading the journal and completing the self-assessment examination and evaluation form, which may take up to 2 hours. Credits for this self-study program are available from November 20, 2011 through November 19, 2012. There is no fee for this program. Please note that this self-study program may also be viewed online at http://www.cme.med.umich.edu.

University of Michigan Privacy Statement
http://www.cme.med.umich.edu/privacy.asp

Oversight and Accreditation
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Disclosures
The Accreditation Council for Continuing Medical Education and the Association of American Colleges have standards and guidelines to ensure that individuals participating in CME activities are aware of relationships between authors and commercial companies that could potentially affect the information presented. To be disclosed to participants are all personal financial relationships with a commercial interest whose products are relevant to the content of this CME activity. The University of Michigan Medical School follows these national policies to ensure balance, independence, objectivity, and scientific rigor in all its CME activities. Each author was asked to complete a disclosure information form for this activity. Disclosures are reported below:

Dr Levine reports no potential conflicts.
Dr Chin reports no potential conflicts.
Dr Austin reports no potential conflicts.
Dr Santiago-Munoz reports no potential conflicts.
Dr Zwicke reports an advisory relationship with Gilead and Pfizer.

CME Reviewer
Kevin Chan, MD, Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan Health Systems, Ann Arbor, Michigan

Dr Chan has received grant/research support from Alnylam Pharmaceuticals and Gilead.
THE EPIDEMIOLOGY OF PAH WITH RESPECT TO GENDER

The precise incidence of pulmonary arterial hypertension (PAH) is difficult to determine with accuracy for a variety of reasons, including tertiary care center bias and community underreporting; regardless, most studies to date predominantly evaluated prevalent cases. While affecting patients of all ages and both genders, since its earliest descriptions PAH has been undeniably a disease that preferentially affects females more than males (Figure 1).10,11

Determining incidence and prevalence rates according to gender is difficult. A large multicenter French study attempted to address incidence by evaluating 674 cases of PAH from 17 university hospitals across France during a 1-year period from October 2002 to October 2003.6 Among those 674 PAH cases, 65.3% were females. They found that 18% (121 of 674) of PAH cases were incident diagnoses (57.0% female) during the period of the study. The remaining 553 cases were prevalent cases, of which 67.1% were females. At that time, they concluded an overall female predominance among PAH patients of 1.9 females: 1 male, with the exception being portal hypertension-associated PAH and HIV-associated PAH (both slightly favored males).

Those 674 subjects were subsequently followed prospectively and reanalyzed three years later. Among the interesting findings to emerge from those analyses were confirmation of female predominance and a suggestion of survival benefit according to gender. In particular, among those with heritable PAH (HPAH), idiopathic PAH (IPAH) and anorexigen-associated PAH, female gender associated with improved survival at 3 years; ie, despite similar treatment regimens, male patients may be at greater risk of mortality.12,13 As survival may have more to do with right heart adaptation to a load stress by the pulmonary vasculature, this raised an intriguing question: does female gender negatively influence pulmonary vascular disease pathogenesis, but positively influence right heart adaptation to pulmonary hypertension?

In North America, the Actelion-sponsored Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) database provided a large observational cohort study of PAH, which remains ongoing. The registry was designed to enroll prevalent and/or incident patients in the United States with WHO Group 1 PAH, to characterize their baseline characteristics as well as to examine their clinical progression and responses to therapy over time.14 The baseline characteristics on the first 2525 adult patients enrolled between March 2006 and September 2007 were reported, as well as a follow-up survival study.15,16 One of the most interesting findings to emerge from REVEAL to date is an even larger predominance of females than anticipated, with 79.5% of the adult PAH patients in the registry classified as female. Specifically, the female-to-male ratio of 4.1:1 among IPAH patients is much higher than that reported in the 1987 National Institutes of Health registry (1.7:1)11 or in the French registry (1.9:1), but is similar to that observed in the Surveillance of Pulmonary Hypertension in America registry (4.3:1).17

REVEAL also provided a more in depth evaluation of PAH subjects according to gender across subtypes of PAH, demonstrating a marked predominance of females across PAH subtypes, with the exception of portal hypertension-associated PAH (Table 1). With regard to survival, REVEAL investigators determined that older males had a survival disadvantage among PAH patients. Specifically, men over 60 years of age had poorer survival compared with men ≤60 years of age at the time of assessment and compared with female patients regardless of age.16 While not an identical analysis, this similarity to
survival data in the French registry is certainly intriguing.

Of note, while the French and REVEAL registry studies described a lack of female predominance among those with portal hypertension-associated PAH (termed portopulmonary hypertension), not all studies agree on this conclusion. In a prospective cohort of patients with portal hypertension, Kawut and colleagues found that female gender was independently associated with portopulmonary PAH. Specifically, of 106 patients with portal hypertension (53 with portopulmonary PAH, 53 without), females had 3-fold higher odds of portopulmonary PAH compared to males on adjusted analysis irrespective of the underlying etiology of liver disease.18 Subsequent analysis of this population demonstrated that genetic variation in estrogen signaling was associated with the risk of portopulmonary PAH—they found that genetic polymorphisms in both estrogen receptor 1 (ESR1) (also known as estrogen receptor α) and aromatase (CYP19A1) associated with disease expression, as did elevated plasma estradiol levels.19

**COULD SEX HORMONES EXPLAIN THE GENDER DISCREPANCY IN HUMAN PAH?**

There is thus significant epidemiologic evidence that gender is a profound mod-

![Figure 1: Pedigree of a large family with HPAH, with color-coding added to highlight the gender of those with HPAH. Subjects with HPAH are demonstrated by colored symbols: blue squares for males, red circles for females. Symbols are standard for pedigree analysis otherwise. Note the large percentage of HPAH patients in this family who are female.](image)

**Table 1: Data From the REVEAL Study: Comparison of Gender Ratios Observed in PAH Patients With Different Types of WHO Group 1 PAH**

<table>
<thead>
<tr>
<th>Type of Group 1 PAH</th>
<th>Number of Patients (%) Female</th>
<th>Ratio of Females: Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with Group 1 PAH</td>
<td>2525 (79.5%)</td>
<td>3.9:1</td>
</tr>
<tr>
<td>IPAH</td>
<td>1166 (80.3%)</td>
<td>4.1:1</td>
</tr>
<tr>
<td>CHD-PAH</td>
<td>250 (73.6%)</td>
<td>2.8:1</td>
</tr>
<tr>
<td>CTD-PAH</td>
<td>639 (90.1%)</td>
<td>9.1:1</td>
</tr>
<tr>
<td>PHTN-PAH</td>
<td>136 (50.0%)</td>
<td>1:1</td>
</tr>
<tr>
<td>Drugs/Toxins-PAH</td>
<td>134 (84.3%)</td>
<td>5.4:1</td>
</tr>
</tbody>
</table>


IPAH = idiopathic PAH; CHD = congenital heart disease; CTD = connective tissue disease; PHTN = portal hypertension
Data to Suggest that Female Sex Hormones are not Detrimental. While not designed to assess hormone exposures as a primary endpoint, the International Primary Pulmonary Hypertension Study included 66 female patients classified at that time as having primary pulmonary hypertension compared to 265 matched female controls. One query in that study concerned exposure to female reproductive hormones. Their findings did not demonstrate statistically significant differences in terms of recent pregnancy exposure (odds ratio 1.9, 95% CI 0.6-6.0) or oral contraceptive (odds ratio 1.3, 95% CI 0.6-3.1) use among females with PAH.25-27

Acute Effects of Estrogens. Estrogens appear acutely protective in the pulmonary vasculature. This is largely attributed to acute vasodilation and attenuation of the vasoconstrictor response caused by various stimuli, including hypoxia. Interestingly, physiologic variations in estrogen levels (as might be seen in menstruating females) appear to correlate with the degree of pulmonary artery vasoconstriction in response to hypoxia, with less hypoxic vasoconstriction with exposure to increased circulating estrogens.30 The mechanism appears to involve stimulation of compounds known to promote pulmonary artery relaxation: estradiol, the principal estrogen parent compound, increases prostacyclin release and enhances the production of nitric oxide (NO) acutely in vitro.7

Classically, these effects by estradiol and other estrogenic compounds are thought to occur via binding to 1 of 2 estrogen receptors, ERα and ERβ.31,32 For example, recent work in animals by Lahm and colleagues using Sprague-Dawley rats attributed the acute vasodilatory effects of estradiol specifically to acute ligand binding by estradiol to both estrogen receptor β (ERβ) and estrogen receptor α (ERα). In those studies, NO appeared to be the central mediator of acute pulmonary vascular relaxation mediated by binding to both ERα and ERβ.33 However, estrogens’ influence on vascular function may also occur through nongenomic signaling primarily mediated through the g-coupled protein receptor GPR30.34

Chronic Effects of Estrogens. The long-term impact of estrogens on vascular homeostasis is a complex process, with the balance of evidence to date suggestive that estrogens promote the pulmonary vascular proliferative processes that cause PAH. Experimental data implicate estrogens as promoters of inappropriate pulmonary vascular proliferation and cell damage. In vitro, estrogen is mitogenic and promotes proliferation of pulmonary vascular smooth muscle cells, while the anti-estrogen drug tamoxifen blocks this effect.35 In addition, growing evidence suggests that estradiol may directly promote angiogenesis via direct effects on

Data to Suggest that Female Sex Hormones are Protective of Disease. The female predominance of connective tissue disease-associated PAH, such as scleroderma, is significant. While predominantly females, unlike HPAH and IPAH patients, connective tissue disease-associated PAH patients are often postmenopausal at the time of diagnosis15,28; this could suggest a protective effect of estrogens among this at-risk population, although this is not clear. Nonetheless, a retrospective study of 61 scleroderma patients without echocardiographic evidence of pulmonary hypertension at the time of menopause demonstrated the development of PAH in the subsequent postmenopausal years among 0 out of 20 patients on hormone replacement therapy (mean 7.2 ± 3.5 yrs); in contrast, 8 out of 41 patients not receiving hormone replacement therapy developed PAH after a similar period of time post menopause (7.5 ± 3.9 yrs).29 The biologic significance of this finding requires further study.

SEX HORMONES AND THE PULMONARY VASCULATURE: ARE ESTROGENS ACUTELY PROTECTIVE BUT CHRONICALLY DETERMINAL? The impact of sex hormones on the pulmonary vasculature is complex and incompletely understood, with both acute and chronic influences: acutely protective, estrogens may be detrimental on a chronic basis.
endothelial cell migration, largely mediated through rapid signaling pathways; in concert with endothelial dysfunction, angiogenesis characterizes severe PAH in humans, and this could be a feature accentuated by estrogens.37

Effects of Androgens. Androgens appear to act acutely upon smooth muscle cells more specifically. Testosterone and dehydroepiandrosterone (DHEA) have been shown to induce significant vasodilatation in the rat pulmonary vasculature via acute calcium antagonism in smooth muscle cells.38 This direct action was recently demonstrated in human pulmonary arteries from both genders, as well.39 Consistent with these findings, hypoxic human pulmonary artery smooth muscle cells exposed to the DHEA had diminished production of hypoxia-inducible factor 1α, suggesting a protective effect against pulmonary hypertension. It was also recently demonstrated that DHEA inhibits Src/STAT3 activation in the pulmonary artery smooth muscle cells of patients with PAH, with downstream consequences including upregulation of BMPR2 and miR-204.40 However, as discussed below male rodents may be more susceptible to most forms of experimental pulmonary hypertension, but treatment with DHEA is protective in some animal models. The data to date suggest that androgens should be further evaluated as a therapeutic agent for PAH for their beneficial acute and chronic effects, and animal studies are underway.41

ANIMAL MODELS, SEX HORMONES, AND PAH

The use of animal models to study PAH has been an area of controversy for many years, as there is no perfect model and each animal model has advantages and drawbacks. Regardless, several animal model studies have been used to evaluate the acute and chronic effects of estrogen administration, with most but not all research in the hypoxia and monocrotaline models of PAH. In contrast to the human data presented above, most animal models of pulmonary hypertension demonstrate a protective effect associated with female gender, which appears to be mediated via parent compound estrogens, such as estradiol.

In most rodent models (eg, hypoxia, monocrotaline, apolipoprotein E knockout) of pulmonary hypertension and in swine (hypoxia), exposure to chronic hypoxia or monocrotaline (a vinca alkaloid) causes pulmonary hypertension. However, it has been well known that female animals do not develop significant pulmonary hypertension in these models, in contrast to males.42-45 More recently, exogenous administration of estradiol to male Sprague-Dawley rats exposed to monocrotaline has been shown to both prevent and reverse severe pulmonary hypertension,46,47 while ovariectomy of females allowed for pulmonary vascular changes in both models.48 The beneficial effects of estrogen using the monocrotaline model appear to be mediated via ERβ specifically, and this discovery may help to fine tune therapeutic approaches.46 Further studies in additional animal models of PAH to investigate the influence of specific estrogens on the pulmonary vasculature and right heart should be helpful. For example, a study of DHEA using the chronic hypoxia/VEGF inhibitor (SUGEN) model is apparently underway (presented by Oka M et al, Grover Conference 2011, Sedalia, CO).

Not all animal models display a bias toward male pulmonary hypertension and female protection, however. MacLean and colleagues used a genetic-based model of rodent PAH, using manipulation of the serotonin transporter (SERT), to develop a model of PAH that demonstrates female bias. Specifically, in hypoxia female mice that overexpress the serotonin transporter (SERT; SERT+ mice) exhibit PAH and exaggerated hypoxia-induced PAH, while male SERT+ mice do not.50,51 However, ovariectomy abolished the PAH in the female mice, while estradiol reestablished the PAH phenotype. The work on this model has implicated estradiol-induced vascular proliferation and connected it to enhanced serotonin activity, which forms a particularly plausible biologic and epidemiologic connection.51,52

Not surprisingly, androgenic compounds have been used to treat experimental pulmonary hypertension as well. For example, DHEA is synthesized in the adrenal cortex and is a precursor of both androgens and estrogens. Its sulfated ester, DHEA-S, is about 200 times higher in circulation and readily converted back into DHEA.53 Experiments in male rats using hypoxic and monocrotaline models have demonstrated a beneficial effect of DHEA treatment, and further studies are ongoing.40,46,54,55 Further studies in additional animal models of PAH to investigate the influence of DHEA and other androgens on the pulmonary vasculature and right heart should be helpful. For example, a study of DHEA using the chronic hypoxia/VEGF inhibitor (SUGEN) model is apparently underway (presented by Oka M et al, Grover Conference 2011, Sedalia, CO).

SEX HORMONE METABOLISM MAY INFLUENCE ESTROGENIC EFFECTS

There is growing interest from our group and other groups in the role of sex hormone metabolites as mediators of both estrogenic and anti-estrogenic effects on the pulmonary vasculature. Variability in metabolism may account for the apparent contradictory influences of estrogens noted above. For example, while it appears that most parent compound estrogens (eg, estradiol) are pro-proliferative on a chronic basis, some of their major metabolites behave quite differently from one another. In fact, some have anti-estrogenic actions, although the specifics of these differences have yet to be fully elucidated.

