

Advances in Pulmonary Hypertension

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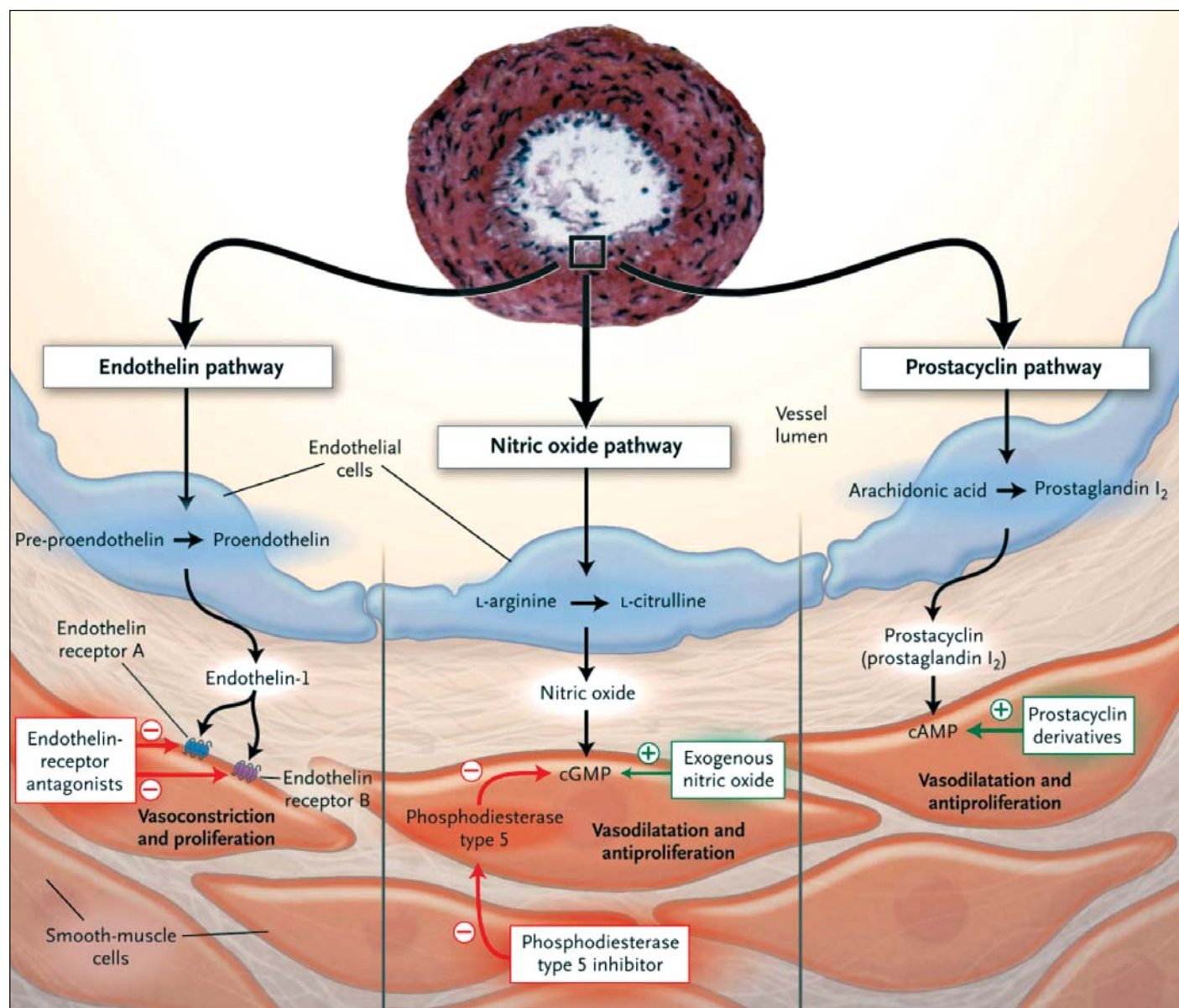
Emerging Therapies

Oral Therapies for PAH: State-of-the-Art and Investigational Approaches
*Michelle A. Beutz, MD,
Todd M. Bull, MD,
David B. Badesch, MD*

Advances in Prostanoid Therapy: New Studies, New Methods of Delivery
Victor F. Tapson, MD

Combination Therapy for PAH: Current Rationale, Future Concepts
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PH Roundtable
Recapping the last 5 years,
Exploring a New Paradigm



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Cover image:

Targets for current or emerging therapies in pulmonary arterial hypertension. Three major pathways involved in abnormal proliferation and contraction of the smooth-muscle cells of the pulmonary artery in patients with pulmonary arterial hypertension are shown. (Reprinted with permission of *New England Journal of Medicine*; Humbert et al. 2004;351:1425-36.)

Editor's Memo

Reflecting on Progress in PH and Appreciating the Contributions of Our Physicians



The theme of this year-end issue is “emergence” as we survey the ever-expanding role of new therapies, from emerging combinations to new orally administered agents to advances in prostanoid treatment. As the acronyms of new trials have worked their way into our lexicon, we have grown accustomed to refer to new studies such as VISION, TRIUMPH, COMPASS, FREEDOM, and PHIRST, and await the latest results that will help guide patient management choices in the future. Emergence is the theme of the contents, but it also applies to the role of physicians on our Editorial Boards as we welcome physicians who have stepped forward to help guide the journal in the years ahead and express appreciation to those who have contributed their time and energy.

Medical journals thrive on an infusion of new ideas reflected in the transition to new editors-in-chief and editorial advisory boards. By passing the torch to a new group of editors we promote an even greater exchange of ideas and keep the level of enthusiasm as high as it can be for producing the most comprehensive source of information on pulmonary hypertension available to practicing physicians. Somewhat like members of Congress but, thankfully, in a completely different arena, we also must observe term limits. In our case we have a self-imposed 2-year limit on the verge of expiring, and I wish to welcome physicians who will help guide this journal through the end of 2008.

I am pleased to welcome a new Editor-in-Chief, Ronald J. Oudiz, MD, beginning with the next issue of *Advances in Pulmonary Hypertension*. Dr Oudiz is an exemplary physician, a distinguished colleague, and a close personal friend who has demonstrated a tremendously strong commitment to the pulmonary hypertension community for many years. In turning over the job of leading the journal, I am confident that he will strive for the same editorial independence, unbiased perspective, and excellence that we have established over the first 5 years of the journal's existence and that characterize our approach to developing scientific content.

Dr Oudiz has already contributed in many ways to the selection of relevant and timely topics and to development of our content. His pivotal role in programs offered by the Pulmonary Hypertension Association (PHA) speaks volumes for the dedication he has shown to medical research, patient advocacy, and quality of care. I wish him well in this new endeavor during 2007 and 2008.

No journal can succeed without a supporting cast of physicians whose experience at the bench and bedside helps to create reference points from which we can select appropriate topics and a context for chronicling the evolution in care. During the last 2 years we have been graced with the contribution of three outstanding clinicians who served as Associate Editors: Ramona Doyle, MD, Karen Fagan, MD, and Olivier Sitbon, MD. We thank them for their service to the journal and helping us in the kind of peer review essential to the journal's integrity.

We are also pleased to welcome back to our Editorial Advisory Board Richard Channick, MD, as an Associate Editor and Editor-in-Chief Elect. His enthusiastic participation in Roundtable discussions over the years has given readers a clear and thoughtful perspective on important clinical issues. Similarly, we welcome

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Advances in Pulmonary Hypertension is committed to help physicians in their clinical decision making by informing them of important trends affecting their practice. Analyzing the impact of new findings and covering current information in the peer-reviewed literature, *Advances in Pulmonary Hypertension* is published four times a year. *Advances in Pulmonary Hypertension* is the official journal of the Pulmonary Hypertension Association.

Each article in this journal has been reviewed and approved by members of the Editorial Advisory Board.

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- Developing and disseminating knowledge for diagnosing and treating pulmonary hypertension
- Advocating for patients with pulmonary hypertension
- Increasing involvement of basic and clinical researchers and practitioners

More information on PHA's Scientific Leadership Council and associated committees can be found at:
www.phassociation.org/SLC/



Profiles in Pulmonary Hypertension

Victor Tapson, MD: Clinical Trialist, Role Model, and Mentor to the Next Generation of PH Specialists



Victor F.
Tapson, MD

If they ever award a patent for passion in pulmonary hypertension research, Victor Tapson, MD, is favored to receive it. But with his characteristic generosity of spirit and keen sense of collegiality he will share it with every physician he meets. Ask any researcher who knows him and he or she will offer similar personal impressions regarding his boundless enthusiasm

and excitement for his work in pulmonary hypertension and thromboembolic disease, work that established him at a relatively early age as a preeminent investigator in each of these fields. A brief chronicle of this physician's career demonstrates how a researcher cultivates an interest in his chosen field of concentration, contributes to the growing knowledge in his field under the mentorship of other specialists, and later assumes the role of mentor for the next generation of researchers.

"Vic's undying passion for pulmonary hypertension is evident in everything he does," said Vallerie V. McLaughlin, Director of the Pulmonary Hypertension Program at the University of Michigan Health System, Ann Arbor, Michigan. "Whether it's patient care, a research trial, a symposium, or the creation of a journal such as *Advances in Pulmonary Hypertension*, Vic's contributions to the field are unsurpassed. He has served as a role model for the next generation of pulmonary hypertension specialists. I am honored to be his colleague and friend."

Dr Tapson is an award-winning Professor of Medicine, Division of Pulmonary and Critical Care Medicine, and Director, Duke Pulmonary Vascular Disease Center, at the Duke University Medical Center, Durham, North Carolina. Beginning with his internship at Duke, the university medical center has largely been the base for his postgraduate training and research activity, with the exception being a fellowship at Boston University before returning to Duke in 1989.

"We didn't have much to offer patients with pulmonary hypertension when I was an intern," he recalls, tracing his interest in pulmonary hypertension to a time

when he was "rounding on the pulmonary service and I saw a patient, a minister from South Carolina with pulmonary hypertension. The patient went up to Hopkins for a lung transplant—one of the first in the world—and that got me interested in PH. When I returned to Duke after my fellowship in Boston, I tried to contact Gary, but he had died of chronic rejection after living a number of years following this pioneering procedure." Fascinated with pulmonary hypertension, Dr Tapson spoke about it during his senior lecture as a third-year resident at Duke; he subsequently played a major role in organizing the lung transplant program at Duke in 1990 where more patients with pulmonary hypertension were among those with end-stage lung disease arriving at the medical center.

The pivotal time in his career, however, was soon to follow when he became associated with Robyn Barst, MD, and Lewis Rubin, MD, in the landmark epoprostenol trial, results of which were published in the *New England Journal of Medicine* in 1996. This trial helped launch a new era in treatment for pulmonary hypertension patients and Dr Tapson considers Dr Rubin as his mentor and professional role model even though he has never worked directly with him. At the same time, Dr Tapson was pursuing his other research interest in thromboembolic disease and treatment of pulmonary embolism, and this has been a focus he remains interested in as he pursues two distinct but parallel paths of investigation. Following in the steps of Dr Rubin, he considers himself an "early second generation clinical trialist," continuing the pivotal work begun by the first group of epoprostenol researchers that included Dr Rubin, Dr Barst, and Stuart Rich, MD.

In the early 1990s while doing lab research on thromboembolism and getting the transplant program under way, he also served as Director of the Duke Pulmonary Outpatient Clinic. Appointed Director of the Duke University Pulmonary Hypertension Center in 1992, he was joined by Abby Krichman, RRT, who "not only helped get the program off the ground, but continues to be a vital force in our center." We started getting tons of referrals, from all over the southeastern United States." Building on this reputation, the Duke center is now widely recognized throughout the country as one of the premier locations for pulmonary hypertension care.

Looking ahead to new horizons, Dr Tapson plans to be part of the next generation of clinical trials during the coming decade and "I would like to continue doing the thromboembolic work. I don't consider myself a true expert in thromboembolic pulmonary hypertension because the San Diego group is light years ahead of most of us."

(continued on page 5)

Advances in Pulmonary Hypertension Author Guidelines 2006

Scope of Manuscripts

Advances in Pulmonary Hypertension considers the following types of manuscripts for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics in a scholarly fashion and format.
- Letters to the Editor
- Clinical Case Studies

Manuscript Submission

Authors are required to submit their manuscripts in an electronic format, preferably by email to the Editor-in-Chief, Vallerie V. McLaughlin, MD, at vmclaugh@med.umich.edu. Please provide manuscripts in a word processing program. Images should be submitted electronically as well.

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Contact information: List all authors, including mailing address, titles and affiliations, phone, fax, and email. Please note corresponding author.

Peer Review and Editing: Manuscripts will be peer reviewed. Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with American Medical Association (AMA) style.

Manuscript Preparation

Length: Full-length manuscripts should not exceed 4,000 words, including references. Please limit the reference list to 50 citations. Manuscripts should be accompanied by figures and/or tables. Generally, 4 to 5 figures and 2 to 3 tables are preferred for each manuscript. Please include a brief description to accompany these items, as well as a key for all abbreviated words.

Spacing: One space after commas and periods. Manuscripts should be double spaced. Manuscripts should not contain an abstract but an introduction is recommended.

References: All submissions should include numbered references that are referred to in the text by superscripts and that conform to AMA style. Example: Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest*. 2001;119:818-823.

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Profile - Victor F. Tapson, MD

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One of the areas he says is particularly deserving of more focus concerns patients with pulmonary hypertension who have some degree of pulmonary fibrosis, COPD, or other diseases "but who do not fit into the current clinical trials." Nevertheless, he adds, some of these patients may benefit from drugs used in these trials. "Some may have a genetic predisposition to PH. They do not have severe enough parenchymal disease

to develop PH but they get it anyway. This group may have a predisposition and their underlying disease or hypoxemia acts as a trigger. We need more data; they outnumber the patients with idiopathic PAH."

Whatever shape or form his research will take, he will bring to it the same passion that has helped produce hundreds of peer-reviewed articles and abstracts in the medical literature, a passion that has also fueled his deep interest in medical publishing and in promoting consensus statements guiding the quality of care in pulmonary hypertension and thromboembolic disease. ■

IN PAH, TAKE AIM AT ET-1 THROUGH ET_A SELECTIVITY

Circulating levels of ET-1, the most potent subtype of ET, have been associated with disease severity in PAH.¹ The deleterious effects of elevated ET-1 include cellular proliferation, vasoconstriction, and vascular remodeling.²⁻⁴

In pulmonary arterial hypertension (PAH), endothelin (ET-1) exerts its cardiovascular effects through 2 receptors: ET_A and ET_B. When ET-1 activates the ET_A receptor on the vascular smooth muscle, it leads to vasoconstriction and vascular remodeling.^{4,5} Endothelial ET_B receptors mediate the release of vasodilating nitric oxide (NO) and prostacyclin (PGI₂), while inhibiting and clearing ET-1 from circulation.^{5,6} Blockade of ET_B receptors may significantly impair the balance of endothelium-derived vasodilating substances.^{4,7}

Endothelial dysfunction has been shown to improve with selective ET_A blockade.⁸ Hence, preemptive targeting of ET-1 through selective ET_A receptor antagonism can slow the progression of PAH, and may even provide better overall outcomes.^{2,4,8}

TARGETED ET-1 TREATMENTS MAY PROVIDE BETTER OUTCOMES

Imbalances in the key endothelial cell-derived mediators NO, PGI₂, and specifically ET-1 are thought to be central to the pathogenesis of PAH.⁹ NO and PGI₂ are potent vasodilators with antiproliferative activity.¹⁰ ET-1 is a potent vasoconstrictor with proliferative activity.⁵ Chronically elevated levels of ET-1 are associated with pulmonary vascular resistance, excessive scar formation and cardiac remodeling, cellular proliferation, and cardiac hypertrophy.^{1,11-13}

A reduction of excess ET-1 levels may result in positive outcomes for patients with PAH. It has been shown that in patients with congestive heart failure, elevated ET-1 plasma

Figure 1: ET_A receptor pathway

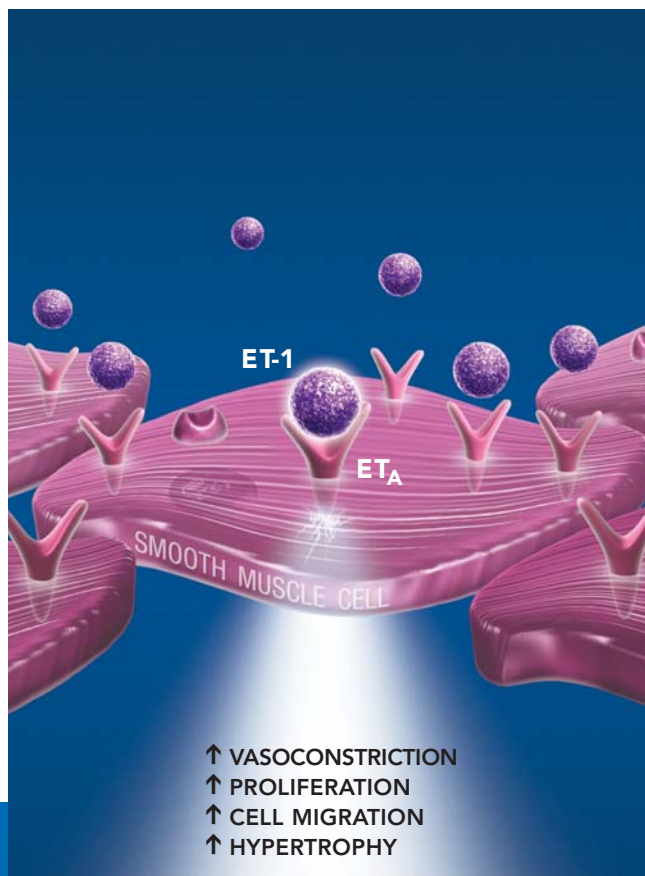
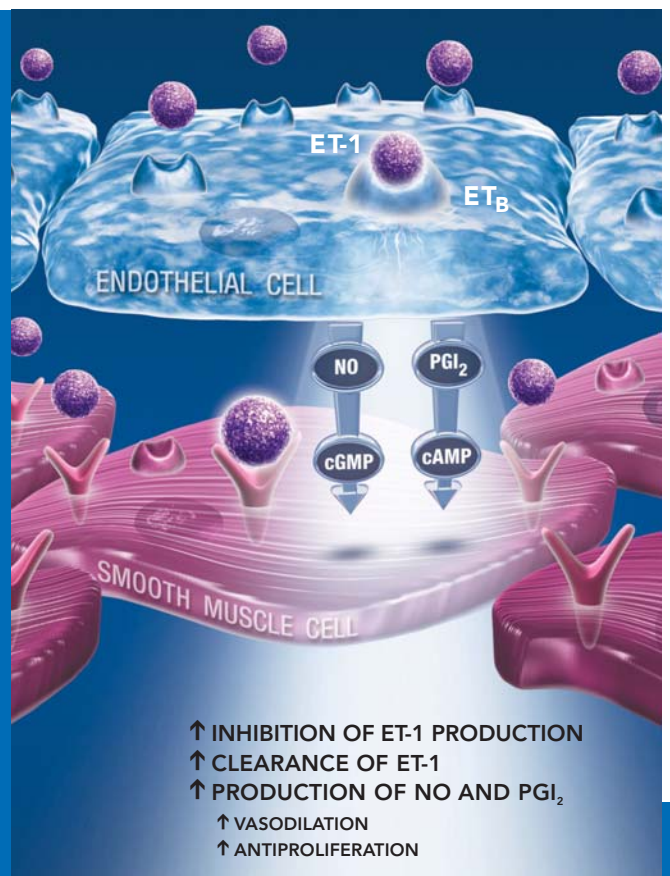


Figure 2: ET_B receptor pathway





levels are at least partly associated with impaired ET_B receptor-mediated clearance.¹³ Furthermore, the long-term administration of a selective ET_B receptor antagonist was found to have unfavorable effects on vascular remodeling.⁴ This is in sharp contrast to the benefits of selective ET_A antagonism.¹⁴

THE DIFFERENCE LIES IN ET_A SELECTIVITY

Vasoconstriction, cellular proliferation, and vascular remodeling are the hallmarks of PAH.¹² Studies have demonstrated that selective ET_A antagonists play a pivotal role in the regulation of ET-1 levels in PAH and have been beneficial for vascular remodeling.^{4,7,13}

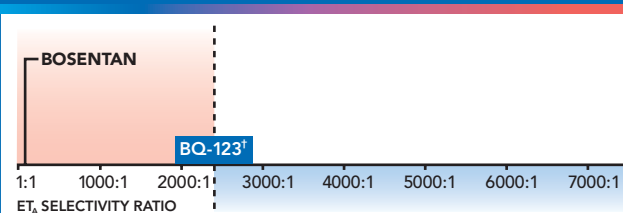
ET-1 AND RECEPTOR-MEDIATED ACTIVITIES

Highly selective ET_A blockade maintains ET-1 clearance, NO and PGI₂ levels, and reduces or maintains circulating ET-1 levels, resulting in vasodilation, increased blood flow, and repair of remodeled vasculature compared to less selective agents.^{5-7,14} (See Figures 1,2)

HOW SELECTIVE TO ET_A SHOULD TREATMENT BE?