Cytochrome P450 (CYP) constitutes a gene superfamily that plays an essential role in the metabolism of exogenous chemicals present in the diet and environment, as well as endogenous substances such as the sex hormones.56 The initial step in the metabolism of estrogens is typically an oxidative process, via CYP1B1 and other CYP enzymes (Figure 2). CYP1B1 is highly expressed in the lung. CYP1B1 catalyzes the oxidation of estrogens to 2-hydroxy (2-OHE1/2) and 4-hydroxy (4-OHE1/2) estrogens, and metabolizes environmental toxins including tobacco smoke.57 Oxidation of estrogens also occurs by hydroxylation at the C-16 position by other P450 enzymes, predominantly resulting in 16α-hydroxyestrone.58
(16α-OHE1) and “16-estrogens.”68,69 Data suggest that “2-estrogens” are anti-mitogenic, while “16-estrogens” stimulate cellular proliferation by constitutively activating the estrogen receptors. In addition to being more mitogenic, “16-estrogens” may also be more genotoxic via the formation of unstable DNA adducts.60,61 Thus, individuals who produce a higher ratio of “16-estrogens” may be at increased risk of diseases that result from both the mitogenic and genotoxic effects of estrogens.62-67

West et al used expression arrays to examine gene expression by immortalized lymphocytes from BMPR2 mutation carriers, and found that CYP1B1 was low in female but not in male PAH patients in the study. In fact, quantitative measures of CYP1B1 expression showed 10-fold lower expression levels in female patients compared to healthy BMPR2 mutation carriers.68

We subsequently demonstrated that a specific urinary profile of estrogen metabolites was associated with the occurrence of PAH in BMPR2 mutation carriers. Subjects with PAH had a significantly lower ratio of 2-hydroxyestrogens (2-OHE1/2) to 16α-hydroxyestrone (16α-OHE1) compared to unaffected BMPR2 mutation carriers.69 Second, we showed that certain functional polymorphisms in CYP1B1 (a cytochrome P450 enzyme critical to estrogen metabolism) were associated with PAH.69

The influence of estrogen metabolites remains an area in need of much work. While estradiol is converted to 2-OHE1/2, they are converted to 2-methoxyestrogens (2-ME1/2) by catechol-O-methyltransferase (COMT) (Figure 2). Tofovic and colleagues have convincingly shown that 2-methoxyestrogens prevent and treat monocrotaline-induced pulmonary hypertension, as well as bleomycin-induced pulmonary hypertension.70,72 Variations in receptor specificity may help to explain why some estrogen metabolites are more detrimental, but this requires further study. It is also likely that not all of the enzymes involved in estrogen synthesis and metabolism are equally important. Determining the critical point of control, be it CYP1B1 or another enzyme such as aromatase, will be an important step moving forward.

CONCLUSION

In humans, female predominance is a definitive characteristic of Group 1 PAH patients. While sex hormones are increasingly implicated in pathogenesis, the precise mechanisms to explain why females are at greater risk remain elusive, as is an explanation of the emerging data suggesting survival disadvantage for older females. Unraveling these mysteries may not only shed light on the biologic processes that promote PAH, but also provide novel targets for therapeutic interventions.

Sources of Support and Conflicts of Interest

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Contraceptive Options for the Patient with Pulmonary Arterial Hypertension

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The World Health Organization describes contraception as desirable for many reasons. It allows families to make informed choices about their reproductive years. It allows family planning, with spacing of children, leading to better bonding between mother and child, higher exclusive breastfeeding rates, and improved health of the mother for a future pregnancy.¹

Unintended pregnancies continue to occur at an astronomically high rate in the US, as high as 35% by most recent data,² and of course, since women with pulmonary arterial hypertension (PAH) are not exempt from this statistic, it is imperative that as care providers, we help our patients to plan ahead. In their case, maternal health is our main concern.

Weiss and colleagues, reporting on pregnancy outcomes with PAH between 1978 and 1996, found a maternal mortality of 36% in Eisenmenger syndrome, 30% in idiopathic PAH, and 56% in secondary PAH.³ A more recent systematic review reported slightly more optimistic pregnancy outcomes from 1997 to 2007. Still, maternal mortality ranged from 17% to 33%, depending on the exact etiology of pulmonary hypertension.⁴ It is therefore very clear that in the setting of PAH, contraception is important and potentially lifesaving.

PULMONARY HYPERTENSION IN PREGNANCY
PAH can be idiopathic or related to other medical problems. Regardless of its cause, significant pulmonary hypertension creates problems during pregnancy. Many of the risk factors for PAH including HIV, collagen vascular disease, and congenital heart disease are not uncommon during the reproductive years, so as medical practitioners, we can expect to see any number of patients with PAH at risk for pregnancy.⁵

The hemodynamic changes seen in pregnancy are substantial. In a normal pregnancy, there is a 50% increase in blood volume, a similar increase in cardiac output, as well as increases in heart rate and stroke volume. Systemic vascular resistance and blood pressure both decrease during gestation.⁶ During the delivery, sudden changes in venous return and right ventricular filling may occur related to expected blood losses, decreased venous return related to systemic vasodilation from epidural anesthesia or from pooling of blood in the lower extremities from vena caval compression by the gravid uterus.⁷ This can worsen right ventricular preload and lower cardiac output, leading to sudden deterioration, and in many cases, can lead to maternal death. At the same time, volume excess on top of an already enlarged right ventricle can cause left ventricular compression via ventricular interdependence, also reducing cardiac output.

Those women who choose to proceed with pregnancy in the setting of PAH can expect to be severely limited in their activities. They should anticipate early hospitalization, perhaps as early as fetal viability, for maternal and fetal surveillance. They will need supportive therapy with supplemental oxygen and vasodilating drugs. To prevent thromboembolic events, they may need anticoagulation, and volume status must be watched carefully.⁸ Management should be carefully coordinated with the pulmonary hypertension team, who may consider inhaled nitric oxide therapy periprocedurally as treatment to reduce pulmonary vascular resistance while sparing the systemic vascular resistance. Additionally, adjustments to long-term pulmonary hypertension therapy will generally be required.

Perhaps a patient might be willing to tolerate all these risks for the sake of motherhood, but the fetus is not exempt from morbidity and mortality. Data suggest that there is an increased risk of pre-maturity and fetal growth restriction, and a risk of stillbirth or neonatal death that ranges from 7% to 13%.⁹ In addition, medications typically used in PAH carry significant fetal risks as well. Warfarin, a widely used oral anticoagulant, is a known human teratogen, with varying effects on the fetus, depending on the period of exposure to the drug. Exposure during organogenesis, particularly the sixth through ninth weeks, puts the fetus at risk for warfarin embryopathy. Warfarin embryopathy involves typical facial features of nasal and midface hypoplasia, and stippled vertebral and femoral epiphyses. Exposure during the first trimester can also lead to increased risk of miscarriage: in those patients taking over 5 mg of warfarin daily, the incidence of spontaneous abortion can be as high as 72%.⁸ Second- and third-trimester exposures can result in hemorrhage, leading to deformation of several fetal organs. Congenital malformations associated with second- and third-trimester exposure to warfarin include agenesis of the corpus callosum, Dandy-Walker malformation, midline cerebellar atrophy, microcephaly, ophthalmic atrophy, and blindness. Developmental delay and mental retardation have also been described.⁹

Among the three major classes of drugs used for the treatment of PAH, endothelin receptor antagonists such as bosentan (trade name Tracleer) have also shown teratogenic effects in animal studies and must be avoided. Though there are no studies in human pregnancy, studies in
rats and rabbits have shown that bosentan can lead to malformations of the fetal head, mouth, face, and large blood vessels. Extra precautions are necessary when using bosentan since it can interfere with metabolism of contraceptives, making them less effective. The prescribing information for this drug recommends a highly effective method of contraception or two methods of less effective birth control when taking bosentan. Similar methods are also recommended with ambrisentan, another endothelin receptor antagonist, though it has not been shown to decrease the effectiveness of combination contraceptives.

Although pregnancy is never recommended in PAH, some women do become pregnant—either because they were newly diagnosed with pulmonary hypertension during the pregnancy, because of contraceptive failures, or occasionally intentionally, despite the advice of their physicians. For these patients, the two other classes of PAH medications can be considered for use during pregnancy. Phosphodiesterase inhibitors like sildenafil (trade name Revatio) have been assigned to pregnancy category B by the FDA. Animal data have not shown increased risk of teratogenicity even at doses correlating with 40 times the maximum recommended human dose. However, there are no controlled data in human pregnancy and no long-term observational studies to assure its safety. Similarly, prostacyclins like epoprostenol (trade names Flolan and Veletri) have been assigned to pregnancy category B by the FDA. Most experts suggest that the benefits of using this drug in pregnancy outweigh the potential embryo-fetal risks. Animal studies have failed to reveal evidence of fetotoxicity or impaired fertility at doses from 2.5 to 4.8 times the recommended human dose. As in the case of the phosphodiesterase inhibitors, there are no controlled data in human pregnancy.

The following review will describe a number of contraceptive options available to a patient with PAH, their effectiveness, and potential side effects. The long-term benefits to maternal health should be quite obvious, given that pregnancy itself could be the biggest contributor to shortening a patient’s life expectancy.

**CONTRACEPTIVE OPTIONS**

**Reversible Contraception**

**Estrogen and progestin combinations.** Estrogen and progestin pills have been available in the United States since 1960. Dosage and formulations have changed over the years, making them safer and more tolerable, and side effects have diminished. More recently, various alternative delivery systems have come on the market, including transdermal patch, and transvaginal ring.

*Combination oral contraceptive pills* consist of an estrogen and a progestin. They are safe and effective, and well tolerated by most women, but do need to be taken on a daily basis. Their effectiveness decreases substantially with inappropriate use, as evidenced by the higher failure rate with typical use vs perfect use, 8% vs 0.3% respectively. The estrogen-progestin combination is taken daily for 3 weeks; during the fourth week, a placebo is administered, leading to withdrawal bleeding. Some prescription formulations are also available for those patients who want to minimize withdrawal bleeding, with extended administration of estrogen and progestin, providing the placebo approximately every 3 months.

The main mechanism of action of estrogen-progestin combination contraceptives is prevention of ovulation by suppression of the hypothalamic-pituitary axis. Estrogen specifically suppresses follicle stimulating hormone (FSH) release; and progestins suppress luteinizing hormone (LH). Progestins also thicken cervical mucus, making sperm passage into the uterus more difficult. Both estrogen and progesterone have local effects on the endometrial milieu, rendering it unfavorable for implantation.

Patients taking estrogen-progestin combinations can expect a fairly predictable cycle, less bleeding than when not using contraception, and less pain associated with menses. Other benefits include increased bone density and decreased risk of endometrial and ovarian cancer. In some studies, they have also been shown to be useful in treatment of mild acne and premenstrual syndrome. The most common side effects of estrogen-progestin combinations are headache, dizziness, breast tenderness, breakthrough bleeding, and decreased libido. Most of these tend to resolve over time, or can be minimized by choosing the lowest dose pill that would be effective for each patient.

The *transvaginal ring* (trade name NuveaRing), with etonogestrel and ethinyl estradiol, has the same mechanism of action as combination birth control pills. The hormones are released from the core of the ring at a steady rate and ovulation is prevented. A new ring has to be placed within 5 days of the first day of the woman’s menstrual cycle. After 3 weeks, the ring is removed, and the patient will then have her normal cycle. The method is considered highly effective, with a failure rate equivalent to that of combination pills.

The *contraceptive patch* (trade name Ortho Evra) provides transdermal administration of norelgestromin and ethinyl estradiol. A new patch is applied to the skin every week for 3 weeks; a patch-free week follows, to allow withdrawal bleeding. The novel delivery system may be appealing to those patients who prefer weekly application of the patch, rather than daily dosing of the birth control pill. Although still an effective method, with 1.2 pregnancies per 100 woman years, with typical use, the failure rate can be as high as 8%. This may be related to the known increased risk of failure in women who weigh over 90 kg, in addition to variations in transdermal absorption from patient to patient.

**Progestin-only contraception.** Progestins, like estrogen and progesterone in combination, prevent pregnancy by thickening cervical mucus, and thinning out the endometrial lining, turning it into an inhospitable environment to the fertilized egg wishing to implant. The effect on suppression of ovulation will vary depending on the dose of progestin. For example, the mini pill will only suppress ovulation about 50% of the time, whereas moderate and high-dose progestrone delivery systems will prevent anywhere from 97% to 100% of all ovulations.
With many progestin-only methods, unfortunately, a common side effect will be irregular periods. Some other common side effects include mood swings, weight gain, headache, acne, and depression.

The progestin-only pill (trade name Micronor), is commonly known as the “mini pill.” It contains norethindrone, a progestin found in many combination birth control pills, but in this scenario, it acts alone to prevent ovulation. The mini pill may be prescribed to those patients who are post partum, who are using lactational amenorrhea as a method of contraception. In combination with breastfeeding, the norethindrone pill is virtually 100% effective at preventing pregnancy and does not impair breast milk production. Norethindrone by itself does not consistently prevent ovulation, so it relies mostly on its effect on the cervical mucus and on the endometrium for prevention of pregnancy. One disadvantage is that it has to be taken daily, and at the same time every day. For the nonlactating patient, the progestin-only pill has a higher pregnancy rate than combination pills, and would not be considered reliable contraception for the patient with PAH.

As an injectable progestin, depot medroxyprogesterone acetate (trade name Depo-Provera) has been in use in the United States since 1992. The dose of 150 mg is given intramuscularly every 90 days. The mechanism of action is the same as for other progestins. Among its many advantages is the long duration of action, with a contraceptive effectiveness that is comparable to combination birth control pills. Among its disadvantages, irregular bleeding is the most common side effect. In addition, loss of bone mineral density has been reported. Reassuringly, this bone loss is reversible once the drug has been stopped. Depot medroxyprogesterone could be useful in those patients with PAH who need effective contraception while transitioning to one of the more longer-acting and effective methods.

The subdermal implant with etonogestrel (trade name Implanon) (Figure 1) is a very reliable method of long-acting contraception; it is more than 99% effective. It is approved for use for up to 3 years. Like other progestin-only methods, its mechanism of action is to suppress ovulation, thicken the cervical mucus, and render the atrophic endometrium averse to implantation. Return to fertility upon removal is relatively quick, so a second implant should be inserted at the time of the first’s removal to prevent an unintended pregnancy. If another implant is not placed, another highly effective method of contraception should be chosen. Though the implant has an irregular bleeding profile that may be bothersome to some patients, this common side effect should not prevent them from choosing this excellent method of contraception.

A levonorgestrel-containing intrauterine device (IUD), shown in Figure 2, is available (trade name Mirena) in the United States and is approved for up to 5 years of use. The typical failure rate of this device is 0.1%. Since it releases the progestin locally into the uterus, there are fewer systemic side effects, although they are still possible. The levonorgestrel thickens cervical mucus, thins the endometrium, and may make sperm less mobile. Like the copper IUD that we will discuss later, this device is an excellent choice for patients with PAH, given that it is long acting and highly effective.

Thromboembolic Risk Controversy
Before moving on to a review of nonhormonal contraceptive options, an important question is worth discussing: is the fear of hormonal contraception warranted in PAH patients who are anticoagulated?