The more selective, the better. One should always be aware of the varying degrees of selectivity, as they equate to differences in blockade of the ET_A and ET_B receptors and resulting levels of ET-1.^{8,15,16} Figure 3 illustrates the difference between a less selective agent and highly selective agents. These in vitro selectivity ratios demonstrate the stark differences in ET_A selectivity. Figure 4 depicts how agents with low selectivity of the ET_A receptor (<2400) increase ET-1 levels whereas highly selective ET_A receptor (>2400) antagonists have been shown to

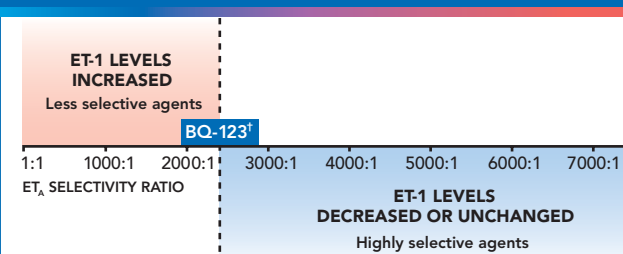
Selectivity to the ET_A receptor^{15,17*}



*Based on in vitro studies.
†BQ-123 is a peptide probe used to measure ET_A selectivity of agents.

Figure 3

Effect of ET_A receptor selectivity on ET-1 levels^{8,15,16}



Note: Studies in patients with cardiovascular disease and healthy volunteers.
†BQ-123 is a peptide probe used to measure ET_A selectivity of agents.

Figure 4

decrease ET-1 levels or leave them unchanged.^{6,8,15} The benefits of ET_A selectivity are being recognized.

TOWARD BETTER OUTCOMES IN PAH

Currently, there are no highly selective ET_A antagonists available for the treatment of PAH. In vivo studies have shown that highly selective ET_A antagonism may lead to better overall outcomes.^{7,8,12}

References: 1. Rubens C, Ewert R, Halank M, et al. Big endothelin-1 and endothelin-1 plasma levels are correlated with the severity of primary pulmonary hypertension. *Chest*. 2001;120:1562-1569. 2. Lüscher TF, Yang Z, Tschudi M, et al. Interaction between endothelin-1 and endothelin-derived relaxing factor in human arteries and veins. *Circ Res*. 1990;66:1088-1094. 3. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature*. 1988;332:411-415. 4. Murakoshi N, Miyauchi T, Kakinuma Y, et al. Vascular endothelin-B receptor system in vivo plays a favorable inhibitory role in vascular remodeling after injury revealed by endothelin-B receptor-knockout mice. *Circulation*. 2002;106:1991-1998. 5. Peacock AJ, Rubin LJ, eds. *Pulmonary Circulation: Diseases and Their Treatment*. 2nd ed. London: Arnold; 2004. 6. Fukuroda T, Fujikawa T, Ozaki S, Ishikawa K, Yano M, Nishikibe M. Clearance of circulating endothelin-1 by ET_B receptors in rats. *Biochem Biophys Res Commun*. 1994;199:1461-1465. 7. Verhaar MC, Strachan FE, Newby DE, et al. Endothelin-A receptor antagonist-mediated vasodilatation is attenuated by inhibition of nitric oxide synthesis and by endothelin-B receptor blockade. *Circulation*. 1998;97:752-756. 8. Halcox JPJ, Nour KRA, Zalos G, Quyyumi AA. Coronary vasodilation and improvement in endothelial dysfunction with endothelin ET_A receptor blockade. *Circ Res*. 2001;89:969-976. 9. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med*. 1993;328:1732-1739. 10. Hankins SR, Horn EM. Current management of patients with pulmonary hypertension and right ventricular insufficiency. *Curr Cardiol Rep*. 2000;2:244-251. 11. Spieker LE, Noll G, Ruschitzka FT, Lüscher TF. Endothelin receptor antagonists in congestive heart failure: a new therapeutic principle for the future? *J Am Coll Cardiol*. 2001;37:1493-1505. 12. Jeffery TK, Wanstall JC. Pulmonary vascular remodeling: a target for therapeutic intervention in pulmonary hypertension. *Pharmacol Ther*. 2001;92:1-20. 13. Lüscher TF, Barton M. Endothelins and endothelin receptor antagonists: therapeutic considerations for a novel class of cardiovascular drugs. *Circulation*. 2000;102:2434-2440. 14. Chen SJ, Chen YF, Oppenorth TJ, et al. The orally active nonpeptide endothelin A-receptor antagonist A-127722 prevents and reverses hypoxia-induced pulmonary hypertension and pulmonary vascular remodeling in Sprague-Dawley rats. *J Cardiovasc Pharmacol*. 1997;29:713-725. 15. Ihara M, Noguchi K, Saeki T, et al. Biological profiles of highly potent novel endothelin antagonists selective for the ET_A receptor. *Life Sci*. 1992;50:247-255. 16. Williamson DJ, Wallman LL, Jones R, et al. Hemodynamic effects of bosentan, an endothelin receptor antagonist, in patients with pulmonary hypertension. *Circulation*. 2000;102:411-418. 17. Clozel M, Breu V, Gray GA, et al. Pharmacological characterization of bosentan, a new potent orally active nonpeptide endothelin receptor antagonist. *J Pharmacol Exp Ther*. 1994;270:228-235.

Fundraise for the Cause!

You do so much for the PH community, from providing vital medical services to offering hope through research. More and more, clinicians, nurses, and their staff are also joining forces with patients and others to raise much-needed **awareness** and **funds** for the cause.

Special events fundraising provides more than 80% of PHA's research budget as well as support for other vital PHA programs and services. There are many ways to get involved, from hosting your own event to supporting those in your community that are planned by others.

Interested?

Consider what other medical professionals have done:



- For six straight years, the **Vera Moulton Wall PH Center at Stanford University** has been organizing its ever-popular Race Against PH 5K Race/Walk fundraiser bringing in

thousands of dollars each year for PH research and the PH community.



- The **UC San Diego PH Clinic** teamed up with local patients and raised over \$35,000 with its first annual Fun Walk, which took place on hospital grounds!



- The **Mayo Clinic PH Clinic** coordinated three major galas. Last year's event, a 50s-themed dinner, raised \$90,000 to support vital PHA services.

- A PH nurse teamed up with her local PHA Support Group leader to organize the **Annual Long Island PH Fun Walk**. The event has already had two successful years raising thousands of dollars.



- With the encouragement of their local PH physician, and in coordination with his medical clinic, support group leaders in **Florida** organized statewide educational conferences with evening fundraising events. In the first year, their jazz-cruise event raised over \$15,000; in the second year a costume ball raised more than \$22,000 dollars.

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START WITH CONFIDENCE™

REVATIO: for patients with PAH as early as class II

Proven effective for patients with Pulmonary Arterial Hypertension (WHO Group I)

- Increased 6-minute walk distance as early as week 4
- Significantly reduced mean pulmonary arterial pressure

In a long-term, uncontrolled extension study

94% of patients were still alive at 1 year

- Walk distance and functional class appeared stable
- Without a control group, these data must be interpreted cautiously

The lowest-priced oral PAH therapy^{1*}

- REVATIO 20-mg tablets tid

REVATIO contains sildenafil citrate, the same active ingredient found in Viagra®

*Actual pharmacy or out-of-pocket costs may vary. Price comparisons do not imply comparable efficacy or safety. The clinical trial for REVATIO included patients who were predominantly functional classes II and III, and the clinical trial for the other oral PAH treatment included patients who were predominantly functional class III.

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability. The efficacy of REVATIO has not been evaluated in patients currently on bosentan therapy.

The use of REVATIO and organic nitrates in any form, at any time, is contraindicated.

Co-administration of REVATIO with potent CYP3A4 inhibitors, eg, ketoconazole, itraconazole, and ritonavir, is not recommended as serum concentrations of sildenafil substantially increase.

Before starting REVATIO, physicians should consider whether 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.

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.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported rarely 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 REVATIO.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events were generally transient and mild to moderate.

Please see brief summary of prescribing information on adjacent page.

Revatio
sildenafil citrate

Start With Confidence™

Reference: 1. Based on wholesale acquisition cost: First DataBank Inc, 2005.

Brief summary of prescribing information

Revatio[®]

sildenafil citrate

INDICATIONS AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability. The efficacy of REVATIO has not been evaluated in patients currently on bosentan therapy.

CONTRAINDICATIONS

Consistent with its known effects on the nitric oxide/cGMP pathway (see **CLINICAL PHARMACOLOGY**), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

REVATIO is contraindicated in patients with a known hypersensitivity to any component of the tablet.

WARNINGS

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A4 inhibitor) substantially increases serum concentrations of sildenafil, therefore co-administration with REVATIO is not recommended (see **Drug Interactions and Dosage and Administration**).

REVATIO has vasodilator properties, resulting in mild and transient decreases in blood pressure (see **PRECAUTIONS**). Prior to prescribing REVATIO, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, for example patients with resting hypotension (BP <90/50), or with fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction.

Pulmonary vasodilators 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 veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

There is no controlled clinical data on the safety or efficacy of REVATIO in the following groups; if prescribed, this should be done with caution:

- 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 with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases);
- Patients currently on bosentan therapy.

PRECAUTIONS

General

Before prescribing REVATIO, it is important to note the following:

- Caution is advised when phosphodiesterase type 5 (PDE5) inhibitors are co-administered 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 (see **Drug Interactions**), cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported. No cases of syncope or fainting were reported during these interaction studies. Consideration should be given to the fact that 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.
- REVATIO should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (such as 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 erections greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of erection could result.
- 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 had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.
- 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%). The incidence of epistaxis was also higher in sildenafil-treated patients with concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist).
- The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration.

Information for Patients

Physicians should discuss with patients the contraindication of REVATIO with regular and/or intermittent use of organic nitrates.

Sildenafil is also marketed as VIAGRA[®] for male erectile dysfunction.

Non-arterial anterior ischemic optic neuropathy (NAION) has been reported rarely post-marketing in temporal association with the use of PDE5 inhibitors when used in the treatment of male-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 REVATIO.

Drug Interactions

In PAH patients, the concomitant use of vitamin K antagonists and sildenafil resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo.

Effects of Other Drugs on REVATIO

In vitro studies: Sildenafil metabolism is principally mediated by the CYP3A4 (major route) and CYP2C9 (minor route) cytochrome P450 isoforms. Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

In vivo studies: Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance and/or an increase of oral bioavailability when co-administered with CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers. These were the only factors with a statistically significant impact on sildenafil pharmacokinetics.

Population data from patients in clinical trials indicated a reduction in sildenafil clearance when it was co-administered with CYP3A4 inhibitors. Sildenafil exposure without concomitant medication is shown to be 5-fold higher at a dose of 80 mg t.i.d. compared to its exposure at a dose of 20 mg t.i.d. This concentration range covers the same increased sildenafil exposure observed in specifically-designed drug interaction studies with CYP3A4 inhibitors (except for potent inhibitors such as ketoconazole, itraconazole, and ritonavir). Cimetidine (800 mg), a nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers. When a single 100 mg dose of sildenafil was co-administered with erythromycin, a CYP3A4 inhibitor, at steady state (500 mg twice daily [b.i.d.] for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In a study performed in healthy volunteers, co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg t.i.d.) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. Stronger CYP3A4 inhibitors will have still greater effects on plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION**).

In another study in healthy volunteers, co-administration with the HIV protease inhibitor ritonavir, a potent CYP3A4 inhibitor, at steady state (500 mg b.i.d.) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates (see **WARNINGS and DOSAGE AND ADMINISTRATION**). Although the interaction between other protease inhibitors and REVATIO has not been studied, their concomitant use is expected to increase sildenafil levels.

In a study of healthy male volunteers, co-administration of sildenafil at steady state (80 mg t.i.d.), with the endothelin receptor antagonist bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of cytochrome P450 2C19) at steady state (125 mg b.i.d.) resulted in a 63% decrease of sildenafil AUC and a 55% decrease in sildenafil C_{max} . The combination of both drugs did not lead to clinically significant changes in blood pressure (supine or standing). Concomitant administration of potent CYP3A4 inducers is expected to cause greater decreases in plasma levels of sildenafil.

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 study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 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 (see **PRECAUTIONS: General**). Concomitant administration of oral contraceptives (ethinyl estradiol 30 µg and levonorgestrel 150 µg) did not affect the pharmacokinetics of sildenafil.

Concomitant administration of a single 100 mg dose of sildenafil with 10 mg of atorvastatin did not alter the pharmacokinetics of either sildenafil or atorvastatin.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of sildenafil.

Effects of REVATIO on Other Drugs

In vitro studies: Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC₅₀ >150 µM).

In vivo studies: When sildenafil 100 mg oral was co-administered with amlodipine, 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.

No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

Sildenafil (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

In healthy subjects, co-administration of 125 mg b.i.d. bosentan and 80 mg t.i.d. sildenafil resulted in a 63% decrease in AUC of sildenafil and a 50% increase in AUC of bosentan.

In a study of healthy volunteers, sildenafil (100 mg) did not affect the steady-state pharmacokinetics of the HIV protease inhibitors saquinavir and ritonavir, both of which are CYP3A4 substrates.

Sildenafil had no impact on the plasma levels of oral contraceptives (ethinyl estradiol 30 µg and levonorgestrel 150 µg).

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 33 and 37 times, for male and female rats, respectively, the human exposure at the Recommended Human Dose (RHD) of 20 mg t.i.d. Sildenafil was not carcinogenic when administered to male and female mice for up to 21 and 18 months, 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 vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocyte and *in vitro* 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 19 and 38 times, for males and females, respectively, the human exposure at the RHD of 20 mg t.i.d.

Pregnancy

Pregnancy Category B. No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in pregnant rats or rabbits, dosed with 200 mg sildenafil/kg/day during organogenesis, a level that is, on a mg/m² basis, 32- and 66-times, respectively, the RHD of 20 mg t.i.d. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m² basis). There are no adequate and well-controlled studies of sildenafil in pregnant women.

Nursing Mothers

It is not known if sildenafil citrate and/or metabolites are excreted in human breast milk. Since many drugs are excreted in human milk, caution should be used when REVATIO is administered to nursing women.

Pediatric Use

Safety and Effectiveness of sildenafil in pediatric pulmonary hypertension patients has not been established.

Geriatric Use

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, but studies did not include sufficient numbers of subjects to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger pulmonary arterial hypertension 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.

ADVERSE REACTIONS

Safety data were obtained from the pivotal study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg t.i.d. were studied.

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dose of 20 mg t.i.d. was low (3%) and the same as placebo (3%). In the pivotal 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 t.i.d.) 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. Sildenafil Adverse Events in ≥3% of Patients and More Frequent Than Placebo

| ADVERSE EVENT % | Placebo (n=70) | Sildenafil 20 mg t.i.d. (n=69) | Placebo Subtracted |
|---------------------|----------------|--------------------------------|--------------------|
| Epistaxis | 1 | 9 | 8 |
| Headache | 39 | 46 | 7 |
| Dyspepsia | 7 | 13 | 6 |
| Flushing | 4 | 10 | 6 |
| Insomnia | 1 | 7 | 6 |
| Erythema | 1 | 6 | 5 |
| Dyspnea exacerbated | 3 | 7 | 4 |
| Rhinitis nos | 0 | 4 | 4 |
| Diarrhea nos | 6 | 9 | 3 |
| Myalgia | 4 | 7 | 3 |
| Pyrexia | 3 | 6 | 3 |
| Gastritis nos | 0 | 3 | 3 |
| Sinusitis | 0 | 3 | 3 |
| Paresthesia | 0 | 3 | 3 |

At doses higher than the recommended 20 mg t.i.d. 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 predominantly color-tinge to vision, but also increased sensitivity to light or blurred vision.

In the pivotal study, the incidence of retinal hemorrhage at the recommended sildenafil 20 mg t.i.d. 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 post-marketing experience with sildenafil citrate at doses indicated for male 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 citrate, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Non-arterial anterior ischemic optic neuropathy (NAION) has been reported rarely post-marketing in temporal association with the use of PDE5 inhibitors when used in the treatment of male-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 REVATIO.