Quite clearly, the risks of progestosterone-only contraceptives have not been substantiated in the literature, and remain a safe option for patients with PAH, whether anticoagulated or not. But what is it about estrogen-containing contraception that gives us pause? Estrogen increases hepatic production of factor VII, factor X, and fibrinogen, thus increasing the risk of venous thromboembolic events (VTE) in users of combination estrogen-progestin contraceptives. A case-control study done in the US, involving 196 cases of VTE and 746 age-matched controls, showed an odds ratio (OR) of 4.07 for venous thromboembolism associated with current combination oral contraceptive use. In absolute terms, however, the risk of VTE during pregnancy is higher than the risk associated with combination hormonal contraception warranted in PAH patients who are anticoagulated. Indeed, the risk of death is higher in pregnancy, across all age ranges, than with use of any contraceptive method, whether estrogen-containing or not, as shown in Table 1. For the pulmo-
Pulmonary hypertension patient specifically, consensus guidelines recommend use only if a patient is receiving concomitant anticoagulation. An added issue for some PAH patients is that warfarin can also lead to menorrhagia. Thus, in well-anticoagulated women, the use of combination oral contraceptives could be useful, particularly to reduce menstrual blood loss, without increasing the risk of VTE.

Nonhormonal contraception. The copper-T IUD (trade name Paragard) shown in Figure 2 is approved for use for up to 10 years. Other than permanent sterilization, it is the longest-acting contraceptive available today. Though the precise mechanism of action of IUDs in general has not been clearly defined, they are thought to prevent fertilization. The copper ions released by the IUD trigger an intense local inflammatory reaction, leading to lysosomal activation and other inflammatory events that are spermicidal. In addition, the endometrium is rendered unsuitable for implantation precisely because of the same inflammatory reactions. Menstrual cycles can be very predictable with the copper-T, and with a failure rate of 0.8%, it is a great contraceptive choice for patients with PAH.

Barrier methods include male and female condoms, diaphragm, and cervical cap, preferably used in combination with spermicides and microbicides. They act as a physical and chemical barrier so that sperm cannot get to the ovum. Spermicides on their own are not considered effective contraception. Mechanical barrier methods, if used at all, should be used in combination with a spermicide. With failure rates as high 36% with typical use, they should not be considered reliable for patients with PAH.

Natural family planning methods include the calendar rhythm method, the symptothermal method, and the cervical mucus rhythm method, among several others. These methods tend to be cumbersome, and rely on a patient’s cycle being very predictable. They all include some degree of abstinence that varies depending on where the patient is on her menstrual cycle. The patient attempts to time intercourse to avoid her fertile days, whether by detecting slight basal temperature changes that occur post ovulation, evaluating the consistency of cervical mucus, or by using home testing kits to detect the preovulatory LH rise. Quite clearly, these methods do not provide the effectiveness that other methods provide. Their failure rate can range anywhere from 2%-3% with perfect use to 20% with typical use. They are mentioned in this review for completeness, and not to endorse them in any way in the contraceptive management of a patient with PAH.

Table 1: Birth-Related or Method-Related Deaths Per 100,000 Fertile Women by Age Group

<table>
<thead>
<tr>
<th>Method</th>
<th>15-24 Years</th>
<th>25-34 Years</th>
<th>35-44 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>5.1</td>
<td>5.5</td>
<td>13.4</td>
</tr>
<tr>
<td>Abortion</td>
<td>2.0</td>
<td>1.8</td>
<td>13.4</td>
</tr>
<tr>
<td>Intrauterine device</td>
<td>0.2</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Rhythm, withdrawal</td>
<td>1.3</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Barrier method</td>
<td>1.0</td>
<td>1.3</td>
<td>2.0</td>
</tr>
<tr>
<td>Spermicides</td>
<td>1.8</td>
<td>1.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>1.1</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Implants/injectables</td>
<td>0.4</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Tubal sterilization</td>
<td>1.2</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

From Williams Gynecology, 2008, with permission.

Permanent Contraception

Female sterilization. These procedures can be performed post partum, post abortion, or electively if nonpuerperal. The surgical approach can vary depending on timing. For example, a patient immediately post partum may undergo sterilization via a periumbilical incision, while a patient who just underwent termination of pregnancy, and whose uterus would be substantially smaller than someone who had just delivered a term infant, would...
require a supravulcinal incision. Once in the abdominal cavity, most sterilization procedures are essentially the same. They involve ligation and resection of a segment of Fallopian tube, which is sent to the pathologist for tissue confirmation.

Procedures done electively can also be done by a laparoscopic approach: these involve both ligation and resection of a segment of the Fallopian tubes, or interruption of the tubes via a variety of permanent surgical clips or rings. All of these methods have favorable long-term success rates.

For all these procedures, there is the inherent risk of surgery—infecion, increased blood loss, damage to other internal organs—and in the case of laparoscopic procedures, the greater risk of death due to complications of general anesthesia.

More recently, hysteroscopic sterilization procedures have become en vogue. These are done going through a natural orifice, the patient’s cervix, to go into the endometrial cavity, visualize the tubal ostia, and obliterate them in a variety of ways. Two examples of these hysteroscopic procedures are the Adiana® and Essure® systems. The first uses a medical-grade silicone insert and radiofrequency to block the tubes, while the latter (Figure 3) uses a titanium insert. Both of these procedures are usually done in a physician’s office, under local anesthesia, and sometimes with conscious sedation. For a patient with PAH, the safest place to perform any procedure would be the operating room, but a procedure that limits surgical time and the need for regional or general anesthesia would certainly be desirable.

Male sterilization. Safe and effective, vasectomy is performed under local anesthesia. A small incision is made in the scrotum, and a segment of vas deferens is removed bilaterally, to prevent the passage of sperm from the testes. A procedure that averages about 20 minutes to perform in the outpatient setting, vasectomy is cheaper than female sterilization, has fewer complications, and a 10- to 37-fold lower failure rate. It is important to realize, however, that vasectomy is not immediately effective since the sperm that were beyond the resected segment of vas deferens will take approximately 3 months to be expelled. Since the procedure-related mortality rate is 12 times higher with female sterilization, vasectomy remains the safest, most efficacious, and least expensive method of sterilization. For any couple and especially for the partners of our patients with PAH, physicians should recommend vasectomy when providing counseling on sterilization, despite the popularity of bilateral tubal ligation procedures.

It is clear that in terms of effectiveness and permanence, sterilization is the best method to prevent pregnancy for the patient with pulmonary hypertension. For those patients who are not good surgical candidates, it is important to remark on the effectiveness and high desirability of long-acting reversible contraception (LARC) as the most reliable nonpermanent option for patients with PAH. As shown in Figure 4, those methods that fall under this category would be contracep-
tive implants, such as the etonogestrel single-rod implant, and either of the IUDs. Their effectiveness approaches that of sterilization. These first-choice reversible methods require “a single act of motivation for long-term use,” eliminating adherence and user dependence from the effectiveness equation. They should be discussed with our patients as being among the best contraceptive options available.

CONCLUSION
For most women, especially those with PAH, contraception poses far less risk than pregnancy. Even with the real increased risk of thromboembolic events in those using estrogen-containing contraception, albeit counteracted by chronic anticoagulation, pregnancy with PAH carries such a high risk of mortality that any efforts to prevent it are warranted. Safe and effective LARC methods are available, and if feasible based on lower surgical risk, permanent sterilization should be advised in these patients.

References
PAH and Pregnancy: Physiologic Changes, Challenges, and Outcomes

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PHYSIOLOGIC CARDIOVASCULAR AND PULMONARY CHANGES DURING A NORMAL PREGNANCY

The increased metabolic needs of pregnancy are met by many physiologic adaptive changes that permit adequate delivery of oxygenated blood to the peripheral tissues and the growing fetus. Women without heart disease will usually adapt well and cardiac complications are exceedingly rare. However, women with PAH will not respond favorably to these otherwise “normal” adaptive changes.

Hemodynamic and Cardiopulmonary Changes Normally Seen in Pregnancy

Blood volume. Blood volume increases progressively from 6-8 weeks’ gestation, reaching a maximum at 32-34 weeks, with a total 40%-100% plasma volume increase from baseline. Most of this excess volume is contained in the uterus, breast, muscle, and skin. The red cell mass only increases by 20%-30%, thus creating a “physiologic anemia.” This reduces the impact of the delivery blood loss, typically 300-500 cc for a vaginal delivery and 750-1000 cc for a C-section. Immediately after delivery, there is an auto transfusion of the excess blood supply from the uterus, as it contracts postpartum.

Cardiac output. There is an increase in cardiac output that parallels the increased blood volumes. A 34% increase in cardiac output occurs during the first trimester, with a steady and gradual increase until the 36th-39th weeks of gestation. An average cardiac output by 8-11 weeks is 6.7 L/min, reaching a maximum of 8.7 L/min during the 36th-38th weeks. Most of these changes are accounted for by a 35% increase in the stroke volume. A minimal component (15%) is secondary to an increase in the basal heart rate. This hemodynamic circulation associated with pregnancy and aided by a progesterone-mediated vascular relaxation causes a steady decrease in the systemic vascular resistance throughout the pregnancy. The decrease in vascular tone begins at the fifth week and reaches a nadir at 20-32 weeks. After 32 weeks, the resistance slowly begins to increase until term. A split S2 with inspiration (early), distended neck veins (mid), and an S3 gallop (late) may be heard with the progressive increases in vascular volume.

Blood pressure. By mid-pregnancy the diastolic pressure decreases, the systemic systolic pressure remains the same or slightly decreases, and the pulmonary arterial pressure remains the same. Vascular tone is more dependent on sympathetic control, with more significant episodes of hypotension with sympathetic blockade with spinal or extradural anesthetics.

Cardiac position and EKG. Mild dilatation of both ventricles is normal, but contractility remains normal. The ventricular end diastolic volumes increase progressively beginning at the 10th week of gestation and peak in the third trimester. Bi-atrial dilatation is also seen in some normal patients. Mild dilatation of the tricuspid ring (secondary to right ventricular [RV] dilatation) commonly increases the tricuspid regurgitation flow to grade I-II/VI, with a detectable murmur. The enlarging uterus shifts the diaphragm upward. Commonly seen EKG changes with a gravid uterus include left axis deviation, sagging ST segments, and inversion or flattening of the T-wave in lead III. Premature atrial and ventricular contractions may become more frequent.

Aortocaval compression. Beginning in mid-pregnancy, the enlarging uterus compresses both the inferior vena cava and the aorta whenever lying supine. This obstruction of the vena cava can reduce venous return to the right heart, with a fall in cardiac output by as much as 24% near term. Obstruction of the lower aorta and its branches can decrease arterial flow to the kidneys, the utero-placental unit, and the lower extremities. Positioning on the left side (lateral position) will improve flow in both the vena cava and the aorta.

Venous dilatation. Venous pooling increases by 150% in most pregnant women. This process decreases the absorption/delivery of drugs administered subcutaneously or intramuscularly. Hands and feet are warm and erythematous, along with nasal congestion resulting from this.

Renal changes. Renal blood flow increases during pregnancy, peaking in the third trimester at 60%-80% above the pre-pregnancy level. This calculates to a 50%
increase in the glomerular filtration rate (GFR). There is an increase in renin and angiotensin levels, resulting in increased retention of salt and water.

**Hematologic changes.** Pregnancy induces a relative hypercoagulable state including decreases in protein S, increases in factors I and X, and progressive resistance to protein C activity.

**Respiratory changes.** The respiratory rate remains unchanged. Minute ventilation, tidal volume, and oxygen consumption increase by 20%-40% beginning in the first trimester of pregnancy, and are mediated by elevated progesterone level. By term, the arterial carbon dioxide level falls to 28-32 torr, with a decreased plasma bicarbonate level of 18-21 mEq/L. This results in biologic hyperventilation and the sensation of dyspnea. The functional residual capacity decreases by 10%-25%, whereas the total lung capacity decreases only minimally due to the thoracic cage widening to compensate. Hypoxemia can rapidly develop in the setting of hypoventilation or apnea.

During labor, the cardiac output increases by another 10%-15% and is augmented by the return of 300-500 mL of blood to the central circulation from uterine contractions. Immediately postpartum, there is a marked increase in preload, resulting in an increased cardiac output that remains elevated for about 48 hours. There is a relatively vigorous and spontaneous diuresis during the first 72 hours postpartum, which is ongoing at a slower rate for the next 2 weeks. Hormone levels return to normal over the next 6 weeks.

**PAH AND PREGNANCY: HEMODYNAMIC AND ECHO-CARDIOGRAPHIC CHANGES**

The multiple cardiovascular and pulmonary changes seen in a normal pregnancy become pathologic adaptations in the pregnant patient with PAH. The increased plasma volume, increased cardiac output, increased renin and aldosterone levels, decreased systemic vascular resistance (SVR), venous dilatation and pooling, elevated progesterone levels, and increased metabolic rate rapidly bring forth the pregnant patient with new clinical right heart failure. The presentation of a pregnant and newly or previously diagnosed PAH patient frequently includes all or some of the following: dependent lower extremity edema, DOE, orthopnea, decreased exercise tolerance, widely split S2, pulmonic and tricuspid murmurs, early satiety secondary to liver congestion, hepatomegaly, RV-S3 gallop, and jugulovenous distention (JVD). This typically occurs during the 15th-18th weeks of gestation, but may present at any time. The marked increase in renin and angiotensin levels result in premature volume expansion and third-spaced fluid retention. In turn, this overloads the already compromised RV, which becomes progressively more dilated and hypocontractile. The pulmonary vascular disease from the PAH causes an increase in the pulmonary vascular resistance (PVR), resulting in a pressure overload of the RV, in addition to the already existing volume overload. Many times, the pressure-volume overload of the right heart results in opening of the PFO (patent foramen ovale), with resultant hypoxemia from a right to left or bidirectional shunting. Development of increasing tricuspid regurgitation, a natural dilatation with pregnancy, and a maladaptive finding from volume/pressure overload of the RV may lead to atrial fibrillation from a right atrial origin.

The pathologic changes found in the lung secondary to PAH are progressive and destructive (Figure 1).

The pathologic changes frequently result in decreased gas exchange surface area, as well as decreased flow through tortuous and pruned peripheral vasculature of the lung. To compound these abnormalities, the increased plasma volumes associated with pregnancy result in increased flow to the lung, followed by further RV dysfunction and RV failure from the pressure/volume overload. The supply decreases and is not able to meet the demand of the high metabolic rate of supporting a pregnancy. The respiratory rate increases (not found in normal pregnancy) and the work of breathing increases because of the decreased cardiac output and the increased work of the respiratory muscles. This combination of pathophysiologic derangements may be fatal for the pregnant PAH patient and her fetus, with reported mortality rates ranging between 37% and 57% for the mother. Therefore, at present, all female patients with WHO Group 1 PAH should be counseled about the dangers of pregnancy and about the suitable contraceptive options (see article on Pregnancy and Contraception), as stated in the latest American Heart Association/American College of Cardiology Foundation guidelines.

Unfortunately, there are some women who aren’t diagnosed until they are well into their pregnancy, and the clinician is faced with a seriously ill PAH patient with a high risk of mortality by the end of the pregnancy or shortly thereafter. If one suspects pulmonary hypertension during pregnancy, the initial management should include a complete diagnostic evaluation and confirmation of the PAH diagnosis, including a right heart catheterization. If confirmed, immediate treatment and close monitoring is necessary, which should be initiated as an inpatient. Treatment goals include reducing intravascular volume, reducing RV afterload by use of PAH pharmacologic agents (usually a prostracyclin), increasing RV systolic function by use of intravenous (IV)/inhaled prostracyclins, digoxin, and/or dobutamine, and control of any arrhythmias.

Diagnostic testing must include an echocardiographic study, with a bubble study immediately the day of presentation. Depending upon the severity of the disease, findings may include (Figure 2):

- Dilatation of the right atrium and ventricle
- Hypocontractility of the RV, abnormal tricuspid annular plane systolic excursion (TAPSE)
- Flattening of the interventricular septum with RV systolic pressure $>50$ mm Hg
- Dilated inferior vena cava (IVC), with decreased respiratory variation
- Tricuspid and pulmonic regurgitation (typically mild-moderate)
- Pericardial and pleural effusion
- Normal/hear normal left heart
- Bubble study—right to left intracardiac shunt, late return to left heart with arteriovenous malformation (AVM)
The normal images (Fig 2, A and B) demonstrate the smaller size of the RV compared to the left ventricle (LV). The image shows the smaller size of the RV, while it shows the LV to be perfectly circular—no pressure/volume overload of the RV that compresses the interventricular septum (the D shaping we talk about in severe PAH). Note also that adequate views of the RV, as shown, allow visualization of the free wall and the size of the RV. Additionally, RV ejection fraction (RVEF) can be estimated on moving images and summed by looking at 3-4 different views. The other 2 images (Fig 2, C and D) are comparable images in a patient with severe PAH. The 4-chamber view shows significant dilatation of the RV and hypertrophy of the RV wall, while the moving image would show a significantly decreased RVEF. The short axis view demonstrates the ECHO findings of markedly elevated RV pressure, with D shaping of the LV (loss of the circular configuration of the LV). This is from pressure-volume overload of the RV. The RVSP is usually >60 mm Hg before the D shaping occurs, while flattening occurs at pressures >50 mm Hg.

**PATIENT SUBSETS**

**Congenital Heart Disease**
The congenital heart patient requires complete evaluation of the RV, LV, and valves to guide therapy throughout the
gestational period, as well as delivery and the peripartum period. Pathologically, the pulmonary vessels have been exposed to higher pressures over many years and have adapted. They are usually thick, stiff, and have luminal narrowing with the typical pruning of the peripheral pulmonary vessels that is seen in IPAH. Additionally, the shunt physiology often seen in this population will need to be monitored closely. Treatment strategies for the congenital heart patient with PAH are similar to the IPAH patient. The PAH drugs work in a similar fashion, except that inhaled nitric oxide tends to cause more intrapulmonary shunting than in other PAH etiologies. This patient population may have LV dysfunction along with RV dysfunction, compounding the complexity of the physiologic abnormalities. Standard treatment with loop diuretics, potassium and magnesium replacement, digoxin, PAH medications, oxygen if indicated, and low-dose hydralazine (if LV dysfunction is present) may be appropriate. Many of these patients are responsive to prostaclins. Management of pregnancy with PAH will need to be individualized for the congenital heart disease patient, as this is a very heterogeneous population due to different congenital abnormalities and differences in the timing of any corrections that were performed. Patients with congenital heart disease have often had years to accommodate their anatomic and hemodynamic abnormalities, and patients with some forms of congenital heart disease may therefore tolerate a pregnancy better than patients with other forms of PAH. Reported outcomes in the literature, however, are still relatively poor, and patients with Eisenmenger’s physiology in particular have high mortality rates with pregnancy. This can lead to very premature deliveries and decompensation of the right and left ventricular function. Specific treatment strategies therefore need to be individualized for congenital disease PAH patients, dependent on the stage of their disease.1,2

Mitral Valve Disease

Patients with mitral valve disease can be divided into 3 groups: mitral regurgitation, mitral stenosis, and persistent PAH after mitral valve repair/replacement. Persistent pulmonary hypertension following repair or replacement of the mitral valve is known to occur in some patients. Most of these patients have had a longstanding history of the valve lesion prior to intervention and likely have an element of precapillary pulmonary hypertension as well. The common identification time for this disorder is in the cardiovascular surgical ICU (while Swan-Ganz catheter is in place), as the pulmonary artery pressures remain elevated. The other commonly seen population is the <30-day readmission after mitral valve surgery. These patients will have had persistent elevation of the pulmonary artery pressures, which often smoldered postoperatively (some even reintubated), followed by discharge to reha-

![Figure 2: Transthoracic echo images, normal (A and B) vs severe PAH (C and D).](image-url)
bilitation centers or home. The common characteristics include “failure to thrive” after surgery, chronic right heart failure with persistent lower extremity edema refractory to diuretics, poor appetite, and readmission via the emergency department with clinical right heart failure. Treatment for this population, once recurrent mitral valve obstruction is ruled out, is the same as any other PAH patients, with the diagnosis being PAH. The hemodynamic criteria for this population are the same as for other Group 1 PAH patients. Swan readings can be utilized from the post-operative time or a repeat right heart catheterization can be performed. The PVR and mean pulmonary artery pressure need to be evaluated as in any other case of PAH. Clinical treatment is no different and needs to be directed to improved inotropic performance of the RV (dobutamine), followed by IV loop diuretics, and initiation of PAH drugs. All drug classes have shown hemodynamic and clinical improvement.

**PAH IN THE SICKLE CELL DISEASE PATIENT**

PAH in sickle cell disease (SCD) is complicated, as there are issues with the mother and the fetus. The medical literature suggests that 6%-11% of patients with SCD will develop PAH. SCD is a hypercoagulable state (platelet activation and activation of the coagulation system), with hyperdynamic flow states, all of which will be worsened by pregnancy. The mother has greater risks of precipitous delivery/spontaneous abortion, higher risks of infections, greater incidence of hypertension and preclampsia, pulmonary emboli (clots from hypercoagulable state, abnormal sickle cells occluding peripheral vessels, and hemolysis), pulmonary infarctions, and hypoxia. Use of prostacyclins, phosphodiesterase type 5 (PDE-5) inhibitors, and endothelin receptor antagonists (ERAs) have all been reported in the literature. Recent studies were discontinued early for monotherapy with bosentan and sildenafil; therefore, the data are limited with respect to sickle cell patients. Anticoagulation is often considered, but is always problematic during pregnancy. There is an increased risk of intracranial and retinal bleeding with SCD, so the use of anticoagulation needs to be weighed carefully. ERAs should be avoided as they are contraindicated in pregnancy. Delivery strategies are similar to other PAH patients. The fetus has a greater risk of intruterine growth retardation, stillbirth, and fetal distress.

**Systemic lupus erythematosus.** The physiologic stressors of pregnancy may bring forth a quiescent diagnosis of lupus in patients not previously identified or lead to a lupus flare. These patients need close observation by all treating physicians, including the pulmonary hypertension physician, high-risk obstetrics physician, and rheumatologist. PAH needs aggressive therapy, frequently with an infusion of prostacyclin and another oral pharmacologic agent. A lupus flare may present atypically as volume overload, and will not respond with increased diuretics alone. An observation seen thus far is that the RV function in the lupus patient may remain somewhat depressed after delivery and does not return to the pre-pregnant measurements/function.

**CONCLUSION**

Even with the advances in PAH therapies over the past decade, pregnancy and PAH remain a fatal combination. Unfortunately, some women have their first presentation of PAH during pregnancy or shortly thereafter due to the rapid physiologic changes that occur, which are poorly tolerated by the pulmonary circulation and RV. For these patients, admission to a PH specialty center with the ability to administer IV prostanooids, inotropes, vasopressors, and the team and tools including high-risk obstetricians, cardiac anesthesia, extracorporeal membrane oxygenation, and a high-level NICU may permit survival beyond pregnancy for this high-risk group.

**References and Bibliography**

1. Maternal mortality for pulmonary hypertension patients in the most recent series was reported at which of the following percentage?
   a. <10%
   b. 12%-16%
   c. 17%-33%
   d. 34%-56%

2. All of the following are considered “very effective methods of contraception,” but failure rate does vary. Which has the highest measurable failure rate?
   a. Female sterilization
   b. IUD
   c. Contraceptive implants
   d. Combination oral contraceptive pills

3. True or false: Combination oral contraceptive pills (estrogen + progestin) must always be avoided in pulmonary hypertension, even in patients on anticoagulation.
   a. True
   b. False

4. True or false: Progestin-only oral contraceptive pills are an acceptable form of birth control for women with pulmonary arterial hypertension.
   a. True
   b. False

5. In the REVEAL registry, a large US registry of pulmonary arterial hypertension, more women than men were diagnosed with all forms of pulmonary hypertension except:
   a. Idiopathic PAH
   b. Congenital heart disease-related PAH
   c. Connective tissue disease-related PAH
   d. Portal hypertension-related PAH

6. In the most commonly used animal models of pulmonary hypertension (hypoxic, monocrotaline), do males or females develop more severe pulmonary hypertension?
   a. Males
   b. Females

7. True or false: Women with idiopathic pulmonary arterial hypertension, on average, live longer than men with idiopathic pulmonary arterial hypertension.
   a. True
   b. False

8. During a normal pregnancy, all of the following occur except:
   a. Increased cardiac output
   b. Increased systemic blood pressure
   c. Increased blood volume
   d. Increased hypercoagulability

9. Which of the following medication classes is pregnancy category X (always avoided)?
   a. Endothelin-1 antagonists
   b. Prostacyclins
   c. Phosphodiesterase type 5 inhibitors
PH in Women

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Circle one correct answer.

1. a b c d  6. a b
2. a b c d  7. a b
3. a b  8. a b c d
4. a b  9. a b c
5. a b c d

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The Challenges of PAH in Pregnancy

PAH patients who become pregnant—certainly against medical advice—or whose disease is diagnosed while pregnant present myriad challenges. On October 17, 2011, a group of physicians who have dealt with these complicated issues met by telephone to discuss their approaches and thoughts on dealing with these unique patients. Co-guest editor Deborah Jo Levine facilitated the discussion among Drs Ron Oudiz, Director of the Pulmonary Hypertension Center at Los Angeles County Harbor-UCLA Medical Center; Irene Lang, cardiologist at the Medical University of Vienna; Evelyn Horn, Director of the Heart Failure, Mechanical Circulatory Support, Pulmonary Hypertension Program at Cornell and adjunct professor at Columbia; and Dianne Zwicke, Medical Director of the Pulmonary Hypertension Clinic at Aurora St. Luke’s Medical Center in Milwaukee, University of Wisconsin School of Medicine.

Dr Levine: Good morning, this is Debbie Levine and I would like to thank everybody for joining me and participating in this roundtable discussion. This issue of Advances in Pulmonary Hypertension is devoted to several topics concerning women with PAH. We hope to devote the next hour together to discussing an issue that, although not truly very common, is very complicated and poorly defined. We will discuss the evaluation, management, and therapy of the pregnant patient with PAH. Most often, these are women who are initially diagnosed with PAH during their pregnancy, and occasionally a woman with known PAH who becomes pregnant against medical advice. In either case, we’ll discuss the options available to optimize the chance of successful maternal and fetal outcomes for those women who opt to carry their child to term. The true incidence of PAH in pregnancy has not recently been reported, but there are multiple case studies over the last several years showing a mortality rate ranging from 25 to 60%. The more recent studies that report mortality as low as 25% or less show some improvement in outcomes. But despite this apparent improvement, the risk of maternal death is still unacceptably high. Patients with PAH should always be advised to avoid pregnancy. Contraception and counseling for this first-line recommendation are discussed and detailed within other sections of this issue of Advances, so here we will focus on the approach each one of us takes when we encounter these patients in our own centers. Before we get started, can everyone mention who they are and where their center is.

Dr Horn: I am Director of the Heart Failure, Mechanical Circulatory Support, Pulmonary Hypertension Program at Cornell. I am an adjunct professor at Columbia and I continue to advise my Columbia colleagues for much of the high-risk cardiac OB program, particularly these patients.

Dr Lang: I am Irene Lang from the Medical University of Vienna, Austria, and I’m a cardiologist working in the interventional lab and I have a clinic for pulmonary hypertension together with 2 other physicians.

Dr Oudiz: I’m Ron Oudiz, a cardiologist at the Los Angeles County Harbor-UCLA Medical Center, and the Director of the Pulmonary Hypertension Center here, working with 2 of the most excellent PH nurses.

Dr Zwicke: Dianne Zwicke. I’m a cardiologist and the Medical Director of the Pulmonary Hypertension Clinic at Aurora St. Luke’s Medical Center in Milwaukee, Wisconsin. We are academically affiliated with the University of Wisconsin School of Medicine and Public Health. I also cross-cover the mechanical assist device, advanced heart failure, and heart transplant services.

Dr Levine: Great, so glad you all could attend today. Why don’t we start with the type of early approach we take when a patient is first referred to us--either a pregnant patient newly diagnosed with PAH or one of our patients with known PAH who becomes pregnant? What approach do you take, in terms of getting the right people in your center together to help to evaluate, monitor, and manage these patients? Evelyn, can you tell us how you start off with that?

Dr Horn: We should first address the possibility of early termination, depending on when during pregnancy they are presenting.

Dr Levine: Okay, this is a good place to start, can you tell us how you go about getting to this point?

Dr Horn: The first aspect is for any woman who has not had a right heart cath. Again, everything that we are talking about, particularly termination and mortality, hinges on the definitive diagnosis of PAH; this means having right heart catheterization data even during pregnancy. If a woman comes to me from another institution with an echocardiographic diagnosis of pulmonary hypertension, I will perform a right heart cardiac catheterization to confirm the diagnosis. The right heart catheterization should first be tried without fluoroscopy; and if necessary, then fluoroscopy needs to be done. I would preface all comments by saying we must be 100% sure the diagnosis is precapillary PAH and not...
pulmonary venous hypertension, obesity, or obstructive sleep apnea with PH. This information is critical before counseling the patient about possible termination of pregnancy.

**Dr Lang:** I think that sometimes in the literature, these success stories cases may not be true PAH; that is, the hemodynamic diagnoses are not correct. For example, there are some pregnancies that are described being managed with very little medication who make it through until the last month of pregnancy. And sometimes I’m not sure whether pulmonary hypertension is truly precapillary because they have this large mixture of postcapillary patients who look just like precapillary. I think what you said is very correct. You need to do a good right heart cath and be sure about the pulmonary capillary wedge pressure (PCWP). If there is any question about the accuracy of the PCWP, then one should obtain a left ventricular end diastolic pressure (LVEDP) in parallel just to make sure that you’re looking at precapillary disease.

**Dr Horn:** Right, and emphasize, don’t be afraid to do that catheterization even while they’re pregnant.

**Dr Lang:** Right, exactly.

**Dr Horn:** I think the next aspect is up until when would we perform a termination of pregnancy. In general, if a woman presents early, and once that diagnosis is made, much of the focus is spent on termination, because I still believe that despite all of our successes with medication and differences in mortality, mortality remains extremely high and we should advise the patient to terminate the pregnancy. The question is at what stage is delivery of a dead fetus as problematic as an attempt of a live delivery? I have had a high-risk PAH patient with systemic level PAP terminate as late as 22 weeks’ gestation.

**Dr Levine:** I think this is important, as we know that a termination procedure itself is not entirely without risks as well.