OVERDOSAGE

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

July 2006

Give your patients with pulmonary arterial hypertension NYHA Class II–IV...

Streamlined infusion



The power of continuously infused prostacyclin with:

- No ice packs
- Miniaturized pump options
- 4-hour half-life
- Up to 48 hrs (IV) or 72 hrs (SC) between reservoir changes

REMODULIN® has an expanded indication:

REMODULIN is now the first and only prostacyclin:

"...indicated to diminish the rate of clinical deterioration in patients requiring transition from Flolan®; the risks and benefits of each drug should be carefully considered prior to transition"

- REMODULIN is also indicated as a continuous subcutaneous (SC) infusion or intravenous (IV) infusion (for those not able to tolerate an SC infusion) for the treatment of pulmonary arterial hypertension in patients with New York Heart Association (NYHA) Class II–IV symptoms to diminish symptoms associated with exercise

IMPORTANT SAFETY INFORMATION: REMODULIN is contraindicated in patients with hypersensitivity to REMODULIN, its ingredients, or similar drugs. The most common side effects of REMODULIN included those related to the method of infusion. For subcutaneous infusion, infusion site pain and infusion site reaction (redness and swelling) occurred in the majority of patients. These symptoms were often severe and could lead to treatment with narcotics or discontinuation of REMODULIN. For intravenous infusion, line infections,

sepsis, arm swelling, tingling sensations, bruising, and pain were most common. General side effects (>5% more than placebo) were diarrhea, jaw pain, vasodilation, and edema. REMODULIN is a potent vasodilator. It lowers blood pressure, which may be further lowered by other drugs that also reduce blood pressure. REMODULIN may increase the risk of bleeding, particularly in patients on anticoagulants. Abrupt withdrawal or sudden large reductions in dosage of REMODULIN may result in worsening of PAH symptoms.

For important safety and other information, please see brief summary of full prescribing information on the back of this page.

REMODULIN is a registered trademark of United Therapeutics Corporation.

Flolan is a registered trademark of GlaxoSmithKline.

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**REMODULIN**[®]
(treprostinil sodium) Injection
Prostacyclin Power. Streamlined.

REMODULIN® (treprostinil sodium) Injection

BRIEF SUMMARY

The following is a brief summary of the full prescribing information on Remodulin (treprostinil sodium) Injection. Please review the full prescribing information prior to prescribing Remodulin.

INDICATIONS AND USAGE

Remodulin® is indicated as a continuous subcutaneous infusion or intravenous infusion (for those not able to tolerate a subcutaneous infusion) for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise.

Remodulin is indicated to diminish the rate of clinical deterioration in patients requiring transition from Flolan® risks and benefits of each drug should be carefully considered prior to transition.

DESCRIPTION

Remodulin® (treprostinil sodium) Injection is a sterile sodium salt supplied in 20 mL vials in four strengths, containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, 6.3 mg sodium citrate, and water for injection.

CONTRAINDICATIONS

Remodulin is contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds.

WARNINGS

Remodulin is indicated for subcutaneous or intravenous use only.

PRECAUTIONS

General

Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH. Remodulin is a potent pulmonary and systemic vasodilator. Initiation of Remodulin must be performed in a setting with adequate personnel and equipment to physiological monitoring and emergency care. Therapy with Remodulin may be used for prolonged periods, and the patient's ability to administer Remodulin and care for an infusion system should be carefully considered. Dose should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacologic effects or for unacceptable infusion site symptoms. Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided.

Information for Patients

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous or surgically placed indwelling central venous catheter via an infusion pump. Therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a catheter and to use an infusion pump should be carefully considered. In order to reduce the risk of infection, aseptic technique must be used in the preparation and administration of Remodulin. Additionally, patients should be aware that subsequent disease management may require the initiation of an alternative intravenous prostacyclin therapy Flolan® (epoprostenol sodium).

Drug Interactions

Reduction in blood pressure caused by Remodulin may be exacerbated by drugs that by themselves alter blood pressure, such as diuretics, antihypertensive agents, or vasodilators. Since Remodulin inhibits platelet aggregation, there is also a potential for increased risk of bleeding, particularly among patients maintained on anticoagulants. During clinical trials, Remodulin was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications. Remodulin has not been studied in conjunction with Flolan or Tracleer® (bosentan).

Effect of Other Drugs on Remodulin

In vivo studies: Acetaminophen - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

Effect of Remodulin on Other Drugs

In vitro studies: Remodulin did not significantly affect the plasma protein binding normally observed concentrations of digoxin or warfarin.

In vivo studies: Warfarin - Remodulin does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous Remodulin at an infusion rate of 10 ng/kg/min.

Hepatic and Renal Impairment

Caution should be used in patients with hepatic or renal impairment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. In vitro and in vivo genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

Pregnancy

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostinil sodium during organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the starting human rate of infusion, on a ng/m basis) and about 16 times the average rate achieved in clinical trials, resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human rate of infusion, on a ng/m basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. Because animal reproduction studies are not always predictive of human response, Remodulin should be used during pregnancy only if clearly needed.

Labor and delivery

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

Nursing mothers

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Remodulin is administered to nursing women.

Pediatric use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients. In general, dose selection should be cautious.

Geriatric use

Clinical studies of Remodulin did not include sufficient numbers of patients aged 65

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 decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Patients receiving Remodulin as a subcutaneous infusion reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials with subcutaneous infusion of Remodulin, infusion site pain and reaction were the most common adverse events among those treated with Remodulin. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment. In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported in postmarketing experience.

Percentages of subjects reporting subcutaneous infusion site adverse events:

| | Reaction | | Pain | |
|----------------------------|----------|-----------|---------|-----------|
| | Placebo | Remodulin | Placebo | Remodulin |
| Severe | 1 | 38 | 2 | 39 |
| Requiring narcotics* | NA** | NA** | 1 | 32 |
| Leading to discontinuation | 0 | 3 | 0 | 7 |

*based on prescriptions for narcotics, not actual use

**medications used to treat infusion site pain were not distinguished from those used to treat site reactions

Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea, and these are generally considered to be related to the pharmacologic effects of Remodulin, whether administered subcutaneously or intravenously.

Adverse Events During Chronic Dosing:

The following table lists adverse events that occurred at a rate of at least 3% and were more frequent in patients treated with subcutaneous Remodulin than with placebo in controlled trials in PAH.

Adverse Events in Controlled 12-Week Studies of Patients with PAH, Occurring with at Least 3% Incidence and More Common on Subcutaneous Remodulin than on Placebo.

| Adverse Event | Remodulin (N=236) | Placebo (N=233) |
|------------------------|---------------------|---------------------|
| | Percent of Patients | Percent of Patients |
| Infusion Site Pain | 85 | 27 |
| Infusion Site Reaction | 83 | 27 |
| Headache | 27 | 23 |
| Diarrhea | 25 | 16 |
| Nausea | 22 | 18 |
| Rash | 14 | 11 |
| Jaw Pain | 13 | 5 |
| Vasodilatation | 11 | 5 |
| Dizziness | 9 | 8 |
| Edema | 9 | 3 |
| Pruritus | 8 | 6 |
| Hypotension | 4 | 2 |

Reported adverse events (at least 3%) are included except those too general to be informative, and those not plausibly attributable to the use of the drug, because they were associated with the condition being treated or are very common in the treated population.

Adverse Events Attributable to the Drug Delivery System

In controlled studies of Remodulin administered subcutaneously, there were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 4 Placebo) reported non-serious adverse events resulting from infusion system complications. Adverse events resulting from problems with the delivery systems were typically related to either symptoms of excess Remodulin (e.g., nausea) or return of PAH symptoms (e.g., dyspnea). These events were generally resolved by correcting the delivery system pump or infusion set problem such as replacing the syringe or battery, reprogramming the pump, or straightening a crimped infusion line. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration. There are no controlled clinical studies with Remodulin administered intravenously. Among the subjects (n=38) treated for 12-weeks in an open-label study 2 patients had either line infections or sepsis. Other events potentially related to the mode of infusion include arm swelling, paresthesias, hematoma and pain.

OVERDOSAGE

Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

In controlled clinical trials, seven patients received some level of overdose and in open-label follow-up on treatment seven additional patients received an overdose; these occurrences resulted from accidental bolus administration of Remodulin, errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope). One pediatric patient was accidentally administered 7.5 mg of Remodulin via a central venous catheter. Symptoms included flushing, headache, nausea, vomiting, hypotension and seizure-like activity with loss of consciousness lasting several minutes. The patient subsequently recovered.

DOSE AND ADMINISTRATION

Remodulin® is supplied in 20 mL vials in concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL. Remodulin can be administered as supplied or diluted intravenous infusion with Sterile Water for Injection or 0.9% Sodium Chloride Injection prior to administration.

Initial Dose for Patients New to Prostacyclin Infusion Therapy

Remodulin is administered by continuous infusion. Remodulin is preferably infused subcutaneously but can be administered by a central intravenous line if the subcutaneous route is not tolerated, because of severe site pain or reaction. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated because of systemic effects, the infusion rate should be reduced to 0.625 ng/kg/min.

Dosage Adjustments

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Remodulin (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction). The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first four weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. There is little experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided (see PRECAUTIONS).

Administration

Subcutaneous Infusion

Remodulin is administered subcutaneously by continuous infusion, via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and subcutaneous infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) be adjustable to approximately 0.002 mL/hr, (3) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (4) have delivery accuracy of ±6% or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

For subcutaneous infusion, Remodulin is delivered without further dilution at a calculated Subcutaneous Infusion Rate (mL/hr) based on a patient's Dose (ng/kg/min), Weight (kg), and the Vial Strength (mg/mL) of Remodulin being used. During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. The Subcutaneous Infusion rate is calculated using the following formula:

$$\text{Subcutaneous Infusion Rate (mL/hr)} = \frac{\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 0.00006^*}{\text{Remodulin Vial Strength (mg/mL)}}$$

* Conversion factor of 0.00006 = 60 min/hour x 0.00001 mg/ng

Intravenous Infusion

Remodulin must be diluted with either Sterile Water for Injection or 0.9% Sodium Chloride Injection and is administered intravenously by continuous infusion, via a surgically placed indwelling central venous catheter, using an infusion pump designed for intravenous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (3) have delivery accuracy of ±6% or better of the hourly dose, and (4) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass. Diluted Remodulin has been shown to be stable at ambient temperature for up to 48 hours at concentrations as low as 0.004 mg/mL (4.000 ng/mL). When using an appropriate infusion pump and reservoir, a predetermined intravenous infusion rate should first be selected to allow for a desired infusion period length of up to 48 hours between system changeovers. Typical intravenous infusion system reservoirs have volumes of 50 or 100 mL. With this selected Intravenous Infusion Rate (mL/hr) and the patient's Dose (ng/kg/min) and Weight (kg), the Diluted Intravenous Remodulin Concentration (mg/mL) can be calculated using the following formula:

The Amount of Remodulin Injection needed to make the required Diluted Intravenous Remodulin Concentration for the given reservoir size can then be calculated using the following formula:

$$\text{Step 1 Diluted Intravenous Remodulin Concentration (mg/mL)} = \frac{\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 0.00006}{\text{Intravenous Infusion Rate (mg/mL)}}$$

$$\text{Step 2 Amount of Remodulin Injection (mL)} = \frac{\text{Diluted Intravenous Remodulin Concentration (mg/mL)} \times \text{Total Volume of Diluted Remodulin Solution in Reservoir (mL)}}{\text{Remodulin Vial Strength (mg/mL)}}$$

The calculated amount of Remodulin Injection is then added to the reservoir along with the sufficient volume of diluent (Sterile Water for Injection or 0.9% Sodium Chloride Injection) to achieve the desired total volume in the reservoir.

In patients requiring transition from Flolan:

Transition from Flolan to Remodulin is accomplished by initiating the infusion of Remodulin and increasing it, while simultaneously reducing the dose of intravenous Flolan. The transition to Remodulin should take place in a hospital with constant observation of response (e.g., walk distance and signs and symptoms of disease progression). During the transition, Remodulin is initiated at a recommended dose of 10% of the current Flolan dose, and then escalated as the Flolan dose is decreased (see table below for recommended dose titrations).

Patients are individually titrated to a dose that allows transition from Flolan therapy to Remodulin while balancing prostacyclin-limiting adverse events. Increases in the patient's symptoms of PAH should be first treated with increases in the dose of Remodulin. Side effects normally associated with prostacyclin and prostacyclin analogs are to be first treated by decreasing the dose of Flolan.

Recommended Transition Dose Changes

| Step | Flolan Dose | Remodulin Dose |
|------|--------------------------|---|
| 1 | Unchanged | 10% Starting Flolan Dose |
| 2 | 80% Starting Flolan Dose | 30% Starting Flolan Dose |
| 3 | 60% Starting Flolan Dose | 50% Starting Flolan Dose |
| 4 | 40% Starting Flolan Dose | 70% Starting Flolan Dose |
| 5 | 20% Starting Flolan Dose | 90% Starting Flolan Dose |
| 6 | 5% Starting Flolan Dose | 110% Starting Flolan Dose |
| 7 | 0 | 110% Starting Flolan Dose + additional 5-10% increments as needed |

HOW SUPPLIED

Remodulin® is supplied in 20 mL multi-use vials at concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL treprostinil, as sterile solutions in water for injection, individually packaged in a carton. Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25°C (59 to 77°F). Store at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. Diluted Remodulin Solution can be administered up to 48 hours at 37°C when diluted to concentrations as low as 0.004 mg/mL in Sterile Water for Injection or 0.9% Sodium Chloride Injection. A single vial of Remodulin should be used for no more than 30 days after the initial introduction into the vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, Remodulin should not be administered.

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Oral Therapies for PAH: State-of-the-Art and Investigational Approaches



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The development of intravenous epoprostenol was an exciting advance in treating pulmonary arterial hypertension, offering patients improved functional capacity and prolonged survival. However, this form of therapy is complicated, requiring an indwelling central venous catheter, with attendant risks of infection, thrombosis, and dislodgement. The desire to simplify therapy and improve safety has led to a variety of oral agents, generally classified as endothelin receptor antagonists and phosphodiesterase inhibitors. An oral prostanoid is also under development.

Pulmonary arterial hypertension is often difficult to diagnose and challenging to treat. Untreated, it is characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular dysfunction, impairment in activity tolerance, and death. Pulmonary arterial hypertension is defined as a mean pulmonary artery pressure greater than 25 mmHg with a pulmonary capillary wedge pressure under 15 mmHg measured by cardiac catheterization.¹ It may occur in the setting of a variety of underlying medical conditions, such as connective tissue disease or congenital heart disease, or as a vascular disease that primarily affects the pulmonary circulation.

Significant advances in the treatment of pulmonary arterial hypertension have occurred over the past 15 years. The first therapy approved by the Food and Drug Administration (FDA) was chronic intravenous epoprostenol (Flolan). This therapy was shown in randomized and controlled trials to improve exercise capacity in patients with primary or idiopathic disease (IPAH)² and of pulmonary arterial hypertension occurring in association with scleroderma.³ It has since been shown to improve longer-term outcomes^{4,5} and remains a very important part of our therapeutic armamentarium.⁶ However, because of its complexity and risks associated with the requisite indwelling central venous catheter, clinical investigators have sought simpler methods for the administration of prostanoid therapy. Such options now include chronic subcutaneously administered treprostinil (Remodulin)⁷ and inhaled iloprost (Ventavis),^{8,9} both of which are approved by the FDA. Prostanoids have also been developed for oral use, but are not yet approved by the FDA. Oral beraprost was studied, but did not appear to demon-

strate sustained clinical benefit.¹⁰ Another oral prostanoid is currently in clinical trials. The desire for simpler therapies has led to the development of two FDA-approved oral therapies, an endothelin receptor antagonist and a phosphodiesterase inhibitor, and the study of at least two other oral agents.

This article will address these oral therapies and their place in current treatment. The American College of Chest Physicians (ACCP) convened a multidisciplinary panel of experts in 2003-2004 to develop guidelines for the approach to management of pulmonary arterial hypertension patients. These evidence-based guidelines, including a comprehensive overview of treatment, were published as a supplement to *Chest* in 2004.¹¹ The guidelines are currently being updated to incorporate advances that have occurred since that publication.

Vasoreactivity and Use of Calcium Channel Antagonists

Although calcium channel blockers were among the earliest forms of therapy utilized in IPAH, it is now recognized that only a small proportion of patients do well with this form of therapy. This subgroup of patients often demonstrates a favorable response to acute vasodilator testing at the time of cardiac catheterization. Although it was initially thought that perhaps 20% to 25% of patients with IPAH demonstrated acute pulmonary vasoreactivity and a subsequent longer-term response to calcium channel blockers, it has more recently been shown by Sitbon and colleagues in a retrospective analysis of 557 IPAH patients tested acutely with intravenous epoprostenol or inhaled nitric oxide¹² that only 12.6% displayed vasoreactivity as defined by a greater than 20% decrease in both mean pulmonary artery pressure (PAPm) and pulmonary vascular resistance. Furthermore, of the 70 patients who displayed acute vasoreactivity, only 38 (6.8% of the overall study group) had a favorable long-term clinical response to chronic calcium channel blocker therapy. These patients reached a PAPm of 33 ± 8 mmHg with acute vasodilator testing.

As a result, the consensus definition of a favorable response has been revised to require a fall in PAPm of 10 mmHg or more, to a PAPm of 40 mmHg or less, with

unchanged or increased cardiac output. True responders to calcium channel blockers are relatively rare among patients with other forms of pulmonary arterial hypertension. In general, long-acting preparations of nifedipine or diltiazem, or amlodipine are suggested, and because of potential negative inotropic effects, verapamil should probably be avoided. Patients should be followed closely for safety and efficacy, and alternative therapy considered if the patient fails to improve.

Endothelin Receptor Antagonists

Endothelin receptor antagonism is a promising therapeutic approach supported by evidence of the pathogenic role of endothelin-1 in pulmonary arterial hypertension.^{11,13} Endothelin-1 is a vasoconstrictor and a smooth muscle mitogen that might contribute to the development of pulmonary arterial hypertension.¹⁴ In addition, endothelin-1 expression, production, and concentration in plasma^{15,16} and lung tissue¹⁷ are elevated in pulmonary arterial hypertension, and these levels are correlated with disease severity.¹⁷ Two distinct endothelin receptor isoforms, ET_A and ET_B, have been identified.¹⁸ There is controversy as to whether it is preferable to block both the ET_A and ET_B receptors or to target the ET_A receptor.