**Dr Horn:** Absolutely true. And for that procedure, one needs the same support that we would need for delivery in terms of a multidisciplinary team, which includes cardiac anesthesia, OB anesthesia, and often cardiac surgery, not uncommonly for the sickest patients. I have actually had femoral lines placed on occasion so that if we needed to crash onto ECMO we can. Obviously, maternal and fetal medicine (MFM) needs to be present; the difference being the involvement of neonatology for live births. But I think the first aspect is to get people together— including the partner/spouse—to make sure that everybody understands the risks. I think it’s very important for the spouse to understand that the worst possible scenario is that of a marked premature delivery with possible maternal death and marked disability of the child due to prematurity. So that is why lots of early efforts are made in this regard for the sickest patients.

**Dr Levine:** So it sounds like termination early-on is an option, but how does everyone feel about timing as it becomes more of an issue as the pregnancy progresses? So in terms of being too late, is there a “too late” situation where the procedure would be as risky as the delivery itself to the patient?

**Dr Lang:** My obstetrician teaches me it depends on the exact stage of the pregnancy. As the child becomes bigger it becomes a delivery and it carries exactly the same risk as getting the baby. And then early-on it may be a smaller intervention, but still an intervention.

**Dr Zwicke:** I would agree with that because by the time they’re reaching 16 weeks’ gestation they hormonally have had a significant increase in intravascular volume and have had a redistribution of fluid into the third space.

**Dr Horn:** Although 16 weeks’ shows significant hormonal and hemodynamic changes, we haven’t seen the maximal hemodynamic changes in terms of cardiac output.

**Dr Zwicke:** You must pay meticulous attention to the volume status of the mother and be on top of it. You need to treat that and manage it throughout pregnancy and after delivery, be it a live birth or termination. There will be different challenges depending on what the etiology of the pulmonary hypertension is.

**Dr Levine:** So it sounds like from the discussion that the option of early safe termination may be the first discussion to have with the patient who presents early enough in pregnancy. Importantly, both for this procedure as well as with continuing on with the pregnancy, the next step should be setting up a multidisciplinary team of all of those involved. This will help to optimize care through this procedure or though the pregnancy and the delivery. For those patients in whom termination is not an option, for example, those who present too late in pregnancy and they are going to go through with the pregnancy—can we talk about what people’s diagnostic and management algorithms are?
**Dr Zwicke:** So, the person who has diagnosed the pulmonary arterial hypertension is responsible for the first discussion with the patient. This discussion needs to address the new diagnosis, the implications, the effects of pregnancy, and the forward options. Within the next 3 days, it is ideal to have a joint appointment with the patient, significant other, the high risk OB physician, and yourself. The issues of termination versus continuation of the pregnancy need to be fully discussed. If she decides to proceed, we set up an entire team. We pull together the high risk OB team, neonatology, cardiology, pulmonary, and cardiovascular anesthesia, and the OB and ICU nursing staff representatives. We then get a plan in place and designate who is going to be the leader of this team, which is usually the person managing the hemodynamics, treating the PAH, and monitoring the RV function. In my opinion, it is usually the RV function that will dictate the outcome of the patient. Identification of the patient-specific issues early on makes for a safer and more efficient team, should there be an unexpected premature delivery.

**Dr Lang:** We also got advice from a rheumatologist in my last case. She had scleroderma with antiplatelet antibodies, erythrocyte antibodies, and we thought about plasmapheresis; so in addition to the experts you just numbered, we had a rheumatologist on board.

**Dr Horn:** I think we would all echo the same approach in terms of the multidisciplinary team. Occasionally there is a hematologist as well. But pretty much, that’s most of the team.

**Dr Zwicke:** Someone has to be declared the leader of the team, as information from any other person on the multidisciplinary team needs to feed into someone. In my experience, that’s the most important single item in the planning process. Most of the issues through the 2nd and 3rd trimester will be related to right ventricular function as the most important. And if right ventricular function is not the most important, how the mother tolerates the physiological stressors of the pregnancy may be the most important. Do you add diuretics? Do you hospitalize? Do you deliver earlier than planned? Do you put them on dobutamine? Do you alter your initial plan in any way?

**Dr Oudiz:** You bring up the point of not only having a cohesive team with good leadership, but also having a multiple contingency plan. Because you don’t know what’s going to happen nor when it will happen.

**Dr Zwicke:** Well, you have to be prepared to deliver at any point in time if the right ventricle starts to deteriorate and you can’t rescue it. If they ate at a Chinese buffet and had tons of soy sauce 2 days ago, you know the cause of the hypervolemia and can diurese them a little, feeling confident that you have the situation under control. Deterioration of the RV function without an identifiable cause always makes us more nervous. The beauty of the advances in echo technology is that we can reassess the right heart in an office study. We have the luxury to look at the RV function serially. I normally will look at RV function by echo every 2-3 weeks from the first time I meet the patient, moving to every week during the last 6-8 weeks leading up to the designated delivery time. A limited right heart echo only takes about 20 minutes and provides a wealth of information: RV size and function with tricuspid annular plane systolic excursion (TAPSE) with at least 4 views, width of IVC and respiratory variability, RA size, estimated RVSP, degree of tricuspid regurgitation, and RA pressure. Once the patient tells me they’re short of breath or they have swollen feet; we have more objective data serially to make our treatment decisions. You really do need to know that information earlier and I believe serial echo evaluation of RV performance may help the patient assessment prior to the development of clinical symptoms.

**Dr Horn:** We usually have multiple contingencies in terms of planned delivery, emergency delivery; including where, how, what before and after delivery. Are they on the cardiology service? Are they in the CCU or—depending on the comfort level of the nursing on labor and delivery—are they on a high risk L & D unit? Is delivery in the cardiac OR versus on labor and delivery? Is OB nursing going to cardiology or is cardiology nursing going to L & D? All of these things have to be addressed. And we should also address the patients who are new to us who just come via our emergency room, are transferred with this diagnosis previously not on therapy, or patients who are cared for elsewhere already on therapy. I think all of these things vary from case to case. Does the patient have a shunt? Is this congenital heart disease which makes it a little bit more favorable in terms of filling of the left side or is it a patient who has all the bad prognostic aspects and introducing a cardiac surgeon and discussing emergency procedures if necessary is required.

**Dr Levine:** It sounds like evaluation and monitoring—serial monitoring by many specialties—occurs in all of our centers. In terms of a plan and monitoring, at what point and with what types of medications will you follow these patients? And at what point do you consider changing someone from an oral PDE-5 inhibitor to a prostacyclin?
Dr Oudiz: Whether we should be treating patients empirically or expectantly is an important discussion point. In other words, starting a prostacyclin when you might ordinarily otherwise not start a prostacyclin, or treating them on an as-needed basis. And the worry that all of us have is that, like Dianne was saying, if we wait until the patient is symptomatic, then it’s probably too late. The problem is that there just isn’t much evidence in the literature or even anecdotal experience because there is so much heterogeneity in the approach. But I think most of us at the level of a PH specialty center are aware of what the risks and benefits of prostacyclin infusion are for a patient who has an otherwise uncomplicated pregnancy. And therefore we would probably edge toward the side of earlier initiation of prostacyclin, if they’re not already receiving it, rather than expectant initiation of prostacyclin.

Dr Zwicke: I would completely agree with you, Ron. The typical pregnant patient I see enter my practice is in that mid-teens’ weeks of pregnancy. So, they are usually around the 16th–18th week when there is a large fluid shift occurring. They come in because of right heart failure symptoms. When you look at the echo, you see that the RA and RV are dilated and the RV function is depressed, the pressures are high, the PA is dilated, and the IVC is more dilated than what you’d expect to see in pregnancy. It is very helpful to add a bubble study (injection of agitated saline) at the time of the first echo study in your office to rule out an intracardiac right to left or bidirectional shunt – the most common congenital systemic to pulmonary shunt missed in adults is a sinus venous atrial septal defect in an echo-silent area seen by transthoracic echo or a PFO that has opened from the elevated right heart pressures. The right heart catherization is necessary to confirm your diagnosis of pulmonary arterial hypertension and allows a complete oxygen saturation run. The saturation run would also detect anomalous pulmonary veins. If a shunt is not apparent on 2-D echo imaging and you don’t do a bubble study, which can safely be performed on a pregnant woman in the office, you will never know that you are dealing with a shunt and will diagnose this patient with idiopathic PAH instead. The hemodynamic measurements will definitely help you make the best pharmacologic selections for each patient. If the cardiac output/cardiac index is low or even normal, prostacyclins are definitely indicated. All pregnant women would be expected to have elevated cardiac indices. Since these patients are well into their pregnancies, you need to start aggressively treating, as delivery could occur at any time.

This is a time when the “simpler” treatments are probably not appropriate.

Dr Horn: And, I would like to emphasize that the normal pregnancy should have a high cardiac output, so finding a low or even “normal” cardiac output in pregnancy is markedly abnormal.

Dr Lang: I would go as far as to say if it’s truly PAH and the person is pregnant, I don’t see their living through pregnancy without a prostacyclin. I think it’s really the worst if a scleroderma patient who is pregnant gets PAH or a scleroderma patient with PAH gets pregnant. All the pregnant women I have seen have been put on IV epoprostenol.

Dr Horn: I think there may be an occasional patient, for example with a large congenital systemic to pulmonary shunt, who we may not start on intravenous prostanooid therapy.

Dr Zwicke: All of my patients have been treated with IV epoprostenol or IV treprostinil. One patient, long ago, came to me on subcutaneous treprostinil. We need to remember that 20% of the cardiac output goes to the skin in a healthy person, but this can drop as low as 5% with poor RV function. Therefore, it’s risky to administer a drug subcutaneously and not know what amount of drug will be absorbed from day to day, depending on the RV function. The optimal delivery system is IV.

Dr Oudiz: Let me throw a little bit of a wrench into this: when you’re at a public hospital and you have patients that are uninsured and undocumented you are probably okay in the inpatient setting if your drug is on formulary. And you can probably be okay with the emergency insurance during pregnancy. But for the longer term, if the patient has advanced PH and becomes “dependent” on an IV prostacyclin, you’re in big trouble because you’re going to have to either have the hospital pay for it or the patient pay for it.

Dr Zwicke: Actually, there are patient assistance programs for several of the medications now that may apply.

Dr Lang: But Ron, haven’t you seen them actually get worse after the pregnancy is over? They’re even worse than before so it’s foreseeable that they will not be treatable just with a phosphodiesterase inhibitor after the delivery.
Dr Oudiz: Oh, absolutely. That’s the conundrum. We’re in a situation—it’s not an ideal situation—in which you can’t do what you want to do, but rather have to do what you’re able to do.

Dr Lang: You know I was advising in Hungary for a patient, very similar, very ill patient, and they went to the newspapers after the pregnancy was well over on epoprostenol and then she got the money from the state because it was so dramatic—a young woman—and they managed to overcome this because in Hungary there is no epoprostenol. They have iloprost inhaled.

Dr Zwicke: Which doesn’t work that well because of the erratic levels.

Dr Lang: No, it does not.

Dr Oudiz: We had a case several years ago, before we had assistance programs, that wound up being a gigantic ethical issue whereby the referring hospital ended up having to pay for the entire cost of the epoprostenol because they couldn’t ethically stop it.

Dr Levine: We have had the same issue in a couple of cases. In one instance, we started a patient on epoprostenol who had suboptimal funding and we needed to keep her in the hospital for a month after the delivery until she could get emergency Medicaid. She was then able to continue on with epoprostenol at home and eventually switched to treprostinil long term. So this seems as though it is not an infrequent issue.

While we are discussing medications during pregnancy, let’s look into the issue of these patients being at a higher risk for thromboses. What are your thoughts on thromboprophylaxis during pregnancy in these patients?

Dr Zwicke: If they’re collagen vascular or primary etiologies, I do anticoagulate them.

Dr Oudiz: What about in the beginning of the pregnancy?

Dr Zwicke: Subcutaneous heparin, if we are seeing them early in the first 12 weeks.

Dr Oudiz: Do you use subcutaneous heparin because of the risk of teratogenicity with warfarin?

Dr Zwicke: Yes. There are good pregnancy data from England for the use of Coumadin, especially with artificial heart valves. I think they’ve got the largest databank available and have shown that it’s safe to use the subcutaneous heparin early on, and then after first trimester, going to Coumadin, with a return to subcutaneous approaching delivery. They obviously need close observation and monitoring. If you’re uncomfortable with the hemodynamics or overall condition of the patient, it is probably better to use subcutaneous the entire time.

Dr Lang: I had a patient get pregnant on acenocoumarol. We knew she had PAH, and she had a baby with a cleft-lip, a diaphragmatic hernia, and a ventricular septal defect. It was terrible. And I think the perinatal team should look at the babies early on if the patient has been on a vitamin K antagonist, because I don’t think it’s so rare—maybe because I have seen it.

Dr Oudiz: We had an experience where we had a patient on subcutaneous treprostinil and were planning an elective delivery for her. She unfortunately went into preterm labor and ended up having to have a C-section and subsequent rectus abdominis hematoma with considerable bleeding. She survived, but we realized that the physical and temporal proximity of her subcutaneous injections likely contributed to that bleeding.

Dr Levine: Thank you, these are such important anecdotes. And as we discuss delivery, we all know that we can never really plan for it. If we can, let’s focus on the delivery itself. For example, when do you admit a patient for delivery? What type of delivery do you and your team feel is best? What is the best timing for delivery (if undergoing a planned delivery)?

Dr Oudiz: The question is on the mode of delivery, in other words vaginal delivery versus C-section?

Dr Levine: That’s a good place to start.

Dr Oudiz: Well, again, I think there isn’t a great amount of literature that proves one is better than the other. There are certainly those that have had more experience with one versus the other. One argument is that the C-section can be controlled in the OR and there’s less variability, but that the invasiveness of the C-section and the anesthesia required might outweigh the risks of the vaginal delivery that would likely be done in an ICU.

Dr Horn: And, in fact, usually the hemodynamic changes following delivery are more gradual with a vaginal delivery. Having said that, you may have to also go with your center because it takes a lot more...
coordination. I absolutely prefer to do vaginal deliveries and get everybody coordinated. It also depends on what week we’re talking about, likelihood of favorable cervix, etc. The last thing we want to do is sort of pretend that the patient is going to go vaginally and then to crash on to a C-section. Again, with this concept if we really have things going well and we are delivering in a cardiac OR and have people hanging out waiting for 12 to 14 hours, nobody is pleased with us. But that certainly has worked. But I’m certainly cognizant of recognizing a system that can only work with a scheduled C-section. I think all of those things have to be factored in. It also makes a big difference to have the best of the team available for delivery. I should also add that another agent that I often like to use during delivery—in addition to any parenteral prostacyclin—is old-fashioned inhaled epoprostenol. It is useful as additional therapy because you can get much higher pulmonary doses. I find it even better than iloprost or nitric oxide. So it’s not uncommon that I will have patients on combined inhaled epoprostenol at the highest doses tolerated and iNO. The most important issue is to be working with the anesthesiologist and to be there to make the calls for therapy for right heart, for pressors. Not uncommonly we use vasopressin as the pressor of choice and often it can be a minute-by-minute or second-by-second intervention.

Dr Levine: During the C-section it is so important for us to be there with the anesthesiologist and the surgeon or the OB to help direct fluids and medications. Our input can make such a difference.

Dr Horn: Yes, I believe that unless it’s an emergency and we can’t be there, we attend all deliveries.

Dr Oudiz: That presents one of the biggest problems for us. That is, you never know when this patient is going to need you. And while we’re on call for our patients, we’re doubly on call for a delivery and really have to make ourselves available for an extended period in order to be sure that we have the best chance of actually being present. It is important that we call the shots: which pressors are used, the adjustments of the PH medications. It’s very important to have the PAH expert there.

Dr Lang: What I want to point out, what I think is very important to think about, is analgesia. It’s important at any time, even with the small things like an intra-arterial line. They must not have any sensation of pain during these small interventions even in preparation for a C-section or vaginal delivery.

Dr Zwicke: I wanted to share the protocol that I’ve used over the past decade, now for 57 patients. We assemble our team as soon as possible. We select the date for delivery early on, which will always be early in the week (Monday or Tuesday) of the 36th week of gestation. It is important to have accurate dating of the pregnancy by ultrasound. A 36-week baby is usually mature enough and none of them ended up on a ventilator. Only younger babies, some of those less than 36 weeks, required mechanical ventilation. During the last 4 weeks of pregnancy, a PAH mom with a dysfunctional right ventricle retains much more fluid due to hormonally-driven factors than what the normal pregnant mom experiences. If the patient makes it to the designated day of delivery, in the early 36th week, they come in at 5 in the morning for induction. Pitocin is used. An epidural is mandated and was discussed with the patient early on in the initial visits. It’s not presented to them as an option. Cardiac and OB anesthesia work together on that so that it’s a slow onset epidural, avoiding the usual hypotension and subsequent rescue with large bolus infusions of normal saline. It is important to balance vasoconstrictor medications with some saline. The goal is to have a vaginal delivery, unless there is a recognized obstetrical indication for a C-section. Most of our patients delivered by 3 or 4 in the afternoon while the team is available. The only C-sections that we have done were those with a true obstetrical reason for C-sections. One was a footling breech; another was a breech; another was transverse lie; one was very unstable with difficult to control paroxysmal atrial fibrillation; and another was a placenta previa. The interesting observation we’ve made out of our population is that every C-section incision became infected. They all had wound debrideaments and vacuum-assisted closure. The reason was not clear and the deliveries were performed at several hospitals, so it was not just a single hospital technique issue. That was also the information given back to me from distant centers. The reason was not clear and the deliveries were performed at several hospitals, so it was not just a single hospital technique issue. That was also the information given back to me from distant centers.

The vaginal deliveries do much better. With the C-section deliveries you have a much harder time judging how much fluid to take off in forcing diuresis early on day 1-2 postpartum. You usually have to wait until about the 2nd day before you can start actively diuresing them versus the vaginal delivery when we start aggressive diuresis looking at 3 L/day negative output, for 3 days, starting as soon as the epidural has worn off. That’s usually as soon as they can feel their toes and wiggle them. Approximately 1/2 of the deliveries were performed here in Milwaukee, while the other half were done in other countries and other states. We actually have the fortunate situation of having a delivery room right in our ICU. There is a little foyer area for the baby, a nursery, and they can...
deliver right there. The anesthesiologists have to be on board with counting and estimating every cc in, every cc out, because whatever they gave during the delivery has to be diuresed off the patient. The greatest risk time for the mom is the delivery and early the morning of day 3 post partum.

**Dr Horn:** I would pretty much echo a very similar approach. I would also caution that we’ve seen difficulties at the time, and particularly with the C-section, with placental delivery. The experience is overwhelmingly much more positive from the acute hemodynamic management with vaginal delivery. I’ve seen the complications at 72 hours sometimes heralded with low platelets and by how much is hormonally driven and how much is hemodynamically driven.

**Dr Zwicke:** There can be spleen sequestration or the decreased counts known to occur with prostacyclin itself.

**Dr Horn:** Yes, all of the above. So that I actually like patients to remain in the ICU for the 72 hours after delivery.

**Dr Zwicke:** Always. We keep them there; 100% of people are in the ICU and it requires a re-education of the ICU nursing staff. They look well and act well. They’re getting to the bathroom and they’re walking around and they look fine. It’s the potential for disaster; that’s the reason they are there.

**Dr Horn:** And then they can still crash.

**Dr Zwicke:** And their typical crash is 3 am on morning 3. That’s when the majority of deaths are reported. It’s due to the massive fluid shifts back into the vascular tree. They develop acute pulmonary edema and are very difficult to rescue. This accounts for the majority of the pregnancy-related deaths in PAH patients.

**Dr Horn:** Three days, absolutely. And some tell-tale signs; look at the platelets and LFTs.

**Dr Zwicke:** Good point.

**Dr Levine:** Absolutely, and I did want to get to that point. In the literature—especially in the older literature—there is a lot of controversy about the type of monitoring people should use. What are your thoughts regarding using PA catheter versus a CVP monitor during the delivery and postpartum in the ICU?

**Dr Oudiz:** It’s difficult to know whether you’re treating the physician or you’re treating the patient with invasive monitoring. Given the nature of all the issues we’ve just talked about, and the fact that things can creep up on you without being prepared, we tend to empirically place a PA catheter prior to delivery. In our center, our system works better with the surgical approach rather than a delivery in the CCU, which can be very impractical. So prior to any anesthesia or even an anesthesiologist’s seeing the patient, we’ll have the catheter already in the ICU and we’ll keep it there until that critical period is over where we know that they have passed their highest risk of complications, somewhere around 72 hours. This brings up a question about the Pitocin and the induction of labor. Because we don’t know all that well what happens relative to pulmonary vascular changes and pregnancy hormones in the peripartum period, and I think it’s more than just fluid shifts that suddenly cause the right ventricle to acutely fail in the postpartum period.

**Dr Horn:** Well, it’s also the acute change – it’s both the hemodynamic as well as hormonal – because we also have the acute change in the SVR.

**Dr Oudiz:** Right. And so if there is a hormonal component to it, we don’t know what it is, but it would intuitively involve for example, oxytocin, a vasoconstrictor, but also a hormone mediating the milk letdown response postpartum. So I worry a little bit about using Pitocin up front when it may be, at least in part, one of the reasons why patients do poorly postpartum.

**Dr Horn:** I do something close to what Dianne does also. So we start the Pitocin, we do the epidural. We also aim for Monday, Tuesday and in our case the right heart cath goes in at the same time.

**Dr Zwicke:** We used PA catheters initially, until we became more comfortable. Now, it’s pretty much a CVP only. But, if there is any question, certainly put a PA catheter in. You can follow outputs for those patients that you are concerned with. I have found a limited right-heart echo each day more helpful as a diagnostic procedure.

**Dr Oudiz:** Is the CVP monitoring enough for you to know that PVR is or isn’t getting worse?

**Dr Zwicke:** Yes. This is because I’m not treating the PVR, I’m treating the right ventricular function and I will have the echo tech come over after the epidural has worn off, about 4 hours after delivery, and do a right heart echo. I frequently use low-dose dobutamine to augment the RV systolic function during the periods of stress and volume shifts The right ventricle...
Dr Levine: When we do the CVP you can follow the right atrial saturation.

Dr Zwicke: Right. One other thing to remember is that if the postpartum patient begins to desaturate and you haven’t achieved the desired diuresis, they can blow open a previously closed PFO and begin to right to left shunt, causing systemic desaturation. This may also happen at the start of a dobutamine infusion, if it augments RV contractility, increasing the tricuspid regurgitation jet into the RA, opening the PFO. The treatment for both situations is aggressive IV diuresis. As soon as you decrease the intravascular volume, the shunting will decrease or stop.

Dr Levine: Thanks, Dianne. Another area that we should discuss is counseling the patient regarding future pregnancies; that is, contraception, tubal ligation, etc.

Dr Zwicke: Of the people we saw, we counseled 100% while we were following through the pregnancy. So, it was all set up for what type of contraception. We already knew if it was going to be an IUD, Depo, or a tubal ligation and when that was to occur. Necessary consents were already signed before they came in for induction. So, if an intended vaginal delivery converted to a C-section, it was all done. There were no last-minute decisions. It’s all there on the chart. I think that the total preplanning is so important. I have cared for a lot of pregnant PAH patients; I’ll be the first to advise against pregnancy, as the risk is still very high and we have a lot to learn yet. I do not tell patients that it’s “okay” to get pregnant with pulmonary arterial hypertension. But, when they do become pregnant or are diagnosed during pregnancy, it is our job to properly and thoroughly counsel them, provide the best care we can, and provide all of the information we have available to us, so that they can make an informed decision in their situation.

Dr Levine: Thank you. I think you’ve summed it up. I think that’s the message that needs to hit home.

Dr Zwicke: Well, it’s a risk you don’t need to take. All except one patient in our practice arrived pregnant and decided after counseling, not to abort. Since we are a referral center, these patients had already decided not to abort their pregnancies prior to arrival. One intentionally, knowing she had pulmonary hypertension, treated at another center with PDE-5 inhibitors, came to our clinic in the 2nd trimester, unstable, and with mild right heart failure symptoms. She needed to convert to IV prostacyclin and delivered. She proceeded to become pregnant again after that despite all advice to not do so. She was treated for about a year with IV prostacyclins and converted to 2-drug oral therapy. She now has had a tubal ligation.

Dr Oudiz: I would still consider her extremely lucky.

Dr Zwicke: Yes, absolutely. So do I.

Dr Horn: And so I think we would all agree on ending it exactly how Dianne ended it.

Dr Levine: Agreed. Another point I believe we should touch on is where these patients are being managed. Everyone on the call today has had patients in this situation and has built multidisciplinary teams of specialists to help manage these patients when the need arises.

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Dr Levine: Agreed. Another point I believe we should touch on is where these patients are being managed. Everyone on the call today has had patients in this situation and has built multidisciplinary teams of specialists to help manage these patients when the need arises. These patients’ care needs to be individualized and should be done at a specialty center with collaboration of the high risk OB, the anesthesiologist, the PAH specialist, and the rheumatologist (if needed)—everyone who is necessary to help coordinate the treatment of both the pregnancy and the PAH.

Dr Zwicke: I have just one other comment about the team. We leave out the respiratory therapy department frequently. If you are intending to proceed to a vaginal delivery, you can teach these moms to do a small breath Valsalva push without doing the usual deep and extended breath-hold type Valsalva. The normal delivery room nurse will instruct the patient, take a deep breath, bear down, hold until you turn blue. You can’t do that with these patients. So, we actually set up training in our respiratory therapy department to teach the pregnant women how to push using their abdominal muscles and perineal muscles, instead of using the diaphragm. So, that would be one other thing to include in the pre-delivery teaching plan. It can be a partial forceps delivery, but they actually can do some pushing and they do shorter pushes using the abdominal muscles.

Dr Horn: I think that is something that is very important.
Dr Zwicke: But, we don’t think about it until you’re in the delivery room. The team sometimes needs to involve some of the people who have had more experience with some high forceps deliveries too.

Dr. Levine: I agree. Again, having an entire team involved before getting to this point is so important to be able to manage this or any scenario that may (and will) arise during pregnancy or delivery or in the post-partum period. There are, as we have seen today, individual centers that have acquired experience over time with these patients and have developed a team of experts working together when these women are referred. It is very important to have that experience behind us when taking care of these patients.

We are so fortunate to have had this whole group together today to discuss this complicated matter of PAH and pregnancy. This conversation only touches on how complicated and serious this situation can be and how many issues are involved. It also reflects on how little information (aside from case reports and case series) there are to help guide PAH specialists, obstetricians, and the whole team in managing these women when they are referred to us. This hour today has helped drive home the importance of bringing together each center’s collective experience (albeit small) to help to develop guidelines as well as practical strategies to help better care for these women.

I again would like to thank everyone for taking the time to join us today.
PAH Therapies in Men: Often Wondered, Seldom Asked

Note from the Section Editor: Though this issue of Advances in Pulmonary Hypertension is dedicated to specific challenges faced by women, we took this opportunity to ask Dr. Williamson some of the more common questions asked by men with PAH.

Although some etiologies of PAH affect women disproportionately to men, men are clearly also impacted by this devastating disease and require treatment with PAH-specific therapies. A number of adverse effects related to these treatments are seen in both sexes, but gender-specific adverse effects also exist. Perhaps the 2 most frequently asked questions by male patients with PAH are “1) Is it safe for men taking PAH therapies to become fathers?” and “2) While taking PAH medicines, do I need to worry about prolonged erections (priapism)’?”

The abbreviated answer to the first question is that it does appear to be safe for men on PAH medicines to father children, though their ability to do so may be hampered by some treatments. Review of the literature and patient prescribing information for the FDA-approved prostacyclins and phosphodiesterase-5 (PDE-5) inhibitors reveal no evidence of mutagenesis for these drugs. While the endothelin receptor antagonist (ERA) class of medications, including bosentan (Tracleer, Actelion Therapeutics) and ambrisentan (Letairis, Gilead) have been shown to be teratogenic in females as a class effect (package insert), similar mutagenic effects have not been demonstrated in sperm. Company information does indicate, however, that sperm counts can be significantly decreased in patients on bosentan, and likely is a class effect of other ERAs as well. Although not an ERA, tadalafil has also been shown in some animal studies to diminish sperm counts, though the clinical significance in humans is not clear. Given the limited data, some men have opted to bank sperm prior to the initiation of an ERA. These potential issues should be discussed with male PAH patients considering having children.

The risk of priapism is confined to PDE-5 inhibitors such as sildenafil (Revatio, Pfizer) and tadalafil (Adcirca, United Therapeutics). Priapism is not seen with prostacyclins or ERAs. Fortunately, the literature and our clinical experience suggest that priapism is a rare event. Indeed, despite wide-spread use of PDE-5 inhibitors in our PH center, we have not seen a single case of this complication. A review of double-blind placebo controlled trials and post-marketing databases (both primarily related to use in erectile dysfunction) suggests priapism occurs with an incidence between 0.1% (in the clinical trials) to 2.5% (in the post-marketing databases).

Prescription information for PDE-5 inhibitors cautions against using these drugs in patients with anatomical deformations of the penis (eg, angulation, cavernosal fibrosis, Peyonie’s disease) or in patients with co-morbid conditions potentially predisposing to priapism (multiple myeloma, leukemia, sickle cell disease). Interestingly, PDE-5 inhibitors have been used to treat and prevent ischemic priapism, including in patients with sickle cell disease, but clearly reflects off-label use. If a patient does experience an erection lasting 4 hours or longer, it is important they seek emergency medical evaluation immediately as untreated priapism may lead to cavernosal fibrosis and permanently impaired erectile function.

In summary, it appears it is safe for patients on PAH therapies to father children, though ERAs and possibly tadalafil may decrease sperm counts, which may make conception more difficult. Priapism is a rare adverse effect associated with PDE-5 inhibitors, and caution should be used when considering these medicines for patients already pre-disposed to priapism.

References

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Important Safety Information

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered. Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α-blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors, eg, ketoconazole, itraconazole, and ritonavir, is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with CYP3A4 inducers, including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, may alter plasma levels of either or both medications. Dosage adjustment may be necessary.

Non-arteric anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil.