Bosentan

Bosentan (Tracleer) is a relatively nonselective antagonist of both the ET_A and ET_B receptors that is currently approved by the FDA for patients with WHO functional class III-IV disease. The first small, randomized, double-blind, placebo-controlled, multicenter study of bosentan demonstrated improvement in the distance walked in 6 minutes of 70 m (from 360 ± 19 m at baseline to 430 ± 14 m at week 12; $P < .05$), whereas none was seen with placebo (355 ± 25 m at baseline and 349 ± 44 m at week 12).¹⁹ Bosentan also improved cardiopulmonary hemodynamics and functional class. It was associated with asymptomatic increases in hepatic aminotransferases in two patients. In a second larger, double-blind, placebo-controlled study (the BREATHE-1 study), bosentan (125 or 250 mg bid) was evaluated in 213 patients with either IPAH or pulmonary arterial hypertension associated with connective tissue disease for a minimum of 16 weeks (62.5 mg bid for 4 weeks followed by up-titration to the target dose).²⁰ The distance walked in 6 minutes improved by 36 m whereas deterioration (-8 m) was seen with placebo. The difference between groups in the mean change in the 6-minute walking distance was 44 m in favor of bosentan (95% CI: 21 to 67 m, $P = .0002$). The risk of clinical worsening was reduced by bosentan compared with placebo ($P = .0015$, with the log-rank test). Abnormal hepatic function tests, syncope, and flushing occurred more often in the bosentan group. Longer-term outcomes with bosentan therapy have been more recently published. McLaughlin et al²¹ reported that first-line therapy with bosentan, with the subsequent addition or transition to other therapy as needed, resulted in Kaplan-Meier survival estimates of 96% at 12 months and 89% at 24 months. At the end of 12 and 24 months, 85% and 70% of patients, respectively, remained alive and receiving bosentan

monotherapy. Sitbon et al²² compared survival in functional class III IPAH treated with bosentan with historical data from similar patients treated with epoprostenol. Baseline characteristics for the 139 patients treated with bosentan and the 346 treated with epoprostenol suggested that the epoprostenol cohort had more severe disease. Kaplan-Meier survival estimates after 1 and 2 years were 97% and 91%, respectively, in the bosentan-treated cohort and 91% and 84% in the epoprostenol cohort.

Bosentan has more recently been studied in other patient populations or subgroups. In a retrospective study of 86 children with IPAH and pulmonary arterial hypertension associated with congenital heart disease or connective tissue disease,²³ bosentan was used with or without concomitant intravenous epoprostenol or subcutaneous treprostinil therapy. At the time of cutoff, 68 patients (79%) were still treated with bosentan, 13 (15%) were discontinued, and 5 (6%) had died. Median bosentan exposure was 14 months. In 90% of the patients ($n = 78$), functional class improved (46%) or was unchanged (44%) with bosentan treatment. PAPm and pulmonary vascular resistance decreased, and Kaplan-Meier survival estimates at one and two years were 98% and 91%, respectively. Galie et al reported the results of a multicenter, double-blind, randomized, and placebo-controlled study of bosentan therapy in patients with functional class III Eisenmenger syndrome (the BREATHE-5 study).²⁴ Fifty-four patients were randomized 2:1 to receive bosentan or placebo for 16 weeks. Bosentan did not worsen oxygen saturation. Compared with placebo, bosentan reduced pulmonary vascular resistance index, decreased PAPm, and increased exercise capacity. Four patients discontinued because of adverse events, 2 (5%) in the bosentan group and 2 (12%) in the placebo group.

Bosentan is currently used relatively widely in the treatment of patients with pulmonary arterial hypertension. Close follow-up over time of both efficacy and safety are encouraged. The FDA mandates that liver function tests be checked monthly, and that the hematocrit should be checked every 3 months. In addition to potential hepatotoxicity, other side effects may include anemia and the development of fluid retention/edema. Hormonal methods of birth control may be less effective with concurrent administration of bosentan, and barrier techniques should be considered.

Sitaxsentan

Sitaxsentan is a more selective antagonist of the ET_A receptor, and is currently an investigational agent. In a randomized, double-blind, placebo-controlled trial (the STRIDE-1 study), 178 NYHA functional class II, III, and IV patients with IPAH, pulmonary arterial hypertension related to connective tissue disease, or pulmonary arterial hypertension related to congenital systemic to pulmonary shunts, sitaxsentan improved exercise capacity and functional class after 12 weeks of treatment.²⁵ The treatment effects in the sitaxsentan groups were 35 meters ($P < .01$) for the 100 mg dose and 33 meters ($P < .01$) for the 300 mg dose. Functional class and hemodynamics also improved. The incidence of liver function abnormalities was more favorable for the 100 mg dose. The most frequently reported adverse

Program Announcement:

Submission Deadlines: February 1, 2007 June 1, 2007 October 1, 2008

Pulmonary Hypertension
Association (PHA)



National Heart, Lung, and
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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 2007.

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

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.

Congratulations to the 2006 awardee:

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Massachusetts General Hospital, MA

Project Title:

**The Role of the BMP Type II Receptor in
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events with sitaxsentan treatment were headache, peripheral edema, nausea, nasal congestion, and dizziness, and the most frequent laboratory adverse event was increased international normalized ratio or prothrombin time related to the effect of sitaxsentan on inhibition of CYP2C9 P450 enzyme, the principal hepatic enzyme involved in the metabolism of warfarin. A second double-blind, placebo-controlled trial with sitaxsentan (the STRIDE-2 study)²⁶ randomized 247 patients (245 were treated) with IPAH, or pulmonary arterial hypertension associated with connective tissue disease or congenital heart disease: placebo (n = 62), sitaxsentan 50 mg (n = 62) or 100 mg (n = 61), or open-label (6-minute walk tests, Borg dyspnea scores, and WHO functional class assessments were third-party blind) bosentan (n = 60). At week 18, patients treated with sitaxsentan 100 mg had an increased 6-minute walk distance compared with the placebo group (31.4 m, $P = .03$), and improved functional class ($P = .04$). The placebo-subtracted treatment effect for sitaxsentan 50 mg was 24.2 m ($P = .07$) and for open-label

bosentan, 29.5 m ($P = .05$). The incidence of elevated hepatic transaminases (more than three times the upper limit of normal) was 6% for placebo, 5% for sitaxsentan 50 mg, 3% for sitaxsentan 100 mg, and 11% for bosentan.

Ambrisentan

Ambrisentan, also currently an investigational agent, is a relatively selective antagonist of the ET_A receptor. A phase-2 dose-ranging study examined the efficacy and safety of four doses of ambrisentan in patients with pulmonary arterial hypertension.²⁷ In this double-blind study, 64 patients with IPAH or pulmonary arterial hypertension associated with connective tissue disease, anorexigen use, or human immunodeficiency virus infection were randomized to receive 1, 2.5, 5, or 10 mg of ambrisentan once daily for 12 weeks. Ambrisentan increased 6-minute walk distance (+36.1 m, $P < .0001$) with similar increases for each dose group (range, +33.9 to +38.1 m). Improvements were also seen in Borg dyspnea index, WHO functional class, subject

global assessment, PAPm, and cardiac index. Adverse events were generally mild and unrelated to dose, including the incidence of elevated serum aminotransferase concentrations greater than three times the upper limit of normal (3.1%). Two phase-3 clinical trials of ambrisentan in patients with pulmonary arterial hypertension have been completed, and publication of the results is pending.

Phosphodiesterase Inhibitors

Sildenafil

The vasodilatory effects of nitric oxide are dependent on its ability to augment and sustain cGMP content in vascular smooth muscle. Nitric oxide activates soluble guanylate cyclase, which increases cGMP production. Cyclic GMP then causes vasorelaxation, but its effects are short-lived because of the rapid degradation of cGMP by phosphodiesterases.^{28,29} Phosphodiesterases (PDE) are enzymes that hydrolyze cAMP and cGMP, limiting their intracellular signaling properties. Sildenafil is a specific PDE5 inhibitor, previously approved for the treatment of erectile dysfunction, and now approved for the treatment of pulmonary arterial hypertension. Several reports of pulmonary arterial hypertension patients treated with long-term sildenafil suggested therapeutic promise for the drug.³⁰⁻³² The SUPER-1 study was a randomized, double-blind, placebo-controlled clinical trial that assigned 278 patients with symptomatic disease (IPAH or pulmonary arterial hypertension associated with connective-tissue disease or with repaired congenital systemic-to-pulmonary shunts) to placebo or sildenafil (20, 40, or 80 mg) orally three times daily for 12 weeks.³³ The 6-minute walk distance increased from baseline in all sildenafil groups; the mean placebo-corrected treatment effects were 45 m (+13.0%), 46 m (+13.3%), and 50 m (+14.7%) for 20, 40, and 80 mg doses of sildenafil, respectively ($P < .001$ for all comparisons). All sildenafil doses reduced the PAPm, improved functional class, and were associated with side effects such as flushing, dyspepsia, and diarrhea. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil and those treated with placebo. Long-term data (available only at a dose of 80 mg three times daily) in 222 patients completing one year of treatment with sildenafil monotherapy showed improvement from baseline at one year in the 6-minute walk distance (51 m). The FDA-approved dose of sildenafil in patients with pulmonary arterial hypertension is 20 mg administered orally three times daily.

Tadalafil

Another, longer-acting, phosphodiesterase inhibitor is currently undergoing clinical study. It is approved by the FDA for use in patients with erectile dysfunction, but remains investigational in patients with pulmonary arterial hypertension.

Oral Prostanoids

Beraprost

Beraprost is orally active prostacyclin analogue³⁴ that has undergone two randomized, double-blind, placebo-controlled trials in pulmonary arterial hypertension. The first study was a 12-week double blind, randomized, placebo-

controlled trial performed in 130 functional class II and III patients with disease of various etiologies (IPAH, pulmonary arterial hypertension associated with connective tissue diseases, congenital systemic-to-pulmonary shunts, portal hypertension, or HIV infection).³⁵ At a median dose of 80 µg administered orally four times a day, beraprost increased exercise capacity as assessed by the 6-minute walk test. There were no significant changes in hemodynamics or survival. Side effects were frequent, mainly in the initial titration period, suggesting that tolerance may affect the long-term results with beraprost. A second trial evaluated the effects of beraprost in 116 NYHA functional class II and III patients. It was a 12-month double-blind, randomized, placebo-controlled study.³⁶ Beraprost-treated patients had less disease progression at 6 months, and improved 6-minute walk distance at 3 months (+22 m from baseline) and 6 months (+31 m), as compared with placebo. However, this improvement was no longer present at 9 or 12 months. There were no significant changes in hemodynamics at month 12 as compared to baseline. Survival was similar for the treatment groups. Beraprost has previously been approved for pulmonary arterial hypertension in Japan, but is not approved by the FDA.

Another oral prostanoid is currently under study in pulmonary arterial hypertension.

Conclusion

Therapy for pulmonary arterial hypertension has advanced considerably over the last 10 to 15 years, and oral therapies are now available. While it is relatively straightforward to describe the various agents available, as well as the evidence supporting their safety and efficacy, it is far more difficult to create a therapeutic algorithm that guides the provider in choosing the most appropriate therapy for an individual patient. The task of developing such an algorithm generally falls to guidelines or consensus panels of experts in the field, and their challenge is enhanced by the paucity of truly comparative data. Furthermore, the data currently available pertaining to add-on or combination therapy is limited. An update to the previously published ACCP guidelines¹¹ is anticipated in the near future, as is a consensus statement from another professional society. Therapy should obviously be individualized, taking into account the patient's specific clinical situation. It continues to be strongly recommended that patients be referred to centers of excellence, and that long-term care be shared with the referring physician. Close follow-up, with frequent objective assessment of clinical status and therapeutic response, are essential to optimal long-term outcomes. ■

References

1. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126:14S-34S.
2. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med*. 1996;334:296-302
3. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spec-

- trum of disease. A randomized, controlled trial. *Ann Intern Med.* 2000; 132:425-434.
4. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation.* 2002; 106: 1477-1482.
 5. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol.* 2002;40:780-788.
 6. Badesch DB, McLaughlin VV, Delcroix M, et al. Prostanoid therapy for pulmonary arterial hypertension. *J Am Coll Cardiol.* 2004;43:56S-61S.
 7. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med.* 2002;165:800-804.
 8. Olschewski H, Ghofrani HA, Schmehl T, et al. Inhaled iloprost to treat severe pulmonary hypertension. An uncontrolled trial. German PPH Study Group. *Ann Intern Med.* 2000;132:435-443.
 9. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med.* 2002;347:322-329.
 10. Barst RJ, McGoon M, McLaughlin V, et al. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol.* 2003;41:2119-2125.
 11. Badesch DB, Abman SH, Ahearn GS, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126:35S-62S.
 12. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation.* 2005;111:3105-3111.
 13. MacLean MR. Endothelin-1: a mediator of pulmonary hypertension? *Pulm Pharmacol Ther.* 1998;11:125-132.
 14. Kim H, Yung GL, Marsh JJ, et al. Endothelin mediates pulmonary vascular remodelling in a canine model of chronic embolic pulmonary hypertension. *Eur Respir J.* 2000;15:640-648.
 15. Galie N, Grigioni F, Bacchi-Reggiani L, et al. Relation of endothelin-1 to survival in patients with primary pulmonary hypertension. *Eur J Clin Invest.* 1996;26:273.
 16. Yamane K. Endothelin and collagen vascular disease: a review with special reference to Raynaud's phenomenon and systemic sclerosis. *Intern Med.* 1994;33:579-582.
 17. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med.* 1993;328:1732-1739.
 18. Benigni A, Remuzzi G. Endothelin antagonists. *Lancet.* 1999; 353:133-138.
 19. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet.* 2001; 358:1119-1123.
 20. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med.* 2002;346:896-903.
 21. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J.* 2005;25:244-249.
 22. Sitbon O, McLaughlin VV, Badesch DB, et al. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. *Thorax.* 2005;60:1025-1030.
 23. Rosenzweig EB, Ivy DD, Widlitz A, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. *J Am Coll Cardiol.* 2005;46:697-704.
 24. Galie N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation.* 2006;114:48-54.
 25. Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2004;169: 441-447.
 26. Barst RJ, Langleben D, Badesch D, et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol.* 2006;47:2049-2056.
 27. Galie N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol.* 2005;46:529-535.
 28. Beavo JA, Reifsnnyder DH. Primary sequence of cyclic nucleotide phosphodiesterase isozymes and the design of selective inhibitors. *Trends Pharmacol Sci.* 1990;11:150-155.
 29. Ahn H, Foster M, Cable M, et al. Ca/CaM-stimulated and cGMP-specific phosphodiesterases in vascular and non-vascular tissues. *Adv Exp Med Biol.* 1991;308:191-197.
 30. Ghofrani HA, Wiedemann R, Rose F, et al. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med.* 2002;136:515-522.
 31. Bharani A, Mathew V, Sahu A, et al. The efficacy and tolerability of sildenafil in patients with moderate-to-severe pulmonary hypertension. *Indian Heart J.* 2003;55:55-59.
 32. Sastry BK, Narasimhan C, Reddy NK, et al. A study of clinical efficacy of sildenafil in patients with primary pulmonary hypertension. *Indian Heart J.* 2002;54:410-414.
 33. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med.* 2005;353:2148-2157.
 34. Okano Y, Yoshioka T, Shimouchi A, et al. Orally active prostacyclin analogue in primary pulmonary hypertension. *Lancet.* 1997;349: 1365.
 35. Galie N, Humbert M, Vachiery JL, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol.* 2002;39:1496-1502.
 36. Barst RJ, McGoon M, McLaughlin V, et al. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol.* 2003; in press.

Combination Therapy for PAH: Current Rationale, Future Concepts



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The prostanoids have revolutionized treatment of pulmonary arterial hypertension. Intravenous, subcutaneous, and inhaled formulations are approved for use in the United States, while oral preparations are being investigated (**Table**). Prostacyclin (PGI₂; epoprostenol; Flolan) is an endothelium-derived prostaglandin with potent pulmonary and systemic vasodilatory and antiplatelet aggregation properties.¹⁻⁶ Continuous intravenous epoprostenol has been widely used in patients with advanced idiopathic pulmonary arterial hypertension (IPAH), resulting in substantial clinical benefit and improvement in survival.¹⁻³ Favorable observations have also been made in other forms of pulmonary arterial hypertension,⁴⁻⁶ although survival benefit in these diseases has not been clearly confirmed.⁶ Despite the clear benefits, treatment with continuous intravenous epoprostenol has drawbacks. Because of its very short half-life (1 to 2 minutes), epoprostenol must be administered as a continuous infusion through a dedicated central venous catheter. Although life-threatening adverse effects of this drug and delivery system are rare, complications such as catheter-related thrombosis or infection, sepsis, and pump or intravenous-line malfunctions or mishaps can occur. Sudden discontinuation may cause severe symptoms and even death. In view of these issues, other modes of prostacyclin delivery have now been studied using stable prostacyclin analogues administered orally, by inhalation, or via the subcutaneous route.^{7,8} The oral prostacyclin, beraprost, approved in Japan, is covered by Dr Badesch⁹ in this issue. We will briefly review the initial clinical trials and then more recent data involving subcutaneous and intravenous treprostinil (Remodulin, previously UT-15), and then focus on newer data involving intravenous treprostinil. Subsequently, we will provide an update on inhaled prostanoids. Although the clinical trials for oral treprostinil are only now getting under way, we will offer the background and rationale for these studies.

Treprostinil: Background

Treprostinil sodium is a stable tricyclic benzidine analog of epoprostenol (prostacyclin) that is currently available in subcutaneous and intravenous formulations for the treatment of pulmonary arterial hypertension (inhaled and oral treprostinil are

under investigation). This drug has pharmacologic actions similar to those of epoprostenol and it has been shown to have comparable acute hemodynamic effects.⁸ Unlike epoprostenol, however, it is chemically stable at room temperature and neutral pH and has a longer half-life, permitting continuous subcutaneous administration in addition to the more recently studied and approved intravenous route.^{10,11} The elimination half-life at steady state has been shown to be 4.4 hours for intravenous and 4.6 hours for subcutaneous treprostinil and the pharmacokinetics of this drug have been reviewed extensively.¹⁰⁻¹² Its major pharmacological actions are direct vasodilation of the pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.^{13,14} Treprostinil is metabolized extensively by the liver, and the majority of the metabolites are excreted in the urine with 4% excreted unchanged. Treprostinil has not been studied in patients with renal insufficiency. Treprostinil is rated category B for pregnancy, with no human data available. It is unknown if the compound is excreted in breast milk. No long-term data are available on the carcinogenic or mutagenic potential of treprostinil. There has been no proven change in the binding, concentration, or pharmacokinetics of digoxin or warfarin.¹⁵ Adverse effects of subcutaneous or intravenous treprostinil are similar to those commonly associated with other prostanoids^{1,6,9} and include headache, diarrhea, flushing, and jaw and foot or leg pain, as well as infusion site pain with subcutaneous delivery. As with epoprostenol, rapid up-titration may cause hypotension, flushing, nausea, vomiting, diarrhea, dizziness, and anxiety or restlessness.