It is not possible to determine if these events are related to PDE5 inhibitors or to other factors. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including sildenafil.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

Patients with the following characteristics did not participate in the preapproval clinical trial: patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months, unstable angina, hypertension (BP >170/110), retinitis pigmentosa, or patients on bosentan. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

Indication

REVATIO is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

Please see Brief Summary of Prescribing Information on the following pages.
REVATIO® (SILDENAFIL)

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: REVATIO® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of primary pulmonary hypertension (17%) or pulmonary hypertension associated with IND佃osis (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

DOSAGE AND ADMINISTRATION

Pulmonary Arterial Hypertension (PAH)

REVATIO Tablets

The recommended dose of REVATIO is 20 mg three times a day (TID). REVATIO tablets should be taken approximately 4-6 hours apart, with or without food.

In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg TID is not recommended. Dosages lower than 20 mg TID were not tested. Whether dosages lower than 20 mg TID are effective is not known.

REVATIO Injection

REVATIO injection is for the continued treatment of patients with pulmonary arterial hypertension (PAH) who are currently prescribed oral REVATIO and who are temporarily unable to take oral medication. The recommended dose is 10 mg (corresponding to 12.5 mL) administered as an intravenous bolus injection three times a day. The dose of REVATIO injection does not need to be adjusted for body weight. A 10 mg dose of REVATIO injection is predicted to provide pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose.

CONTRAINDICATIONS

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

Hypersensitivity Reactions

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any component of the tablet. Rare cases of hypersensitivity have been reported in association with the use of sildenafil including anaphylactic reaction/shock events and anaphylactoid reaction. The majority of reported events were non-serious hypersensitivity reactions.

WARNINGS AND PRECAUTIONS

Cardiovascular Effects

REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients with resting hypotension [BP < 90/50], fluid depleton, severe left ventricular outflow obstruction, or autonomic dysfunction).

Pulmonary vasodilator may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with PVOD, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

As there are no controlled clinical data on the safety or efficacy of REVATIO in the following conditions, proceed with caution for:
- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with coronary artery disease causing unstable angina;
- Patients with hypertension (BP > 170/110);
- Patients currently on bosentan therapy.

Use with Alpha-blockers

PDE5 inhibitors, including sildenafil, 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. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported [see Drug Interactions].

No cases of syncpe or fainting were reported during these interaction studies. The safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of anti-hypertensive drugs.

Effects on Bleeding

In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. In vitro studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and sildenafil has an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

The incidence of epistaxis was 13% in patients taking sildenafil with PAH secondary to connective tissue disease (CTD). This effect was not seen in primary pulmonary hypertension (PPH) (sildenafil 3%, placebo 2%) patients. The incidence of epistaxis was also higher in sildenafil-treated patients with a concomitant oral vitamin K antagonist (3% versus 2% in those not treated with concomitant vitamin K antagonist).

The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Use with Ritonavir and Other Potent CYP3A4 Inhibitors

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A4 inhibitor) substantially increases serum concentrations of sildenafil; therefore, co-administration of ritonavir or other potent CYP3A4 inhibitors with REVATIO is not recommended.

Effects on the Eye

Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE5 inhibitors, including REVATIO. 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, including sildenafil, when used in the treatment of erectile dysfunction. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors. [see Adverse Reactions].

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Impairment

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors [see Adverse Reactions].

Combination with other PDE5 inhibitors

Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

Prolonged Erection

Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie’s disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Pulmonary Hypertension Secondary to Sickle Cell Anemia

In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

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

- Hypotension [see Warnings and Precautions]
- Vision loss [see Warnings and Precautions]
- Hearing loss [see Warnings and Precautions]
- Priapism [see Warnings and Precautions]
- Naso-occlusive crisis [see Warnings and Precautions]

Clinical Trials 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 practice.

Safety data were obtained from the 12 week, placebo-controlled clinical study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg TID were studied.

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dose of 20 mg TID was 3% and was the same for the placebo group.

In the placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that were reported by at least 3% of REVATIO patients treated at the recommended dosage (20 mg TID) and were more frequent in REVATIO patients than placebo patients, are shown in Table 1. Adverse events were generally transient and mild to moderate in nature.

Table 1. REVATIO All Causality Adverse Events in > 3% of Patients and More Frequent (> 1%) than Placebo

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (n=70)</th>
<th>REVATIO 20 mg TID (n=69)</th>
<th>Placebo-Subtracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>46</td>
<td>37</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Rushing</td>
<td>4</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Erythema</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea nos</td>
<td>0</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Gastrosis nos</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

nos: Not otherwise specified.
At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately corotory to vision, but also increased sensitivity to light or blurred vision. The incidence of retinal hemorrhage at the recommended sildenafil 20 mg TID dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both the recommended dose and at all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.

In a placebo-controlled fixed dose titration study of REVATIO (starting with recommended dose of 20 mg TID and increased to 40 mg TID and then 80 mg TID) as an adjunct to intravenous epoprostenol in pulmonary arterial hypertension, the adverse events that were reported were more frequent than in the placebo arm (≥6% difference) are shown in Table 2.

Table 2. REVATIO-Epoprostenol Adverse Events More Frequent (> 6%) than Placebo

<table>
<thead>
<tr>
<th>ADVERSE EVENTS</th>
<th>Placebo (n=70)</th>
<th>Epoprostenol (n=69)</th>
<th>Revatio 20 mg TID (n=120)</th>
<th>Placebo-Subtracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34%</td>
<td>57%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Edema^n</td>
<td>13</td>
<td>25</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>16</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>17</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>25</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>25</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

^n includes peripheral edema

REVATIO Injection

REVATIO injection was studied in a 66-patient, placebo-controlled study at doses targeting plasma concentrations between 10 and 500 ng/mL (up to 8 times the exposure of the recommended dose). Adverse events in PAH patients were similar to those seen with oral tablets.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events

In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. 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 sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Decreases in and Loss of Vision

When used to treat erectile dysfunction, non-articular anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing 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. [See Warnings and Precautions].

Loss of Hearing

Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including REVATIO. 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 REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors. [See Warnings and Precautions].

Other Events

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

Nervous system: Seizure, seizure recurrence

DRUG INTERACTIONS

Nitrates

Concomitant use of REVATIO with nitrates in any form is contraindicated [see Contraindications].

Ritonavir and Other Potent CYP3A4 Inhibitors

Concomitant use of REVATIO with ritonavir and other potent CYP3A4 inhibitors is not recommended [see Warnings and Precautions].

Alpha-blockers

Use caution when co-administering alpha-blockers with REVATIO because of additive blood pressure-lowering effects [see Warnings and Precautions].

In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these studies, patients were randomized to receive an additional reduction of supine systolic and diastolic blood pressure of 7/7 mmHg, 9.5/9 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Antidopamine

When sildenafil 100 mg oral was co-administered with antidopamine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There is no evidence of teratogenicity, embryotoxicity, or fetotoxicity observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m² basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg TID. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5- to 6-times the RHD on a mg/m² basis). There are, however, no adequate and well-controlled studies of sildenafil in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Laboratory and Delivery

The safety and efficacy of REVATIO during labor and delivery has not been studied.

Nursing Mothers

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of sildenafil in pediatric pulmonary hypertension patients have not been established.

Geriatric Use

Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Renal Impairment

No dose adjustment is required (including severe impairment CrCl < 30 mL/min).

OVERDOSE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for up to 24 months at 60 mg/kg/day, a dose resulting in total systemic exposure (AUC) to unbound sildenafil and its major metabolite S3 and 37 times, for male and female rats respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/m² basis. Sildenafil was negative in in vivo bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and in vitro human lymphocytes and in vivo mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in male or female rats given up to 60 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite of 19 and 38 times for males and females, respectively, the human exposure at the RHD of 20 mg TID.

PATIENT COUNSELING INFORMATION

• Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.

• Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction.

• Advise patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

• Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.

• Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

RX only

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Global PHCR Memberships
In an effort to increase global membership in PH Clinicians and Researchers (PHCR) and foster the sharing of ideas around the world, PHA is offering free first-year memberships for non-US physicians, researchers, residents, and fellows. Benefits of PHCR membership include case-based learning opportunities by top PH specialists, access to the email listserv of a growing number of PHCR members, inclusion in PHA’s Find a Doctor Directory, and more. For medical professionals in countries that have a gross national income per capita of less than $5000 USD, PHCR memberships may be renewed at no cost each year. Learn more at www.PHAssociation.org/PHCR.

PHA’s Understanding PH brochure is back!
PHA’s classic brochure is redesigned and more patient-friendly than ever. Visit www.PHAssociation.org/Store to order a supply of brochures for your office or clinic.

Introducing the Empowered Patient Online Toolkit
The toolkit includes templates and checklists to help patients track their health history, record symptoms and concerns between appointments, organize insurance information, and much more. Point your PH patients to www.PHAssociation.org/OnlineToolkit.

Get Listed in PHA’s Find a Doctor Directory
There’s never been a better time to join PH Clinicians and Researchers (PHCR), PHA’s medical membership network for doctors and PhD-level researchers. Among the many benefits of membership is the exclusive opportunity to be listed in the Find a Doctor Directory on PHA’s Web site. The directory is PHA’s premier resource for patients who are seeking information about PH-treating physicians in a geographic area.

Our new and improved Find a Doctor directory enables physicians to provide more information about their practice, while serving as a more user-friendly and accessible directory for patients: www.PHAssociation.org/FindADoctor.

PHA has also launched multiyear memberships for PHCR in an effort to make renewal easier, and to provide a discount for members who commit to multiple years of membership. Don’t miss the chance to be a part of this rapidly growing network of PH doctors and researchers. Visit www.PHAssociation.org/PHCR, or contact PHCR@PHAssociation.org.

Researchers: Apply to Collect Data at PHA’s 2012 Research Room
PHA’s International PH Conference and Scientific Sessions taking place June 22-24, 2012, in Orlando, Florida, will include a Research Room dedicated to helping researchers further their studies through the collection of data, including biological specimens (cheek swabs and blood samples) from PH patients. This event gives researchers the rare opportunity to collect data from the largest gathering of PH patients worldwide at any given time.

PHA is now accepting applications from interested researchers and institutions. To apply online, fill out an electronic application at www.PHAssociation.org/ResearchRoom/Form. Contact Micaela@PHAssociation.org with any questions.
Calendar of PH Activities

To have your event for PH health care providers considered for listing in future issues of Advances in Pulmonary Hypertension, send your announcement to meghanf@PHAssociation.org.

Society of Critical Care Medicine
Critical Care Congress
February 4-8, 2012
Houston, Texas, USA
www.sccm.org

American College of Cardiology ACC.12
March 24-27, 2012
Chicago, Illinois, USA
www.cardiosource.org

The International Society for Heart & Lung Transplantation 32nd Annual Meeting and Scientific Sessions
April 18-21, 2012
Prague, Czech Republic
www.ishlt.org

American Thoracic Society International Conference
May 18-23, 2012
San Francisco, California, USA
www.thoracic.org

PHA’s 10th International PH Conference and Scientific Sessions
June 22-24, 2012
Orlando, Florida, USA
www.PHAssociation.org/Conference
Cost-saving benefits through Co-PaySolutions

Monthly out-of-pocket expenses capped at $25 for eligible patients with commercial insurance.*

Gilead Sciences is committed to serving the PAH community through financial assistance programs, such as Co-PaySolutions. We understand how important it is for your PAH patients to remain on therapy, and during difficult financial times, every dollar matters that much more.

Co-PaySolutions, part of the Gilead™ Solutions patient assistance program, offers the following benefits to those who qualify:

• Out-of-pocket expenses capped at $25 per month
• Expanded assistance up to a maximum of $9,200 per year

These benefits are automatically applied through LEAP to eligible patients whose co-pay exceeds $25.

To learn more about Gilead™ Solutions, call 1-866-664-LEAP (5327), or contact your LEAP-LabSync Care Manager.

*Certain patients, including but not limited to all patients in Massachusetts, may not be eligible due to federal or state restrictions.
For the treatment of PAH (WHO Group 1) to improve exercise ability

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.

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.

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.

IMPORTANT SAFETY INFORMATION

- 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.
- Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.
- Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants.
- Treatment timing can be adjusted for planned activities.
- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope.
- Additional improvements in 6MWD when added to oral monotherapy.
- Four-times-daily dosing.
- Treatment timing can be adjusted for planned activities.
- Patient-friendly features with the lightweight, portable, handheld Tyvaso Inhalation System.
- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough, headache, throat irritation/pharyngolaryngeal pain, and syncope.

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.

6MWD=6-minute walk distance NYHA=New York Heart Association WHO=World Health Organization

**INDICATIONS AND USAGE**

TYVASO is a prostanoid 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. 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 anticoagulants.

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 235 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most commonly reported adverse reactions to TYVASO included: cough and throat 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 3% and were more frequent in patients treated with TYVASO than with placebo.

| Table 1: Adverse Events in ≥4% of PAH Patients Receiving TYVASO and More Frequent than Placebo |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Adverse Event | TYVASO n = 115 | Placebo n = 120 |
| Cough | 62 (54) | 35 (29) |
| Headache | 47 (41) | 27 (23) |
| Throat Irritation/Pharyngolaryngeal Pain | 29 (25) | 17 (14) |
| Nausea | 22 (19) | 13 (11) |
| Flushing | 7 (6) | 1 (<1) |
| Syncope | 7 (6) | 1 (<1) |

*More than 3% greater than 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 one year. 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 phase reaching a statistical difference to the placebo group included: cough, throat irritation, pharyngeal pain, epistaxis, hemoptysis, and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 8 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

**DRUG INTERACTIONS**

Pharmacokinetic/pharmacodynamic interaction studies have not been conducted in patients with PAH. Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diethanolamine) and subcutaneously administered treprostinil (Remodulin®) have been performed. 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.

In general, symptoms of overdose with TYVASO include flushing, headache, hypotension, nausea, vomiting, and diarrhea. In general, overdose studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (s.c.) infusion of treprostinil sodium at infusion rates higher than the recommended human cc 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.

**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.) infusion of treprostinil sodium at infusion rates higher than the recommended human cc 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—Since TYVASO inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

**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.
LETAIRIS is an endothelin receptor antagonist (ERA) 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%).

Clinical worsening is defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents, or study withdrawal due to early escape.1

MONTHLY SERUM LIVER ENZYME TESTING NO LONGER REQUIRED FOR DISTRIBUTION OF LETAIRIS

Order and review tests for serum liver enzymes as clinically indicated, since some members of this pharmacologic class are hepatotoxic.

In the treatment of pulmonary arterial hypertension

LETAIRIS is an endothelin receptor antagonist (ERA) 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%).

Clinical worsening is defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents, or study withdrawal due to early escape.1

LETAIRIS continues to have a boxed WARNING on the risk of serious birth defects. Because of this risk, LETAIRIS is available only through a special restricted distribution program.

Please see important safety information on the following pages, including boxed WARNING on the risk of serious birth defects, and brief summary of full prescribing information.
LETAIRIS is an endothelin receptor antagonist (ERA) 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%).

Clinical worsening is defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents, or study withdrawal due to early escape.1

**Boxed WARNING: Contraindicated in pregnancy**

*See full prescribing information for complete boxed WARNING.*

Because of the risk of birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS to patients who are enrolled in and meet all conditions of LEAP. Because LETAIRIS may cause fetal harm if taken during pregnancy:

- Exclude pregnancy before the start of treatment
- Prevent pregnancy during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS, in which case no additional contraception is needed
- Obtain monthly pregnancy tests
- Educate and counsel women of childbearing potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure

**LETAIRIS reduced the relative risk of clinical worsening by up to 72% through 12 weeks**

**Clinical Advantages Maintained Through 12 Weeks**

**Time to clinical worsening**

**LETAIRIS**

- 72% relative risk reduction in clinical worsening
- Event-Free (%)

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Event-Free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>72%</td>
</tr>
<tr>
<td>4</td>
<td>89%</td>
</tr>
<tr>
<td>12</td>
<td>89%</td>
</tr>
</tbody>
</table>

**Placebo**

- Event-Free (%)

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Event-Free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>28%</td>
</tr>
<tr>
<td>4</td>
<td>25%</td>
</tr>
<tr>
<td>12</td>
<td>25%</td>
</tr>
</tbody>
</table>

**Incidence of clinical worsening: 3% for LETAIRIS vs. 10% for placebo in ARIES-1 (p=0.030); 6% for LETAIRIS vs. 22% for placebo in ARIES-2 (p=0.005)**

**Warnings and precautions**

- LETAIRIS is available only through a special restricted distribution program
- Mild to moderate peripheral edema. Peripheral edema occurred more frequently in elderly patients (age ≥65 years) receiving LETAIRIS (29%; 76/56) compared to placebo (4%; 1/28). Peripheral edema is a known clinic effect of endothelin receptor antagonists. In addition, there have been postmarketing reports of fluid retention occurring within weeks after starting LETAIRIS that required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure
- Decreases in sperm count have been observed in patients taking endothelin receptor antagonists
- Decreases in hemoglobin have been observed within the first few weeks of treatment with LETAIRIS; measure hemoglobin prior to initiation, at 1 month, and periodically thereafter. Initiation of LETAIRIS therapy is not recommended for patients with clinically significant anemia
- If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as LETAIRIS, the possibility of pulmonary veno-occlusive disease should be considered, and if confirmed, LETAIRIS should be discontinued

**ARIES-1 and ARIES-2 study design**

The efficacy and safety of LETAIRIS were evaluated in two 12-week, randomized, double-blind, placebo-controlled, multicenter studies (ARIES-1, N=201 and ARIES-2, N=192). Eligible patients had idiopathic or heritable PAH (IPAH or HPAH) or PAH associated with connective tissue diseases, HIV infection, or anorexigen use (APAH). The primary endpoint of both studies was the mean change from baseline in 6-minute walk distance (6MWD). Secondary endpoints were time to clinical worsening and others, as compared with placebo. ARIES-1 compared once-daily doses of LETAIRIS 5 mg and 10 mg with placebo, while ARIES-2 compared once-daily doses of LETAIRIS 2.5 mg and 5 mg with placebo. In both studies, LETAIRIS or placebo was added to current therapy, which could have included a combination of anticoagulants, diuretics, calcium channel blockers, or digoxin, but not epoprostenol, treprostinil, iloprost, bosentan, sildenafil, or investigational therapy.
Potential for liver injury removed from boxed WARNING and warnings and precautions

- During 12-week controlled clinical trials, the incidence of aminotransferase elevations >3x the upper limit of normal (ULN) was 0% for LETAIRIS and 2.3% for placebo. In practice, cases of hepatic injury should be carefully evaluated for cause.
- Postmarketing experience: Elevations of liver aminotransferases (ALT, AST) have been reported with LETAIRIS use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). Other ERAs have been associated with aminotransferase elevations, hepatotoxicity, and cases of liver failure. Discontinue LETAIRIS if >5x ULN or if elevations are accompanied by bilirubin >2x ULN or by signs or symptoms of liver dysfunction, and other causes are excluded.
- Early escape criteria were two or more of the following after a minimum treatment period of 4 weeks: 20% decrease in 6-minute walk distance; worsening WHO functional class, worsening right ventricular failure; rapidly progressing cardiac, hepatic, or renal failure; and refractory systolic hypertension <85 mm Hg. Other secondary endpoints: change from baseline in WHO functional class, Borg Dyspnea Index, and SF-36 Health Survey.

9,800 patient-years of exposure in the United States
- Based on patients who have received at least one shipment of LETAIRIS since enrolling in LEAP, a restricted distribution program for LETAIRIS

Over 10,000 patients have received LETAIRIS in post-approval use.

Adverse events

<table>
<thead>
<tr>
<th>Most Common Adverse Events in &gt;3% of PAH Patients Receiving LETAIRIS and More Frequent Than Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Peripheral edema</td>
</tr>
<tr>
<td>Nasal congestion</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Flushing</td>
</tr>
<tr>
<td>Palpitations</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Headache</td>
</tr>
</tbody>
</table>

Note: This table includes all adverse events >3% incidence in the combined LETAIRIS treatment group and more frequent than in the placebo group, with a difference of ≥1% between the LETAIRIS and placebo groups.


Other secondary endpoints: change from baseline in WHO functional class, Borg Dyspnea Index, and SF-36 Health Survey.

Drug interactions
- Multiple-dose coadministration of LETAIRIS and cyclosporine resulted in an approximately 2-fold increase in LETAIRIS exposure in healthy volunteers; therefore, limit the dose of LETAIRIS to 5 mg once daily when coadministered with cyclosporine.
- Studies with human liver tissue indicate that LETAIRIS is metabolized by CYP3A, CYP2C19, and uridine 5'-diphosphateglucuronosyltransferases (UGTs) 1A9, 2B7, and 1A3. In vitro studies suggest that LETAIRIS is a substrate of the Organic Anion Transporting Polypeptides OATP1B1 and OATP1B3, and a substrate but not an inhibitor of P-glycoprotein (P-gp).
- Drug interactions might be expected because of these factors; however, a clinically relevant interaction has been demonstrated only with cyclosporine. LETAIRIS does not inhibit or induce drug metabolizing enzymes at clinically relevant concentrations.

Dosage and administration
- Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated; tablets should not be split, crushed, or chewed.
- Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests.
- Not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of LETAIRIS in patients with mild hepatic impairment; however, exposure to LETAIRIS may be increased in these patients.

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LETAIRIS is a registered trademark of Gilead Sciences, Inc. Gilead and the Gilead logo are trademarks of Gilead Sciences, Inc.
Letairis® (ambrisentan) 5 mg and 10 mg Tablets have not been studied in patients with pulmonary arterial hypertension (PAH).

Food, and consider increasing the dose to 10 mg once daily if 5 mg is 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 been studied in patients with pulmonary arterial hypertension (PAH). Women of Childbearing Potential: Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Tablets should be discontinued before the initiation of treatment with LETAIRIS. In addition, LETAIRIS may be dispensed only to women who are enrolled in and meet all conditions of LEAP [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%).

Dosage and Administration: Adult Dosage: Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is 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 been studied in patients with pulmonary arterial hypertension (PAH). Women of Childbearing Potential: Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Tablets should be discontinued before the initiation of treatment with LETAIRIS. In addition, LETAIRIS may be dispensed only to women who are enrolled in and meet all conditions of LEAP [see Warnings and Precautions].

Dosage Forms and Stengths: LETAIRIS is available as 5 mg and 10 mg film-coated, uncoated tablets.

Contraindications: Pregnancy Category X: LETAIRIS may cause fetal harm when administered to a pregnant woman. Ambienistat was teratogenic at oral doses of ≥ 2.5 mg/kg/day in rats and ≥7 mg/kg/day in dogs; it was not studied at lower doses. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid. Teratogenicity is a class effect of endothelin receptor antagonists. There are no data on the use of LETAIRIS in pregnant women. LETAIRIS is contraindicated in women who are or may become pregnant. 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 hazards to the fetus. Pregnancy must be discontinued before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed [see Dosage and Administration; Warnings and Precautions].

Warnings and Precautions: Prescribing and Distribution Program for LETAIRIS: Because of the risk of birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP [see Warnings and Precautions].

Hepatic Impairment: LETAIRIS is not recommended in patients with moderate or severe hepatic impairment [see Specific Populations]. The use of LETAIRIS in patients with mild hepatic impairment; however, exposure to ambrisentan may be increased in these patients.

Fluid Retention: Peripheral edema is a known adverse event with bosentan and/or the investigational ERA and all-eight had a recurrence of aminotransferase elevations >3x ULN were treated with LETAIRIS. Prior elevations were predominantly moderate, with 64% of the patients with clinically significant anemia. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing LETAIRIS. Pulmonary Veno-occlusive Disease: If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as LETAIRIS, the possibility of pulmonary veno-occlusive disease should be considered, and if confirmed LETAIRIS should be discontinued.

Adverse Reactions: Clinical Trials Experience: See Warnings and Precautions for discussion of hematological changes. 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 placebo-controlled studies in patients with PAH (ARES-1 and ARES-2) and four nonplacebo-controlled studies in 483 patients with PAH who were treated with doses of 1.25, 5, or 10 mg once daily. The exposure to LETAIRIS in these studies ranged from 1 day to 4 years (N=418 for at least 6 months and N=345 for at least 1 year). In ARES-1 and ARES-2, a total of 261 patients received LETAIRIS at doses of 2.5, 5 mg once daily and 121 patients received placebo. The adverse events that occurred in >3% of patients receiving LETAIRIS and were more frequent on LETAIRIS than placebo are shown in Table 1.

Table 1: Adverse Events in >3% of PAH Patients Receiving LETAIRIS and More Frequent than Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>LETAIRIS (N=261)</th>
<th>Placebo (N=132)</th>
<th>Placebo-adjusted (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitations</td>
<td>10 (4)</td>
<td>12 (9)</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (7)</td>
<td>24 (18)</td>
<td>1</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11 (5)</td>
<td>24 (18)</td>
<td>7</td>
</tr>
<tr>
<td>Constipation</td>
<td>12 (5)</td>
<td>17 (13)</td>
<td>5</td>
</tr>
<tr>
<td>Oligospermia</td>
<td>12 (5)</td>
<td>9 (7)</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4 (2)</td>
<td>6 (5)</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (5)</td>
<td>26 (20)</td>
<td>7</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>6 (2)</td>
<td>1 (1)</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (7)</td>
<td>24 (18)</td>
<td>1</td>
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<td>Abdominal pain</td>
<td>24 (11)</td>
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<td>Constipation</td>
<td>12 (5)</td>
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</tr>
<tr>
<td>Oligospermia</td>
<td>12 (5)</td>
<td>9 (7)</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: This table includes all adverse events ≥1% incidence in the combined LETAIRIS treatment group and more than 3% in the placebo group, with a difference of ≥ 3% between the LETAIRIS and placebo groups.

The incidence of treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension was similar for LETAIRIS (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of amniontransferase elevations >3x upper limit of normal (ULN) were 0% on LETAIRIS and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause.

Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Serum Liver Enzyme Abnormalities: In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to amniontransferase elevations >3x ULN were treated with LETAIRIS. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5x ULN, but 9 patients had elevations >8x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of amniontransferase abnormalities that required discontinuation of ERA therapy. All patients had to normal amniontransferase levels on entry to this study. Twenty-five of the 36 patients were receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8x ULN elevation). Of the remaining 34 patients, one patient experienced a mild amniontransferase elevation at 12 weeks on LETAIRIS 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients remaining under the hurdles of LETAIRIS at 10 mg, no patients were discontinued for amniontransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs.
or show that LETAIRIS (ambrisentan) led to lower aminotransferase elevations than would have been seen with these drugs, the study indicates that LETAIRIS may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal. 

Postmarketing Experience: The following adverse reactions were identified during postapproval use of LETAIRIS: Fluid retention (see Warnings and Precautions), heart failure (associated with fluid retention), hypersensitivity (e.g., angioedema, rash), anemia, nausea, and vomiting. Elevation of liver aminotransferases (ALT, AST) have been reported with LETAIRIS use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). Other endothelin receptor antagonists have been associated with elevations of aminotransferases, hepatotoxicity, and cases of liver failure (see Adverse Reactions). Discontinue LETAIRIS if >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

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 ambrisentan to 5 mg once daily when co-administered with cyclosporine (see Clinical Pharmacology).

CONTRAINDICATIONS: Ambrisentan is contraindicated in patients with moderate or severe hepatic impairment. There is no information on the use of LETAIRIS in patients with moderate or severe 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: 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 (see Dosage and Administration).

OVERDOSAGE: There is no experience with overdose 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 overdose could potentially result in hypotension that may require intervention.

PREGNANCY: Patients should be advised that LETAIRIS may cause fetal harm. LETAIRIS treatment should only be initiated in women of childbearing potential following a negative pregnancy test. Women of childbearing potential should be informed of the importance of monthly pregnancy tests and should be advised to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception—one hormone method and one barrier method, or two barrier methods where one method is the male condom. Acceptable hormone methods include: progestosterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring. Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom. Partners's vasectomy must be used along with a hormone method or a barrier method. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant. Educational counseling women of childbearing potential on use of emergency contraception for patients whom have had unprotected sex or known or suspected contraceptive failure (see Warnings and Precautions). Hematological 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.
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— Murali Chakinala, MD
Washington University School of Medicine
Pulmonary Hypertension Associated with Obstructive Lung Disease and Hypoxemia (WHO Group III)

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Learning Objectives
Upon successful completion of this course, participants will be able to:

- Explain the pathophysiology of pulmonary hypertension in lung disease
- Differentiate disproportionate pulmonary hypertension
- Develop a clinical approach to the evaluation and potential treatment of pulmonary hypertension in this setting

Program Description
This course presented by Drs. Charles Burger and John Moss explains the pathophysiology of pulmonary hypertension secondary to chronic lung disease and hypoxemia (WHO Group III). There are a variety of factors that contribute to the development of elevated pulmonary arterial pressures in the setting of chronic lung disease, not the least of which is hypoxic vasoconstriction. In patients with disproportionately high pressures, vascular remodeling may play a more prominent role.

Treatment of the pulmonary hypertension caused by chronic lung disease and hypoxemia differs from the other WHO groups. An appreciation of these differences will enable the clinician to appropriately manage this challenging group of patients.

Intended Audience
This activity has been designed for pulmonologists, cardiologists, rheumatologists, internists and primary care physicians, as well as nurses, physician assistants, and other allied health professionals who help care for patients with PH and wish to learn about the management of patients who also have lung disease.

View the corresponding course for this and other topics on PHA Online University to learn more and earn free CME credits.

www.PHAOnlineUniv.org

Accreditation and Credit Designation
College of Medicine, Mayo Clinic, designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of College of Medicine, Mayo Clinic and the Pulmonary Hypertension Association (PHA). College of Medicine, Mayo Clinic is accredited by the ACCME to provide continuing medical education for physicians.

Faculty Disclosures
Charles D. Burger, MD, is a consultant for Actelion Pharmaceuticals, Gilead Sciences, United Therapeutics and receives grant/research support from Gilead Sciences and Actelion Pharmaceuticals.

John E. Moss, MD, indicates no significant financial relationships to disclose.

Robert P. Frantz, MD, indicates no significant financial relationships to disclose.

Disclaimer
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Program Announcement:

New Application Deadline: February 12, 2012
New Application Deadline: June 12, 2012
Resubmission Deadline: March 12, 2012
Resubmission Deadline: July 12, 2012

Pulmonary Hypertension Association (PHA)
National Heart, Lung, and Blood Institute (NHLBI)

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 2011.

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.

FOR MORE INFORMATION:
Visit: www.PHAssociation.org/MedicalProfessionals/Research

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