Subcutaneous Treprostinil

The drug was first studied in large clinical trials via the subcutaneous route. It is initiated at approximately 1 to 2 ng/kg/min. The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first 4 weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of the infusion, depending on clinical response as tolerated.¹⁶⁻¹⁷ While early studies¹⁸ have suggested that low doses of subcutaneous treprostinil are effective, longer-term subcutaneous studies have utilized higher dosages (approximately 40 ng/kg/min)¹⁹ and intravenous studies suggest that much higher dosages (80 to

120 ng/kg/min) may be required.^{20,21} An international 12-week double-blind placebo-controlled multicenter trial of 470 patients with pulmonary arterial hypertension was completed in 1999, clearly proving the efficacy of the drug and leading to FDA approval in May 2002 for patients with New York Heart Association (NYHA) functional class II-IV pulmonary arterial hypertension.¹⁸ Importantly, infusion-site pain occurred in 85% of patients, was deemed severe in 38%, and led to discontinuation in about 8%. Subsequently, the subset of 90 patients with connective tissue disease from the above randomized multicenter trial was examined and, on the basis of hemodynamic and symptomatic improvement, continuous subcutaneous treprostinil appeared beneficial in this specific population of patients with pulmonary arterial hypertension.²²

The modest improvement (16 meters on 6-minute walk testing) noted in the pivotal subcutaneous treprostinil trial¹⁸ as opposed to improvement (47 and 99 meters in IPAH and scleroderma patients, respectively) noted in epoprostenol trials may be related to functional class since those patients with more severe disease tend to achieve the greatest benefit.^{16,18} Underdosing may be a critical factor in the modest clinical response that was obtained. Additional studies have suggested that stable patients receiving continuous intravenous epoprostenol could be effectively transitioned to subcutaneous treprostinil,²³ potentially solving recurrent difficulties with intravenous line infections or other access-related problems, and facilitating delivery in view of the smaller pump and simpler delivery system. Current clinical use of subcutaneous treprostinil includes de novo initiation (initial therapy), addition to an existing nonprostanoid regimen, and conversion from intravenous epoprostenol.

The primary problem in clinical practice has been pain at the subcutaneous site of delivery, sometimes requiring analgesia or discontinuation of the drug. Less frequent needle site changes may help. However, a recent retrospective multicenter European trial with long-term follow-up has suggested both efficacy and excellent tolerance with sustained use of subcutaneous treprostinil.¹⁹ Ninety-nine patients with pulmonary arterial hypertension and 23 patients with inoperable chronic thromboembolic pulmonary hypertension in NYHA functional class II-IV were followed for a mean of 26.2 ± 17.2 months (range, 3 to 57 months). At 3 years significant improvements from baseline were observed in mean 6-minute walk distance (305 ± 11 to 445 ± 12 meters; *P* = .0001), Borg dyspnea score, and NYHA functional class; the mean dosage was 40 ± 2.6 ng/kg/min (range, 16 to 84 ng/kg/min). The drug was well tolerated, and local pain at the subcutaneous site accounted for treatment interruption in only 5% of the cases. Survival was 88.6% and 70.6% at 1 year and 3 years, respectively. While the study reinforces the earlier pivotal trial data,¹⁸ it is limited by its retrospective, open-label design.

Intravenous Treprostinil

In view of difficulty with site pain with subcutaneous treprostinil in some patients, the use of continuously infused intravenous treprostinil has been prospectively evaluated. The pharmacokinetics for the intravenous route have been discussed above. Intravenous treprostinil must be diluted in

Table. Prostanoid Regimens for Pulmonary Arterial Hypertension*

| Drug | | |
|---------------------------|------------|-----------------------------|
| Generic name | Brand name | Route |
| Epoprostenol | Flolan | Intravenous |
| Treprostinil [†] | Remodulin | Intravenous Subcutaneous |
| Iloprost | Ventavis | Inhaled Intravenous |
| Beraprost | | Oral |

*All regimens are Food and Drug Administration-approved in the United States except for intravenous iloprost and oral beraprost.

[†]Treprostinil is currently under investigation in international trials via the inhaled and oral routes.

sterile water or normal saline prior to infusion and is stable for 48 hours at room temperature; ice packs are not required as with epoprostenol. Gombert-Maitland and colleagues²⁰ evaluated the safety and efficacy of transitioning pulmonary arterial hypertension patients from intravenous epoprostenol to intravenous treprostinil over a 24-to-48-hour period. The intravenous treprostinil dose was adjusted to minimize pulmonary hypertension symptoms as well as side effects. Of the 31 patients, 27 completed the protocol, with 4 requiring transitioning back to epoprostenol. The 6-minute walk distance, Naughton-Balke treadmill test time, functional class, and Borg score were all maintained with intravenous treprostinil at week 12 compared with intravenous epoprostenol prior to transition. At week 12, mean pulmonary artery pressure increased by 4 ± 1 mmHg (*n* = 27; *P* < .01), cardiac index decreased by 0.4 ± 0.1 L/m² (*n* = 27; *P* = .01), and pulmonary vascular resistance increased by 3 ± 1 Wood units/m² (*n* = 26; *P* < .01). Whether the latter hemodynamic changes are clinically meaningful or not remains unclear. The dosage of treprostinil at hospital discharge was 47 ± 24 ng/kg/min (range, 15 to 115 ng/kg/min) and at 12 weeks was 83 ± 38 ng/kg/min (range, 24 to 180 ng/kg/min). It is feasible that some patients were underdosed as the appropriate dose of treprostinil may be two to three times that of epoprostenol.^{20,21} No serious adverse events were attributed to treprostinil. These data suggest that transition from intravenous epoprostenol to intravenous treprostinil is safe and effective; preliminary long-term follow-up data are submitted for publication.²⁴

Intravenous treprostinil has proved effective in an open-label study in which patients not previously treated with a prostacyclin (de novo patients) were treated with intravenous treprostinil.²¹ The 6-minute walk distance increased by 82 meters from baseline to week 12 (319 ± 22 to 400 ± 26 meters; *n* = 14; *P* = .001). There were also significant improvements in the secondary end points of Naughton-Balke treadmill time, Borg dyspnea score, and hemodynamics at week 12 compared with baseline. Side effects were mild and consistent with those reported with epoprostenol

treatment. While there were no specific guidelines on how quickly to titrate up, the dose was increased approximately three times per week in 1 to 2 ng/kg/min increments (approximately 3 to 6 ng/kg/min per week). At week 12 the mean dosage was 41 ± 4 ng/kg/min (range, 20 to 62 ng/kg/min) in the 14 patients completing the 12-week study. As in the transition study,²⁰ it appeared that higher doses of treprostinil were necessary compared with those achieved in the pivotal subcutaneous treprostinil trial.¹⁸ Current use of intravenous treprostinil suggests the need for dosing at approximately 80 to 120 ng/kg/min to optimize symptoms. Further studies and clinical experience will clarify dosing. A preliminary study of treprostinil delivered via a miniaturized infusion (407C) pump indicates that this delivery modality is promising and might make intravenous therapy less cumbersome.²⁵ Treprostinil for intravenous administration was FDA approved in November 2004. While it is approved for functional class II-IV patients, class II patients are generally treated with oral and/or inhaled therapy.

Intravenous Iloprost

Although intravenous iloprost is not approved in the United States for use in pulmonary arterial hypertension, it has been studied²⁶⁻²⁸ and is available in some countries. No data are available comparing intravenous iloprost to intravenous epoprostenol; far more data are available with the latter drug. Data from Germany suggest potential efficacy as salvage therapy in patients in whom inhaled iloprost therapy has failed.²⁸ Iloprost has the advantage of being much more stable than epoprostenol²⁹ and the longer half-life could help prevent the potential consequences of interruption of drug supply.

Who Should Receive Parenteral Prostanoid Therapy, and Which Route?

The sickest pulmonary arterial hypertension patients, ie, those with poor hemodynamics and rapid progression of symptoms, merit intravenous epoprostenol on the basis of proven mortality benefit.¹ However, intravenous or subcutaneous treprostinil may, in fact, be suitable for certain selected late class III and class IV patients; such patients should be observed carefully and changed to intravenous epoprostenol if there is any concern. Patients with advanced disease were included in the de novo intravenous treprostinil study²¹ although it was a small, uncontrolled study. Subcutaneous or intravenous treprostinil is appropriate in less severely ill individuals, particularly those who are not responding to oral and/or inhaled therapy.^{16,30} It is possible that non-IPAH patients with pulmonary arterial hypertension may respond differently to different prostanoids, but this has not been proved.⁴ If site pain from subcutaneous treprostinil can be tolerated, it is easier for the patient than the intravenous route. If it cannot be tolerated and advanced disease precludes oral and/or inhaled therapy, intravenous treprostinil or epoprostenol should be considered. Although no single infusion site pain remedy is effective in all patients, topical hot or cold packs, lidocaine patches, oral analgesics, anti-inflammatory creams, and pluronic lecithin organogel have met with some success.³¹ Another potential adverse effect is the possible increased incidence of gram-

negative bacteremia in patients receiving intravenous treprostinil. This is currently being investigated.

Inhaled Prostanoid Therapy

Inhaled iloprost

Inhaled therapy for pulmonary arterial hypertension offers the potential for selectivity of the hemodynamic effects to the pulmonary vasculature, avoiding the difficulties and potential systemic adverse effects associated with parenteral therapy. Iloprost is a prostacyclin analogue and has the same biologic profile as the natural substance with respect to prostaglandin receptor binding and cellular effects.²⁹ For long-term therapy, repetitive inhalations of iloprost are administered at least six times daily. Each treatment may take up to 10 and occasionally 15 minutes.

In patients with severe pulmonary arterial hypertension, inhalation of aerosolized iloprost has been shown to result in a substantial decrease in mean pulmonary arterial pressure and pulmonary vascular resistance, concomitant with an increase in cardiac output, in the absence of significant systemic arterial pressure drop and ventilation-perfusion mismatch.^{32,33} In uncontrolled studies, inhaled iloprost was effective in decompensated right ventricular failure,³⁴ and showed favorable long-term hemodynamic improvement.³⁵

While the large randomized double-blind placebo-controlled European multicenter (Aerosolized Iloprost Randomized; AIR) study³⁶ was published more than 5 years ago, it was a pivotal trial, leading to FDA approval of inhaled iloprost in the United States in December 2004. This trial included 203 patients with IPAH or pulmonary arterial hypertension occurring in association with appetite-suppressant use, connective tissue disease, or nonoperable chronic thromboembolic pulmonary hypertension. Approximately 50% of patients had IPAH; 60% were in functional class III and 40% were in functional class IV. The primary end point of the study was a composite of improvement in NYHA functional class; at least 10% improvement in the 6-minute walk test; and no deterioration or death. This end point was reached by more than three times as many patients in the iloprost group than in the placebo group (16.8% vs 4.9%; $P = .007$). The 6-minute walk test results favored the iloprost group, with an improvement of 36.4 meters compared with placebo ($P < .01$) and hemodynamics significantly deteriorated in the placebo group. In general, the drug was well tolerated.

A more recently published open-label uncontrolled German study assessed the long-term clinical efficacy of inhaled iloprost as first-line vasodilator monotherapy in 76 patients with symptomatic IPAH.³⁷ Clinical, hemodynamic, and exercise parameters were obtained at baseline, after 3 and 12 months of therapy, and yearly thereafter. Event-free survival at 3, 12, 24, 36, 48, and 60 months was 81%, 53%, 29%, 20%, 17%, and 13%, respectively. More recent investigations with combinations of inhaled iloprost and oral therapy make firm extrapolation of this monotherapeutic approach to current clinical practice unclear.³⁸⁻⁴¹ Clinical trials of combination therapy are clearly on the rise. The STEP trial is a randomized double-blind placebo-controlled safety trial that also studied the effects of 12 weeks of treatment with inhaled iloprost in 65 patients with pulmonary arterial hypertension already being treated with bosentan.¹⁸ In this trial the change in 6-minute walk distance

from baseline was +4 meters in the control group and +30 meters in the iloprost group, resulting in a placebo-adjusted difference of +26 meters in favor of the iloprost group ($P = .051$). This study, as well as other combination trials of bosentan or sildenafil with inhaled iloprost, is covered by Dr. Hoepfer elsewhere in this issue.³⁸

The VISION study (sildenafil plus inhaled iloprost) is a multicenter international trial evaluating the safety and effectiveness of adding iloprost or placebo to sildenafil therapy in pulmonary arterial hypertension.⁴² The study will also examine whether patients taking sildenafil can reduce the number of iloprost inhalations from the approved six doses per day to four doses per day. The primary end point will be change in 6-minute walk distance from baseline following 16 weeks of combination therapy. This study has important implications in potentially facilitating the use of inhaled iloprost.

In summary, inhaled iloprost offers potential efficacy while minimizing the systemic effects of prostanoids as well as the problems with intravenous access. This is particularly attractive in settings in which systemic hypotension is of particular concern. In severely ill patients with very poor right ventricular function and low cardiac output, however, intravenous prostanoid therapy remains the treatment of choice. Medical therapy should probably not be considered as having failed unless intravenous epoprostenol has failed. Patients whose condition deteriorates despite a combination of inhaled iloprost and endothelin antagonists or phosphodiesterase-5 inhibitors should be transitioned to continuous prostanoid therapy.

Inhaled treprostinil

Increasing data are available with inhaled treprostinil.^{43,44} Potential advantages of this drug include less frequent and more rapid administration than for inhaled iloprost. Data from Germany on three clinical studies of 123 patients examining the effects of inhaled treprostinil have been published together, utilizing right heart catheterization.⁴³ These included a randomized crossover-design study of 44 patients, a dose-escalation study of 31 patients, and a study of reduction of inhalation time with a fixed dose of treprostinil in 48 patients. The primary end point was change in pulmonary vascular resistance, and the mean pulmonary arterial pressure of the enrolled population was approximately 50 mmHg in these studies. In the randomized study, both treprostinil and iloprost at an inhaled dose of 7.5 μg displayed a comparable pulmonary vascular resistance decrease, with treprostinil showing a more sustained effect on pulmonary vascular resistance ($P < .0001$) and fewer systemic side effects. In the dose-escalation study, effects of inhalation were observed for 3 hours and a near-maximal acute pulmonary vascular resistance decrease was observed at 30 μg of treprostinil. In the third study treprostinil was inhaled at increasing concentrations with a pulsed ultrasonic nebulizer, mimicking a metered dose inhaler. A dose of 15 μg treprostinil was inhaled with 18, 9, 3, 2 pulses, or 1 pulse, and each mode achieved comparable, sustained pulmonary vasodilation without significant side effects. Thus, the inhalation time could be reduced to one single breath of treprostinil solution. The results of these studies to date suggest favorable benefit with use of inhaled treprostinil.

The combination of oral therapy and inhaled treprostinil

appears promising. Twelve patients remaining symptomatic at NYHA functional class III or IV despite being treated with oral bosentan for at least 12 weeks were treated with treprostinil via a hand-held ultrasonic single-breath inhalation device.⁴⁴ Two dosing regimens were evaluated: six inhalations four times daily, and nine inhalations four times daily. Each treatment was completed in approximately 1 minute. Inhaled treprostinil was associated with a peak (post-inhalation) 67 meter improvement in 6-minute walk distance at 12 weeks, based on results in 11 evaluable patients ($P = .01$). An improvement of 49 meters was observed at the trough period just before inhalation ($P < .01$). Significant improvement was also noted in hemodynamics and functional class. The results of this open-label study paved the way for the ongoing TRIUMPH trial, an international double-blind placebo-controlled clinical investigation exploring the efficacy and tolerability of inhaled treprostinil added to oral bosentan or sildenafil in patients with severe pulmonary arterial hypertension.⁴⁵ The primary outcome is change in 6-minute walk distance from baseline to week 12. Secondary outcomes include NYHA functional class, Borg dyspnea score, signs and symptoms of pulmonary arterial hypertension, and quality of life, as well as time to clinical worsening. This study is currently enrolling patients.⁴⁵

When to Use an Inhaled Prostanoid

At present, FDA approval is only for iloprost. As with parenteral prostanoids, this modality appears to be appropriate for patients with an unsatisfactory response to oral therapy, although also potentially for transitioning (weaning) from parenteral therapy. No large studies yet support the latter indication. It is generally used in combination with oral therapy. Inhaled iloprost should not be considered to be equivalent to utilization of a continuous prostanoid.

Oral Treprostinil

Although oral beraprost is approved for pulmonary arterial hypertension in Japan, no oral prostanoid is currently FDA approved.⁹ Clinical trials of oral sustained-release treprostinil are currently under way evaluating both monotherapy and combination therapy with phosphodiesterase-5 inhibitors and/or endothelin antagonists.^{46,47} ■

References

1. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension: the Primary Pulmonary Hypertension Study Group. *N Engl J Med.* 1996;334:296-302.
2. McLaughlin V, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation.* 2002;106:1477-1482.
3. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol.* 2002;40:780-788.
4. Rosenzweig EB, Kerstein D, Barst R. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. *Circulation.* 1999;99:1858-1865.
5. McLaughlin VV, Genthner DE, Panella MM, et al. Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. *Ann Intern Med.* 1999;130:740-743.
6. Badesch D, Tapson V, McGoon M, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. *Ann Intern Med.* 2000;132:425-434.

7. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med.* 2004;351:1425-1436.
8. Vachiery JL, Naeije R. Treprostinil for pulmonary hypertension. *Expert Rev Cardiovasc Ther.* 2004;2:183-191.
9. Beutz MA, Bull TM, Badesch DB. Oral therapies for pulmonary arterial hypertension. *Adv Pulmonary Hypertens.* 2006;5(4):13-17.
10. Wade M, Baker FJ, Roscigno R, et al. Absolute bioavailability and pharmacokinetics of treprostinil sodium administered by acute subcutaneous infusion. *J Clin Pharmacol.* 2004; 44:83-88.
11. Wade M, Baker FJ, Roscigno R, et al. Pharmacokinetics of treprostinil sodium administered by 28-day chronic continuous subcutaneous infusion. *J Clin Pharmacol.* 2004; 44:503-509.
12. Laliberte K, Arneson C, Jeffs R, Hunt T, Wade M. Pharmacokinetics and steady-state bioequivalence of treprostinil sodium (Remodulin) administered by the intravenous and subcutaneous route to normal volunteers. *J Cardiovasc Pharm.* 2004;44:209-214.
13. Steffen RP, De La Mata M. The effects of 15AU81, a chemically stable prostacyclin analog, on the cardiovascular and renin-angiotensin systems of anesthetized dogs. *Prostaglandins Leukot Essent Fatty Acids.* 1991;43:277-286.
14. McNulty MJ, Sailstad JM, Steffen RP. The pharmacokinetics and pharmacodynamics of the prostacyclin analog 15AU81 in the anesthetized beagle dog. *Prostaglandins Leukot Essent Fatty Acids.* 1993; 48:159-166.
15. Wade M, Hunt TL, Lai AA. Effect of continuous subcutaneous treprostinil therapy on the pharmacodynamics and pharmacokinetics of warfarin. *J Cardiovasc Pharm.* 2003;41:908-915.
16. Badesch DB, McLaughlin VV, Delcroix M, et al. Prostanoid therapy for pulmonary arterial hypertension. *J Am Coll Cardiol.* 2004;43:(suppl):56S-61S.
17. McLaughlin V, Gaine S, Barst R, et al. Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. *J Cardiovasc Pharmacol.* 2003;41:293-299.
18. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med.* 2002;165:800-804.
19. Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. *Chest.* 2006;129:1636-1643.
20. Gombert-Maitland M, Tapson VF, Benza RL, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. *Am J Respir Crit Care Med.* 2005;172:1586-1589.
21. Tapson VF, Gombert-Maitland M, McLaughlin VV, et al. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension. A prospective, multicenter, open-label, 12-week trial. *Chest.* 2006;129: 683-688.
22. Oudiz RJ, Schilz RJ, Barst RJ, Galie N, Rich S, Rubin LJ, and Simonneau G. on behalf of the Treprostinil Study Group. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest.* 2004;126:420-427.
23. Vachiery JL, Hill N, Zwicke D, Barst RJ, et al. Transitioning from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension. *Chest* 2002;121:1561-1565.
24. McLaughlin VV, Barst RJ, Gombert-Maitland M, et al. One year experience with intravenous treprostinil in pulmonary arterial hypertension patients. *Chest.* 2005;128:160S.
25. Tapson VF, McLaughlin VV, Gombert-Maitland M, et al. Delivery of intravenous treprostinil at low infusion rates using a miniaturized infusion pump in patients with pulmonary arterial hypertension. *J Vasc Access.* 2006;7:112-117.
26. Higenbottam TW, Butt AY, Dinh-Xaun AT, Takao M, Cremona G, Akamine S. Treatment of pulmonary hypertension with the continuous infusion of a prostacyclin analogue, iloprost. *Heart.* 1998;79:175-179.
27. Higenbottam T, Butt AY, McMahon A, Westerbeek R, Sharples L. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart.* 1998;80:151-155.
28. Hoepfer MM, Spiekerkoetter E, Westerkamp V, et al. Intravenous iloprost for treatment failure of aerosolized iloprost in pulmonary arterial hypertension. *Eur Respir J.* 2002;20:339-343.
29. Grant SM, Goa KL. Iloprost. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peripheral vascular disease, myocardial ischemia and extracorporeal circulation procedures. *Drugs.* 1992;43:889-924.
30. Galie N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. *Eur Heart J.* 2004;25: 2243-2278.
31. Shapiro S, Zwicke D, Hill W, et al. Road to successful management of infusion site pain associated with Remodulin. Paper presented at: The American Thoracic Society 99th International Conference; May 16-21, 2003; Seattle, Washington.
32. Hoepfer MM, Olschewski H, Ghotrani HA, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH Study Group. *J Am Coll Cardiol.* 2000;35:176-182.
33. Olschewski H, Walmrath D, Schermuly R, Ghofrani A, Glimminger F, Seeger W. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med.* 1996;124:820-824.
34. Olschewski H, Ghofrani HA, Schmehl T, et al. Inhaled iloprost to treat severe pulmonary hypertension. An uncontrolled trial. German PPH Study Group. *Ann Intern Med.* 2000;132:435-443.
35. Hoepfer MM, Schwarze M, Ehlerding S, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med.* 2000;342:1866-1870.
36. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med.* 2002;347:322-329.
37. Opitz CF, Wensel R, Winkler J, et al. Clinical efficacy and survival with first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. *Eur Heart J* 2005;26:1895-1902.
38. Hoepfer MM. Combination therapy for pulmonary arterial hypertension. *Adv Pulmonary Hypertens.* 2006;5(4):23-30.
39. Hoepfer MM, Taha N, Bekjarova A, et al. Bosentan treatment in patients with primary pulmonary hypertension receiving nonparenteral prostanoids. *Eur Respir J.* 2003;22:330-334.
40. Ghofrani HA, Rose F, Schermuly RT, et al. Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. *J Am Coll Cardiol.* 2003;42(1):158-64.
41. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2006;174:1257-1263.
42. The "VISION" trial: Ventavis inhalation with sildenafil to improve and optimize pulmonary arterial hypertension: <http://www.clinicaltrials.gov/ct/show/NCT00302211>
43. Voswinckel R, Enke B, Reichenberger F. Favorable effects of inhaled treprostinil in severe pulmonary hypertension: results from randomized controlled pilot studies. *J Am Coll Cardiol.* 2006;48:1672-1681.
44. Channick RN, Olschewski H, Seeger W, Staub, Voswinckel, Rubin LJ. Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. *J Am Coll Cardiol.* 2006; 48:1433-1437.
45. Clinical investigation into the efficacy and tolerability of inhaled treprostinil sodium in patients with severe pulmonary arterial hypertension (TRIUMPH):<http://www.clinicaltrials.gov/ct/show/NCT001471-99>
46. Oral treprostinil as monotherapy for the treatment of pulmonary arterial hypertension (FREEDOM -M): <http://www.clinicaltrials.gov/ct/show/NCT00325403>.
47. Oral treprostinil in combination with an endothelin receptor antagonist a phosphodiesterase-5 inhibitor for the treatment of pulmonary arterial hypertension (FREEDOM -C): <http://www.clinicaltrials.gov/ct/show/NCT00325442>.

Advances in Prostanoid Therapy: New Studies, New Methods of Delivery



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Two decades ago, pulmonary arterial hypertension was considered an untreatable disease. With the introduction of effective therapies this situation has changed. Today, endothelin receptor antagonists together with prostanoids and phosphodiesterase-5 (PDE5) inhibitors are the mainstays of treatment. All these drugs lead to hemodynamic and functional improvement within 3 to 4 months, and there is evidence to suggest that they also delay disease progression. Unfortunately, none of the currently available treatments offers a chance for cure, and many patients eventually experience progressive disease despite active treatment. Since the different classes of drugs act via different intracellular mechanisms, it appears logical and attractive to use combinations for better disease control. Clinical and scientific evidence to support the use of combination therapy for pulmonary arterial hypertension is rapidly cumulating.

Impact of Currently Available Drugs

Pulmonary arterial hypertension is characterized by extensive pulmonary vascular remodeling resulting from proliferation of endothelial cells, vascular smooth muscle cells, and fibroblasts. Excessive matrix deposition, in situ thrombosis, and pulmonary vasoconstriction contribute to the disease process. The etiology is still unclear, making causal treatment impossible. All currently available drugs act as pulmonary vasodilators but they also affect the mechanisms involved in pulmonary vascular remodeling, as suggested by several lines of experimental evidence.

Prostanoids

Prostanoids replace endogenous prostacyclin, production of which is decreased or absent in the pulmonary vessels of patients with pulmonary arterial hypertension, and exert vasodilatory and antiproliferative effects predominantly via the intracellular second messenger cyclic adenosine monophosphate (cAMP) as well as by some other mechanisms. Several prostanoids are approved for pulmonary arterial hypertension. Intravenous epoprostenol (Flolan), intravenous and subcutaneous treprostinil (Remodulin), and inhaled iloprost (Ventavis)

have all been shown to improve hemodynamics and exercise capacity in patients with various forms of the disease.¹⁻⁴ However, robust long-term survival data are available only for intravenous epoprostenol, and to a lesser extent for inhaled iloprost⁵ and subcutaneous treprostinil.⁶ With intravenous epoprostenol treatment, two long-term observational studies yielded survival rates at 1 year of 85% and 88%, respectively, at 2 years of 70% and 76%, and at 3 years of 63% and 63%.^{7,8} When interpreting these results it has to be kept in mind that these studies enrolled very sick patients. Placebo-controlled survival studies have never been performed in pulmonary arterial hypertension (and never will be for ethical reasons), but the reported survival rates compared favorably with historical controls and also with expected survival as calculated from the National Institutes of Health equation that was developed to estimate survival of patients with idiopathic pulmonary arterial hypertension (IPAH) based on their hemodynamic status.⁹

Data on long-term outcome with inhaled iloprost treatment are sparse. A retrospective study from Germany studying 76 patients with IPAH showed that in patients receiving first-line therapy with inhaled iloprost, survival free of transplantation or change in treatment was only 29% after 2 years, and 42% of the patients were eventually transitioned to intravenous prostanoid therapy.¹⁰

Endothelin receptor antagonists

Endothelin-1 is overexpressed in the pulmonary vasculature of patients with pulmonary arterial hypertension and causes deleterious effects such as pulmonary vasoconstriction and vascular smooth muscle cell proliferation; effects that are blocked by the administration of endothelin receptor antagonists. Endothelin-1 acts via two different endothelin receptor isoforms, ET_A and ET_B. Both the nonselective ET_A/ET_B receptor antagonist bosentan (Tracleer) and the selective ET_A receptor antagonists sitaxsentan (Thelin) and ambrisentan have been approved or are currently being studied for treatment of pulmonary arterial hypertension. All three compounds improve hemodynamics and exercise capacity in

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There are many reasons to join this group, but the benefit I have truly enjoyed is being able to tap into everyone's collective knowledge with the listserv. Many changes are taking place in this field right now and it would be difficult for even the most seasoned veterans to have all the answers. With this, my patients and I can benefit from everyone else's experiences and expertise.

Ginger R. Ward, RN
Duke University Medical Center
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Fernando Torres, MD

Director, Pulmonary Hypertension Clinic
UT Southwestern Medical Center
Dallas, Texas

We are often confronted with treatment issues with no clear answers. Those of us who practice in this field find ourselves navigating through uncharted territories, with the decisions we make on behalf of our patients impacting their outcome. It is so imperative to have a community of colleagues who you can rely on for sound and trusted advice and opinions—that's where PHCR comes in.

Myung H. Park, MD, FACC

Director, Pulmonary Hypertension Vascular Disease Program
Assistant Professor of Medicine
University of Maryland School of Medicine
Baltimore, Maryland



patients with the disease.¹¹⁻¹⁵ Again, long-term data are sparse and so far available only for bosentan. In patients with IPAH, first-line treatment with bosentan has been associated with survival rates of 96% at 1 year and 89% at 2 years.¹⁶ When interpreting these results it is important to note that the survival data were not achieved with bosentan therapy alone, since 23% of these patients eventually required other medications, either alone or in combination with bosentan.

In contrast, a retrospective study from France showed that first-line therapy with bosentan resulted in an event-free survival rate of 44% after 2 years, and 45% of the patients required intravenous prostanoid therapy.¹⁷

Phosphodiesterase-5 inhibitors

PDE5 inhibitors augment the action of endogenous nitric oxide and natriuretic peptides by inhibiting degradation of the second messenger cyclic guanosine monophosphate (cGMP), thereby causing pulmonary vasodilatation and inhibition of vascular smooth muscle cell proliferation. The PDE5 inhibitor sildenafil (Revatio) has been studied most extensively in patients with pulmonary hypertension. A large set of case reports, case series, and randomized, controlled studies has demonstrated beneficial effects on exercise capacity and hemodynamics in patients with pulmonary arterial hypertension.¹⁸ Long-term survival with sildenafil treatment remains to be evaluated, especially since no long-term data are available for the dosage of 20 mg tid, the only dosage that has been approved for pulmonary arterial hypertension. Tadalafil (Cialis), another PDE5 inhibitor with a longer duration of action than sildenafil is currently under investigation for pulmonary arterial hypertension.

Rationale for Combination Therapy

There are several reasons to pursue combination therapy for pulmonary arterial hypertension. As discussed above, all available treatments improve exercise capacity within 3 to 4 months. However, average improvements on 6-minute walk testing range between 30 and 50 meters, and in many patients exercise capacity remains markedly limited despite active treatment. In fact, long-term improvement in functional class is usually achieved in less than 50% of patients with any monotherapy. Perhaps more importantly, none of the available treatment options cures pulmonary arterial hypertension and the disease often progresses despite active treatment. In addition, the three classes of substances currently available for treatment—prostanoids, endothelin receptor antagonists, and PDE5 inhibitors—act via different intracellular pathways as described above. Thus, combining these substances is very likely to produce synergistic effects. Scientific evidence to support these considerations is still limited.

Data for Combination Therapy

Endothelin receptor antagonists and prostanoids

Bosentan and intravenous epoprostenol. Only one randomized, controlled trial has been performed so far to assess combination therapy with bosentan and intravenous epoprostenol, the BREATHE-2 study.¹⁹ This was a true com-

bination study in which 33 patients with advanced disease started intravenous epoprostenol treatment and were simultaneously randomized to receive either bosentan or placebo. Combination therapy appeared to be well tolerated and there was a nonsignificant trend toward a greater hemodynamic improvement in patients receiving combination treatment. However, three deaths occurred during or shortly after the study, all in the group receiving epoprostenol and bosentan. All in all, this study was underpowered to allow definite conclusions.

Data addressing the combination of epoprostenol (or other prostanoids) with either ambrisentan or sitaxsentan are not available.

Bosentan and nonparenteral prostanoids (aerosolized iloprost and beraprost). Two open-label studies have provided preliminary evidence that addition of bosentan to either inhaled iloprost or beraprost (no longer available in the United States and Europe) may be well tolerated and may improve exercise capacity, hemodynamics, and right ventricular function.^{20,21}

More recently, two randomized, controlled studies addressed the opposite approach, ie, addition of aerosolized iloprost to bosentan, the STEP-1 study and the COMBI trial. The STEP-1 (for iloprost inhalation solution safety and pilot efficacy trial in combination with bosentan for evaluation in pulmonary arterial hypertension) study was designed as a randomized, double-blind study and included 65 patients with pulmonary arterial hypertension.²² After 12 weeks of treatment, the difference in the 6-minute walk distance between both groups was 26 meters in favour of the bosentan/iloprost group ($P = .051$). When interpreting these results it has to be noted that the 12-week results were obtained almost immediately after inhalation of iloprost or placebo. In contrast, the preinhalation results at week 12 did not differ significantly in both groups (placebo-adjusted difference, 19 meters; $P = .14$). Nevertheless, time to clinical worsening was significantly delayed with combination therapy.

Like STEP-1, the COMBI (for combination therapy of bosentan and aerosolized iloprost in IPAH) trial was designed to assess whether the addition of inhaled iloprost to bosentan improves exercise capacity in patients with pulmonary arterial hypertension. However, the results of this study differed markedly from those of STEP-1.²³ The COMBI trial was terminated early after a futility analysis predicted failure with respect to the predetermined sample size. At that time 40 patients were randomized to receive either bosentan alone (control group) or bosentan plus inhaled iloprost (combination group) for a 12-week period. The primary end point, change in 6-minute walking distance, was not met (mean changes were +1 meter in the control group and -9 meters in the combination group; $P = .490$). However, these results were markedly affected by three outliers, ie, three patients, all randomized to receive inhaled iloprost, who presented with severe clinical worsening. The trend in the other patients was similar to that in the STEP-1 trial. None of the secondary end points, including functional class, peak oxygen uptake, and time to clinical

worsening, differed significantly between groups.

Taken together, further studies and long-term data are needed to define the efficacy of adding inhaled iloprost to bosentan.

Prostanoids and PDE5 inhibitors

Epoprostenol and sildenafil. The combination of epoprostenol and sildenafil has been studied in a large, multicenter, 12-week, randomized, controlled trial, the PACES study. The full study has not been completely published but the main results have been presented at international congresses. PACES enrolled 267 patients receiving stable dosing of epoprostenol and randomly added sildenafil or placebo. Apparently, improvement in 6-minute walk distance was significantly better with the combination than with epoprostenol alone, but the final results have yet to be presented. It needs to be noted that in this trial sildenafil was started at a dosage of 20 mg tid and titrated up to 80 mg tid, which is substantially higher than the currently FDA-approved sildenafil dosage of 20 mg tid.

Subcutaneous treprostinil and sildenafil. Only a small observational study addressing the combination of subcutaneous treprostinil and sildenafil has been published.²⁴ Sildenafil was used as add-on treatment in 9 patients with pulmonary arterial hypertension receiving treprostinil. This combination was well tolerated and resulted in improved exercise capacity in all patients.

Aerosolized iloprost and sildenafil. So far, the evidence for safety and efficacy of combining aerosolized iloprost and sildenafil is limited to acute hemodynamic intervention studies and one case series. The two hemodynamic studies have provided convincing evidence that the addition of sildenafil to aerosolized iloprost and vice versa has synergistic effects on pulmonary arterial pressure, cardiac output, and pulmonary vascular resistance.^{25,26} However, it remains to be shown how these acute hemodynamic effects translate into long-term clinical outcome. Currently, only a single case series has provided some preliminary information about the combination of inhaled iloprost with sildenafil. Ghofrani et al. studied the effects of sildenafil as add-on medication in 14 patients whose condition deteriorated despite treatment with aerosolized iloprost. The patients had been receiving iloprost treatment for a mean period of 18 months. Addition of sildenafil was well tolerated by all patients and resulted in a mean increase in 6-minute walk distance of 88 meters after 3 months accompanied by hemodynamic improvement. The effects on exercise capacity were maintained throughout the observation period of up to 12 months.²⁷

Endothelin receptor antagonists and PDE5 inhibitors

Bosentan and sildenafil. Only a few case series have been published addressing safety and efficacy of combining bosentan and sildenafil in patients with pulmonary arterial hypertension.²⁸ The first study included 9 patients with severe idiopathic disease. Therapy for these patients was started with bosentan and sildenafil was added when clinical deterioration occurred, after a mean interval of 11

months of bosentan therapy. Three months after addition of sildenafil, the 6-minute walk distance had increased by 115 meters, accompanied by a significant improvement in maximum oxygen uptake as measured by cardiopulmonary exercise testing. The improvement in exercise capacity was maintained throughout the observation period, which lasted between 6 and 12 months. Combination therapy with bosentan and sildenafil was tolerated without adverse events. The second, yet unpublished, series included 18 patients with pulmonary arterial hypertension who either had sildenafil added to bosentan (n = 13) or vice versa (n = 5). Six-minute walk distance improved by 44 meters. Six patients had also been treated with intravenous epoprostenol, and four of them were able to wean off of it. These were highly selected patients who had already experienced marked improvement in hemodynamics and walk distance with epoprostenol, and results should not be generalized to less well compensated patients.

In contrast to the other combination regimens described above, coadministration of bosentan and sildenafil may be associated with relevant pharmacokinetic interactions.²⁹ Sildenafil has inhibitory effects on CYP3A4 activity, which may lead to increased plasma concentrations of bosentan. Bosentan, like other endothelin receptor antagonists, may exert hepatotoxic effects and there is concern about a higher risk of liver damage with combined administration of bosentan and sildenafil. None of the patients in the case series described above experienced elevations in hepatic aminotransferases when sildenafil was added to bosentan, but the small number of patients precludes any meaningful safety analysis. On the other hand, induction of CYP3A4 activity by bosentan may accelerate metabolism of sildenafil, which may decrease the plasma concentrations of sildenafil by as much as 60%. This interaction may be important since sildenafil has been approved for treatment of pulmonary arterial hypertension only at a dosage of 20 mg tid. It is unknown whether lower dosages or lower plasma concentrations are still efficacious. To date, those are theoretical considerations and the clinical relevance of these interactions has not been studied.

Clinical studies addressing the combination of other endothelin receptor antagonists, ie, ambrisentan or sitaxsentan with sildenafil or tadalafil, have not been published. On the basis of pharmacologic data, it is unlikely that drug-drug interactions will play a relevant role when any of these substances are combined. However, clinical studies have to be awaited to show whether this assumption holds true.

Future Concepts and Long-Term Outcome with Combination Therapy

All current treatment guidelines for pulmonary arterial hypertension include the option of combination therapy and place it somewhere near the end of the cascade, ie, for patients with advanced illness not responding sufficiently well to monotherapy. Perhaps, in the future, combination therapy will be introduced right after the diagnosis is made (following the “hit-hard-and-early” concept). However, as long as no data are available to show that such a concept truly improves treatment results, a step-wise approach is a

tension. In fact, it already does so. The introduction of several new active treatments has been a blessing for affected patients, many of whom are already benefiting from the use of combination therapy. The problem is that we still do not know the most effective combinations, which patients benefit the most from combination therapy, and the best time to initiate combination therapy. We also need to make sure that combining several treatments is not associated with increased toxicity. Finally, given the current costs of treatments, identifying the value of combination therapy will have socioeconomic implications.

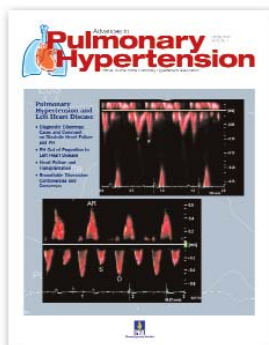
Several clinical trials are under way to study the effects of combination therapy, including VISION (sildenafil and inhaled iloprost), TRIUMPH (bosentan or sildenafil and inhaled treprostinil), COMPASS 1/2 (sildenafil and bosentan), and PHIRST (bosentan and tadalafil). Among these trials, COMPASS-2 stands out as the first study to compare long-term outcome of a combination regimen (bosentan plus sildenafil) versus a monotherapy (sildenafil) in a large group of patients. All these trials are expected to provide important new information, helping to optimize the treatment of patients with pulmonary arterial hypertension. Thus, eligible patients should consider participating in these trials whenever possible, for their own sake as well as for the benefit of the many other patients affected by the disease now or in the future. Physicians treating patients with pulmonary arterial hypertension should be aware of these trials and should not hesitate to inform patients about ongoing studies in which they may be able to participate. ■

References

1. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med.* 1996;334(5):296-302.
2. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med.* 2000;132(6):425-434.
3. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med.* 2002;165(6):800-884.
4. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med.* 2002;347(5):322-329.
5. Hoeper MM, Schwarze M, Ehlerding S, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med.* 2000;342(25):1866-1870.
6. Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. *Chest.* 2006;129(6):1636-1643.
7. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol.* 2002;40(4):780-788.
8. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation.* 2002;106(12):1477-1482.
9. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115(5):343-349.
10. Opitz CF, Wensel R, Winkler J, et al. Clinical efficacy and survival with first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. *Eur Heart J.* 2005;26(18):1895-1902.
11. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet.* 2001;358(9288):1119-1123.
12. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med.* 2002;346(12):896-903.
13. Barst RJ, Langleben D, Badesch D, et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol.* 2006;47(10):2049-2056.
14. Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2004;169(4):441-447.
15. Galie N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol.* 2005;46(3):529-535.
16. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J.* 2005;25(2):244-249.
17. Provencher S, Sitbon O, Humbert M, Cabrol S, Jais X, Simonneau G. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. *Eur Heart J.* 2006;27(5):589-595.
18. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med.* 2005;353(20):2148-2157.
19. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J.* 2004;24(3):353-359.
20. Hoeper MM, Taha N, Bekjarova A, Gatzke R, Spiekerkoetter E. Bosentan treatment in patients with primary pulmonary hypertension receiving nonparenteral prostanoids. *Eur Respir J.* 2003;22(2):330-334.
21. Seyfarth HJ, Pankau H, Hammerschmidt S, Schauer J, Wirtz H, Winkler J. Bosentan improves exercise tolerance and Tei index in patients with pulmonary hypertension and prostanoid therapy. *Chest.* 2005;128(2):709-713.
22. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2006.
23. Hoeper MM, Leuchte H, Halank M, et al. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J.* 2006;28(4):691-694.
24. Gombert-Maitland M, McLaughlin V, Gulati M, Rich S. Efficacy and safety of sildenafil added to treprostinil in pulmonary hypertension. *Am J Cardiol.* 2005;96(9):1334-1336.
25. Wilkens H, Guth A, Konig J, et al. Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. *Circulation.* 2001;104(11):1218-1222.
26. Ghofrani HA, Wiedemann R, Rose F, et al. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med.* 2002;136(7):515-522.
27. Ghofrani HA, Rose F, Schermuly RT, et al. Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. *J Am Coll Cardiol.* 2003;42(1):158-164.
28. Hoeper MM, Faulenbach C, Golpon H, Winkler J, Welte T, Niedermeyer J. Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J.* 2004;24(6):1007-1010.
29. Paul GA, Gibbs JS, Boobis AR, Abbas A, Wilkins MR. Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br J Clin Pharmacol.* 2005;60(1):107-112.
30. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J.* 2005;26(5):858-863.
31. Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation.* 2002;106(3):319-324.
32. Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation.* 2000;102(8):865-870.

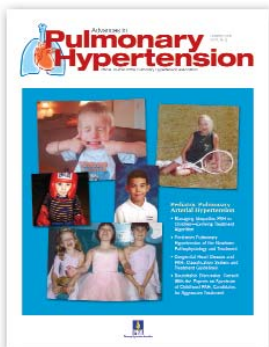
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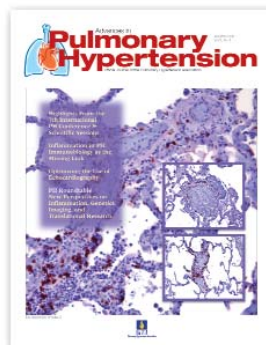
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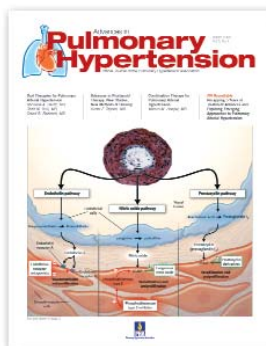
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Pulmonary Hypertension Roundtable: Recapping 5 Years, Exploring Emerging Approaches



Vallerie V. McLaughlin, MD



Richard N. Channick, MD



Ivan M. Robbins, MD



Victor F. Tapson, MD

This discussion was moderated by Vallerie V. McLaughlin, MD, Associate Professor of Medicine and Director, Pulmonary Hypertension Program, University of Michigan Health System, Ann Arbor, Michigan. Panel members included Richard N. Channick, MD, Associate Professor of Medicine, Pulmonary and Critical Care Division, University of California, San Diego Medical Center, San Diego, California; Ivan M. Robbins, MD, Director of the Pulmonary Hypertension Center, Vanderbilt University, Nashville, Tennessee; and Victor F. Tapson, MD, Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina.

Dr McLaughlin: The past 5 years have been remarkable in terms of advances in pulmonary hypertension, and with the fifth anniversary of the journal coming up, let's start with the journal's first editor, Dr Tapson. Vic, what do you think have been some of the most remarkable recent advances in pulmonary hypertension?

Dr. Tapson: Val, over the past 10 or 12 years, basic research and clinical trials have led to FDA approval of five drugs to treat pulmonary arterial hypertension, and more are coming. Four of these five drugs have been approved in the last 5 years. The Pulmonary Hypertension Association has done remarkable work, and the national meeting has blossomed into a tremendous venue. These are exciting times, considering we once had essentially nothing for these patients

Dr McLaughlin: Ivan, would you like to comment on some of the accomplishments over the past 5 years?

Dr Robbins: It's been a truly remarkable collection of journal articles, with the most up-to-date information on pulmonary hypertension treatment and

diagnosis. I don't think you can find anything like this anywhere else. It has been an incredible journal for people who want to learn about pulmonary hypertension.

Dr McLaughlin: Rich, in terms of the therapies now available, in the last 5 years we have seen the approval of at least three agents. When we started the journal all we had was epoprostenol (Flolan). What do you think about the current therapies?

Dr Channick: There's been a remarkable evolution and it's been great to be involved in it. Five years ago there was very little we could use outside of epoprostenol. Having multiple options that clearly are effective and good data showing marked improvement in not just how patients are feeling but in how long they are living is very rewarding. More options also create new challenges and questions that we can talk about as we get more therapies on board.

Dr Robbins: In patients not doing well with monotherapy with oral agents, inhaled iloprost and combination therapy have given us alternatives other than having to start long-term intravenous therapy, with the associated complications and problems we all have encountered with epoprostenol. We certainly have a lot of patients receiving combination therapy now, with either an endothelin receptor antagonist or a PDE5 (phosphodiesterase-5) inhibitor and iloprost, and we've had some good success with this. So it has given us a lot more options in terms of monotherapy and combination therapy.

Dr McLaughlin: Rich, what do you think?

Dr Channick: I certainly agree. Most of us, however, still feel that intravenous epoprostenol is the benchmark against which all new therapies, including other prostacyclins, should be com-

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pared. In a sense the development of other prostacyclins is an effort to provide at least comparable or nearly comparable efficacy to epoprostenol in an easier formulation.

Dr McLaughlin: Rich, do you think anything currently available provides efficacy nearly comparable to that of intravenous epoprostenol?

Dr Channick: In my experience nothing has the efficacy in terms of degree of benefit as well as rapidity of benefit that intravenous epoprostenol does. I don't think we have seen an equivalent drug yet.

Dr McLaughlin: I would agree with that.

Dr Robbins: I would too.

Dr McLaughlin: If some of these other prostacyclins might be friendlier in terms of patient administration but are not quite as efficacious as intravenous epoprostenol, where do they fall in your armamentarium? Give me some idea as to where you might use any of these therapies as opposed to epoprostenol, the gold-standard prostacyclin.

Dr Channick: That's a very good question, but hard to answer given limited data to tell us which alternative combinations to use and in which particular patients. My own approach is this: Treatment in most of our patients is started with an oral therapy, typically bosentan. We then use additional nonintravenous prostanoids as add-on therapy. In the sicker patients we go to intravenous epoprostenol up front. We also have a number of patients receiving two oral drugs, sildenafil and bosentan, plus an inhaled prostanoid, but I think the initial treatment decision is typically whether we start oral therapy versus intravenous therapy up front.

Dr McLaughlin: Aren't there still some patients who come to you relatively advanced in whom you start intravenous therapy as first-line therapy and generally is it intravenous epoprostenol?

Dr Channick: Clearly there are patients who require intravenous epoprostenol right up front. There are fewer of these patients as a result, I believe, of aggressive early therapy with oral and inhaled therapy. However, we don't want to lose sight of the fact that there are still patients who are sick enough who warrant intravenous therapy up front, and when we do use intravenous therapy it is typically epoprostenol. We've had some experience, albeit not a great deal, with intravenous treprostinil, with some benefit, but our "go-to gun" is still intravenous epoprostenol.

Dr McLaughlin: Is there any particular factor that leads you toward intravenous epoprostenol versus intravenous treprostinil?

Dr Robbins: At our center we have used only intravenous epoprostenol. If patients are sick enough for intravenous therapy, we have a lot of experience with epoprostenol. If you're going to go for intravenous therapy these days, until I see data that really show efficacy, we're starting intravenous epoprostenol. The other thing is that there's a huge cost difference between intravenous epoprostenol and intravenous treprostinil.

Dr McLaughlin: Particularly when you take into account the dose of treprostinil required to obtain similar therapeutic effect.

Dr Robbins: There are patients in whom you would want a little more time in case there's a pump malfunction or the Hickman comes out, where they may have somewhat limited support or live a great distance from a medical center.



If the patient is sick enough why not go to intravenous epoprostenol? Having said that, I know there are centers that have a lot of experience with intravenous treprostinil therapy. Treprostinil is clearly an efficacious compound, but the subcutaneous form in my opinion is really limited by the site-pain side effect. – Dr Channick

Dr. Tapson: The advantages of intravenous treprostinil include the longer half life and the lack of need for ice packs. We have a number of patients taking this drug, but also tend to start therapy for our sickest patients with intravenous epoprostenol.

Dr McLaughlin: In some patients there may be a particularly important safety window in terms of having a drug that has a longer half life, like treprostinil compared with epoprostenol, perhaps for

those who live in very rural areas. I didn't hear anyone mention subcutaneous treprostinil. Is there a role for that?

Dr Robbins: Not very much at our center. I know there are some physicians who have patients who have done well with this therapy, but every one of our patients has had either pain or discomfort at the needle site. Also, when we've transitioned a number of patients to inhaled iloprost in combination with an oral therapy, even the patients who were tolerating subcutaneous treprostinil well, once they stopped receiving it, they said, "Wow, I didn't realize I had this sort of underlying discomfort." So I don't see a big role for it, but there are centers that use a lot of it and do well with it.

Dr Channick: I agree with that. We've had a few patients undergoing treprostinil therapy. I agree with Ivan—finding the ideal patient for it is something I am still wrestling with. If the patient is sick enough why not go to intravenous epoprostenol? Having said that, I know there are centers that have a lot of experience with intravenous treprostinil therapy. Treprostinil is clearly an efficacious compound, but the subcutaneous form in my opinion is really limited by the site-pain side effect.

Dr McLaughlin: It is certainly an effective therapy for a niche population—those patients who perhaps want to avoid an intravenous line for a variety of reasons, including infection, and who have probably not done well with inhaled therapy or

who are very active and, for example, work and cannot take an inhaled therapy six times per day. So we have a small population that has done very well with subcutaneous treprostinil, but it is for a very select subgroup of patients.

Dr. Tapson: Irene Lang and colleagues published their very positive experience with subcutaneous treprostinil in *Chest* this year. More than 100 patients with mostly pulmonary arterial hypertension but some with chronic thromboembolic pulmonary hypertension were followed. At 3 years there was clear improvement, but the most interesting thing to me was that only 5% of their patients had to stop the drug because of site pain. We, however, have also tended to use intravenous prostanoid therapy.

Dr Robbins: What's your experience been with inhaled iloprost? We have had some good experience with it, particularly in combination with sildenafil. We've had 3 or 4 patients who did not tolerate it at all, in terms of the side effects from the inhalation—coughing, headache, flushing—and even when we backed the dose down they didn't tolerate it.

Dr Channick: I've had a similar case, a patient who had exactly the same side effects you're describing, cough, flushing, side effects that did not allow us to use the drug. But clearly, many patients experience a clear-cut benefit. There are published data from the STEP trial showing the benefit of inhaled iloprost in addition to bosentan, fairly convincing data mirrored in our clinical experience. But it's not for everybody, and there are those who do not tolerate the therapy.

Dr. Tapson: We've had good experience in general with inhaled iloprost and have also had some success weaning patients from epoprostenol when combining iloprost with an oral drug.

Dr Robbins: I've had some patients who have opted for epoprostenol over inhaled iloprost because of having to take six treatments a day.

Dr McLaughlin: That's one issue and the other is how sick the patient is and how durable the effect. We use inhaled iloprost in patients, for example, who are receiving oral therapy and who are somewhat better but not as well as we would like them to be, somewhat like the patients entered in STEP. But there are other patients who, despite receiving oral therapy, remain relatively ill. Those late functional class III's or IV's are where I tend to go straight to intravenous epoprostenol. So with regard to the inhaled agents, in addition to inhaled iloprost, all of us are doing some research with inhaled treprostinil, which has a longer half life than is delivered via a briefer inhalation four times per day. Rich, you did some of the initial pioneering work with inhaled tre-

prostiniil. Would you like to comment on it?

Dr Channick: We did a pilot study of 12 patients that was recently published in *JACC* [2006 Oct 3;48(7):1433-7]. The study was somewhat similar to the STEP trial except that it was an open-label, phase 2 study adding inhaled treprostinil in patients who were still symptomatic despite bosentan. Hemodynamic measurements as well as exercise capacity and the functional class parameters were assessed. We found a potent effect of adding inhaled treprostinil to bosentan in terms of functional status, exercise capacity, and hemodynamic responses. As you say, Val, there is now a large phase 3 trial of that drug in progress.

Dr McLaughlin: Let's move from the prostacyclins to the endothelin receptor antagonists. Bosentan was the first one the FDA approved nearly 5 years ago and remains the only one commercially available, although there are two investigational endothelin receptor antagonists that we have all had experience with—sitaxsentan and ambrisentan. Ivan, do you want to give us your perspective on the endothelin receptor antagonists, their similarities and their differences? Is one going to emerge as the best in class, or are they all relatively similar in terms of effectiveness, with some differences in the side effect profile?

Dr Robbins: I think it is difficult to say until we have them out there in use with a large number of patients. Bosentan has obviously been out there for quite a while and the number of patients who have been exposed to the drug is around 30,000, so there is a fair bit of data with

this drug. There is also the recent publication by the group in France describing their long-term use of bosentan, so we are pretty familiar with it. As you know, about 10% of patients have liver function test abnormalities that require that they change to another therapy. But relatively few have noticeable side effects. With regard to sitaxsentan, we have certainly had some patients who have done well with this drug.

Dr McLaughlin: And don't forget to mention the warfarin interaction with sitaxsentan.

Dr Robbins: Yes, it is something that we are aware of. I have some concerns in that physicians in the community aren't going to be as diligent about watching out for this interaction. There are certainly many drugs that interact with warfarin, so that is something that people should be aware of, but not always. With regard to ambrisentan, there were certainly some very impressive data presented at the American Thoracic Society this year regarding a phase 3 trial in Europe, showing a mean increase in a 6-minute walk distance of about 61 meters.



We use sildenafil as first-line therapy in some patients and bosentan in others. Certainly underlying liver disease and

coronary disease affect our decision. One of the worries with sildenafil is that because its side effect profile is very good, and because physicians have some familiarity and comfort level with it, it seems to be getting overused in certain patients who either need more aggressive therapy or in whom their pulmonary hypertension is being treated as pulmonary arterial hypertension, and shouldn't be treated at all. – Dr Tapson

Dr McLaughlin: It's a 5 mg dose.

Dr Robbins: Right, and that seems to be very well tolerated. We'll just have to see when it gets out there. Everyone is claiming that their liver function abnormalities are less and those of others are worse. This appears to be a class effect, although through different mechanisms for each endothelin receptor antagonist, but liver function will need to be monitored with this class of drugs in all patients.

Dr McLaughlin: Rich, what is your take on the different endothelin receptor antagonists?

Dr Channick: Clearly, bosentan was a breakthrough in treatment, being the first approved oral therapy for pulmonary hypertension. It is a very effective drug. Is it a cure? No, but again as we said before, we have patients who do dramatically well with the drug. I would say we really don't know where the new endothelin receptor antagonists fit in yet, and we won't until we have a lot more experience. Part of the problem is that we don't have studies comparing these agents to each other in a meaningful way.

Dr Robbins: I'd like to follow up on what you said. Let's say that we have another endothelial receptor antagonist approved here. You know none of these studies show overwhelmingly that one drug is better than the other. There hasn't been much head-to-head competition. What do you think your strategy is going to be if you have patients taking bosentan and they are not improving the way you want them to, or they are getting worse, or need intravenous epoprostenol? Would you consider another endothelial receptor antagonist or would you move to another drug?

Dr Channick: That's a great question, and I've wrestled with that myself. We haven't had that option yet but, presumably, we will. Do you go to combination therapy or substitution? Honestly, I don't have the answer to that question yet.

Dr Robbins: Well, I don't think anyone does. We are thinking about it too. It is sort of like blood pressure medications. Would you go for another calcium channel blocker or would you go to another ACE inhibitor? I don't know. I guess we'll just have to see with experience.

Dr McLaughlin: Great. So, let's move on to the phosphodiesterase inhibitors. This will be a little easier—there is only one commercially available. Vic, how has the availability of sildenafil changed your practice?

Dr. Tapson: We use sildenafil as first-line therapy in some patients and bosentan in others. Certainly underlying liver disease and coronary disease affect our decision. One of the worries with sildenafil is that because its side effect profile is very good, and because physicians have some familiarity and comfort level with it, it seems to be getting overused in certain patients who either need more aggressive therapy or in whom their pulmonary hypertension is being treated as pulmonary arterial hypertension, and shouldn't be treated at all.

Dr Robbins: Well, I don't think it has changed our practice a lot. We use quite a bit of sildenafil. We have had a number of patients with headache and flushing symptoms, which tend to get better, but we have had to discontinue treatment in a few people. In general, I think it is a well-tolerated drug. I think one has to take cost into account, and it is by far the cheapest medication available for the treatment of pulmonary arterial hypertension, and so I tend to start with that drug.

Dr McLaughlin: Do you tend to use sildenafil as a first-line drug, over an endothelin receptor antagonist as initial monotherapy?

Dr Robbins: Yes, in most cases.

Dr McLaughlin: Rich, what about you?

Dr Channick: We don't typically have that approach. And to address the issue of cost, as far as I am aware, the lowest dosage of sildenafil is the approved dosage of 20 mg tid. In my experience, and feel free to disagree, most patients seem to require more than 20 mg tid.

Dr Robbins: I think it is variable. Certainly many patients who were receiving higher doses in studies or who were getting sildenafil (Viagra) at 50 mg, a lot of them were just able to decrease to a lower dose. If a patient is not improving with 20 mg tid, then the cost goes up if you have to double the dosage. However, we have been able to work with insurance companies in a number of cases to get Viagra; then it is a similar cost for 50 mg.

Dr Channick: I get concerned about making this decision about issuing sildenafil first line. There are fewer long-term efficacy data on sildenafil in terms of survival and clinical worsening. So I am not as impressed with the long-term data on sildenafil yet. In our center our general approach would be at this point bosentan first line and sildenafil as add-on therapy. We certainly have had some patients receive sildenafil first, but those are patients in whom there is a contraindication to bosentan.

Dr Robbins: Rich, what would you say your long-term monotherapy is with bosentan? In the French study at least 50% of the patients were receiving another medicine.

Dr Channick: Certainly our experience mirrors that to some degree. The majority of our patients are not receiving monotherapy because our approach is an aggressive one. The question is, however, whether monotherapy really failed in these patients. In some cases it has, but certainly not in all cases. Our threshold for adding the therapy for a patient who, let's say, is still symptomatic, doing okay but not fabulously, is fairly low.

Dr McLaughlin: Let's move on to that next step. When do we decide to add or substitute? There are relatively few data to guide us with respect to that. With very few exceptions, the

trials that we've talked about so far are initial monotherapy trials. So everyone has a slightly different approach to that, and certainly combination therapy is a very hot topic in terms of clinical trials right now. Rich, at what point do you reassess your patients? How do you reassess? How do you decide whether an additional therapy is needed? How do you decide whether you are going to add or substitute therapy?

Dr Channick: We are, of course, always watching for worsening, but routinely we'll see patients back one month after initiating treatment, to evaluate if they are tolerating the therapy, not necessarily looking for efficacy to any great degree. Then at about 3 to 4 months we'll reassess, typically noninvasively, with 6-minute walk testing and clinical assessment. I perform a follow-up right heart catheterization if there is any question that the patient is not doing very well with monotherapy, and the results of that may drive us toward another therapy. But overall, I try to make a composite assessment of whether the patient is feeling better or feeling worse.

Dr. Tapson: We see our patients every 3 months and do a pro-BNP and 6-minute walk test. We do echocardiography, primarily to look at right ventricular function, every 6 months. And we do catheterizations as needed to make therapeutic decisions. We are trying to enroll in the COMPASS study, which is in patients taking baseline sildenafil who are randomized to receive bosentan or placebo, and in the TRIUMPH study, which is the randomized inhaled treprostinil (Remodulin) study in patients taking baseline bosentan or sildenafil. We are also excited about the FREEDOM trials, which will evaluate oral treprostinil.

Dr McLaughlin: What if they're stable, maybe a little bit better, they've improved in how they're feeling but perhaps not to a functional class II? Let's say they're still functional class III. Their 6-minute walk distance is perhaps a little bit improved, but not 400 or 500 meters. What do you do with that sort of patient?

Dr Channick: That's the kind of patient, at least at our center, we're trying to enroll into a trial, specifically now with inhaled treprostinil. It is important to keep in mind that there are centers around the country that are involved in these very important clinical trials to answer questions about combination therapy. For practitioners there is the opportunity to send a patient to a pulmonary hypertension center for enrollment in a trial. That would be the ideal approach in that kind of patient.

Dr McLaughlin: I can't emphasize that enough because we are still learning about the efficacy and safety of blocking more than one pathway. And also, as Ivan has mentioned,

given the costs of these drugs, the cost-effectiveness of using two or more therapies for patients with pulmonary arterial hypertension needs to be evaluated. It's very important for us to take the opportunity that we have now to enroll those sorts of patients in clinical trials of combination therapy so that we can answer those questions in an evidence-based fashion.

Dr Robbins: While you can set strict criteria, and some centers may do that, you really have to look at the individual patient. Let me give you an example. My approach or my aggressiveness would be very different between a 30-year-old woman with idiopathic pulmonary arterial hypertension and a 75-year-old patient with scleroderma. For patients like the one with scleroderma being treated with bosentan or sildenafil, if they are improved somewhat yet remain somewhat limited, I would tend to take a little more time and see

how they go. For patients like the 30-year-old woman with idiopathic pulmonary arterial hypertension being treated with sildenafil or bosentan, I would consider recatheterization in 3 months if they are not doing markedly better with oral therapy.

Dr. Tapson: I agree. It is key to individualize patients. The classic young idiopathic pulmonary arterial hypertension patient or young patient with scleroderma who does not have a stiff left ventricle needs to be treated as aggressively as possible.

Dr McLaughlin: Right, one needs to be more aggressive in a patient like that. We've mentioned some of the combination trials that are going on—the TRIUMPH trial, which is looking at inhaled treprostinil in patients who remain symptomatic while still taking either bosentan

or sildenafil as monotherapy—but there are a number of other ongoing combination trials. The COMPASS-2 trial is looking at the addition of bosentan or placebo in patients who are receiving sildenafil monotherapy and remain symptomatic. The COMPASS-2 trial will be the first morbidity and mortality trial ever in pulmonary arterial hypertension.

Dr Robbins: It is important to find out how these drugs are working. Physicians in the community are not only using bosentan but are also using combination therapy with sildenafil, and with iloprost in some cases, and they're using these agents without data, so it is important to get as much data as we can to make some evidence-based decisions.

Dr McLaughlin: We will prepare ourselves better in the long term if we do that. I got a phone call from one of my referring physicians a couple of weeks ago who said he treated a patient with idiopathic pulmonary arterial hypertension with bosentan and the patient wasn't doing as well as he would



My approach or my aggressiveness would be very different between a 30-year-old woman with idiopathic pulmonary arterial hypertension and a 75-year-old patient with scleroderma. For patients like the one with scleroderma being treated with bosentan or sildenafil, if they are improved somewhat yet remain somewhat limited, I would tend to take a little more time and see how they go. For patients like the 30-year-old woman with idiopathic pulmonary arterial hypertension being treated with sildenafil or bosentan, I would consider recatheterization in 3 months if they are not doing markedly better with oral therapy.

– Dr Robbins

have liked. He tried to add iloprost and the insurance company would not pay for it because there weren't enough evidence-based data to support that. I think we have been under the radar screen in terms of insurers for a long time and now that these therapies are being used with increasing frequency many insurers are starting to develop disease-management plans that question the evidence for many decisions we are making. So there are many combination trials going on with drugs we are very familiar with that target the three pathways we've already discussed. Let's take a minute and discuss some novel therapies. The Rho kinase inhibitors are getting some attention lately and will soon be studied in pulmonary hypertension. Ivan, would you like to comment on those drugs?

Dr Robbins: Rho kinase seems to be involved with virtually every pathway applicable to pulmonary hypertension. The results in animals are pretty impressive but it really acts, from what I've seen, as a vasodilator. Whether it leads to beneficial remodeling, I don't think we know. There's been some efficacy in patients with coronary artery disease and it seems to be reasonably well tolerated. Whether it will provide any benefit over sildenafil or bosentan, I don't know.

Dr McLaughlin: Inhaled vasoactive intestinal peptide (VIP) will, it's hoped, be studied soon. Rich, do you want to comment on that?

Dr Channick: VIP appears to be an important mediator in the development of pulmonary arteriopathy so is a very attractive target for therapy. Giving the drug by the inhalation route is a great idea. As pulmonologists, we really like the concept of inhaled therapy for pulmonary vascular disease. VIP is certainly an attractive player. There are some preliminary data that look positive. Whether it will add anything, we will have to see. There is no way to extrapolate from animal data or in vitro data to what we see when it comes to patient studies. As many of us have joked, we have cured pulmonary hypertension in the mouse but are still working on the human.

Dr Robbins: If you look at VIP, its effects are almost identical to those of prostacyclin. The only data we have out there are from one small study, and the data were incredibly good, remarkable, in fact. Whether the results could be reproduced, I don't know.

Dr McLaughlin: Are there any other novel therapies that may be entering phase 2 or phase 3 clinical trials in the near future?

Dr Robbins: There's imatinib (Gleevec).

Dr McLaughlin: What do you think of that?

Dr Robbins: I think there are some interesting case studies. There are also some recent reports of patients developing some heart failure who have been treated with imatinib for, what is it, chronic myeloid leukemia? We need to be careful. I think there is a small pilot study going on, so we will see what that shows. We've contemplated using it in a few patients in whom other therapies have failed, but we haven't yet. Rich, have you tried it?

Dr Channick: I have not tried it. I am waiting to see the results of those early studies. All I have seen are a couple of case reports that look favorable.

Dr. Tapson: We have not used imatinib yet, but are coming close. We need to be sure that the case report data can be backed up. This sort of salvage therapy, if effective, could lead to new approaches to induction therapy as well.



We've mentioned some of the combination trials that are going on—the TRIUMPH trial, which is looking at inhaled treprostinil in patients who remain symptomatic while still taking either bosentan or sildenafil as monotherapy—but there are a number of other ongoing combination trials. The COMPASS-2 trial is looking at the addition of bosentan or placebo in patients who are receiving sildenafil monotherapy and remain symptomatic. The COMPASS-2 trial will be the first morbidity and mortality trial ever in pulmonary arterial hypertension. – Dr McLaughlin

Dr Channick: Another novel thing is gene therapy. There is a trial with gene therapy going on, is that correct? In Canada?

Dr Robbins: That involves harvesting endothelial progenitor cells and transfecting them with nitric oxide synthase and then readministering them to a patient. Only patients with very advanced disease who have been refractory to many other therapies, I believe, are eligible. I'm not sure that even the first patient has been studied.

Dr McLaughlin: The last question is where and how these patients get treated. It's obviously a complex and relatively rare disease and it requires more than simply prescribing a pill. How do we

ensure that patients with this disease get appropriate and comprehensive care, given the current environment?

Dr Channick: In some cases we are victims of our own success. We have done a fabulous job of educating physicians through journals like this about the disease and the diagnostic approach and treatment options. With that education, however, comes the potential of physicians getting in over their heads and managing cases where a patient would be better served by experienced staff at a pulmonary hypertension center. Of course, we can't dictate how physicians treat their patients, but part of the educational message is that there are physicians who do nothing but take care of these diseases and there's no substitute for experience. Making ourselves accessible to community physicians and making it easy to refer patients to a center is a large part of our mission.

Dr Robbins: That's a good point, to create an environment where you have a partnership with community physicians, but I don't know how you can do quality control. As all of us

stress, you can have patients referred for at least a one-time visit. But we all approach patients a little differently and there are different thresholds for treating patients that we use. There is not one way to do it. I don't know how you can enforce any standards, really.

Dr McLaughlin: Vic, Rich, Ivan, thanks again for your participation. As always, it has been great working with you. ■

Editor's Memo

(continued from page 2)

Erika Berman Rosenzweig, MD, to the team of Associate Editors. Her focus and enthusiasm for the journal are refreshing and will help guide content in 2007.

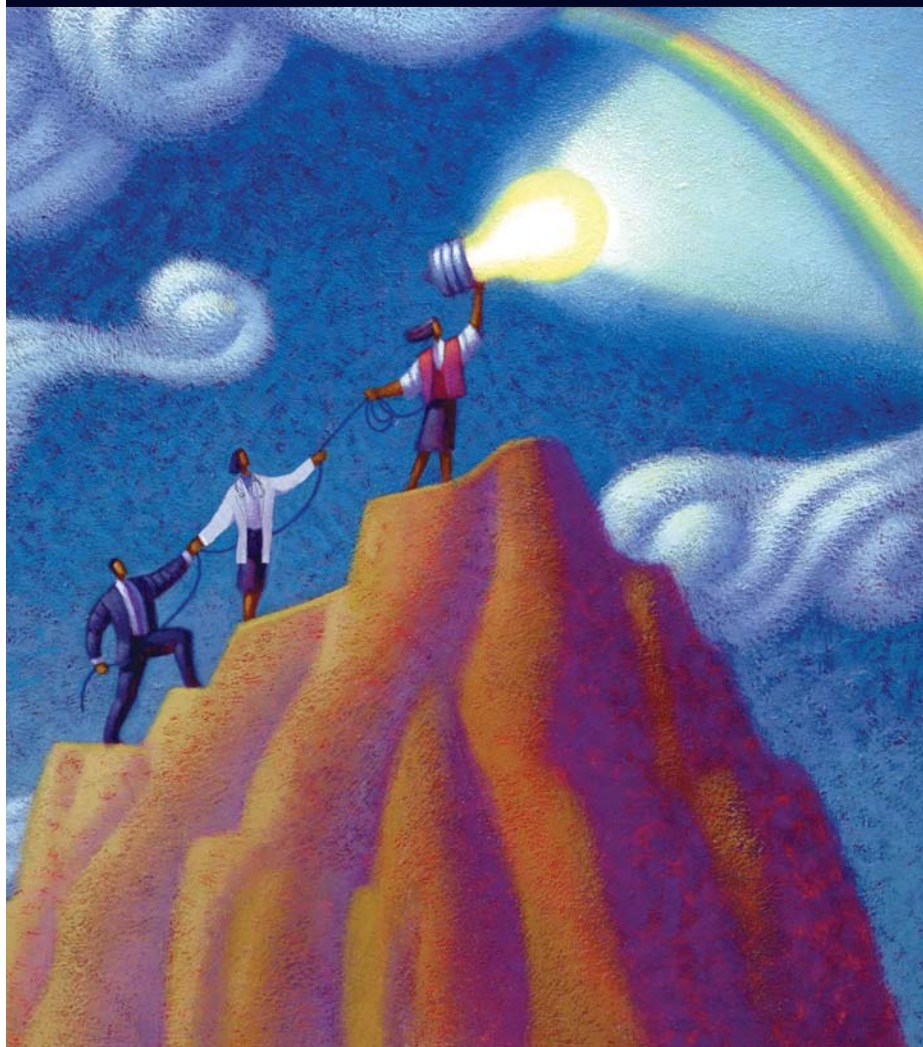
We will benefit also from new input by physicians who are joining our Editorial Board, including Kristin Highland, MD, Ioana Preston, MD, Zeenat Safdar, MD, Rajan Sagggar, MD, and Francisco Soto, MD. They will be taking over from physicians whose contribution as Editorial Board members is also much appreciated: Gregory Ahearn, MD, Jacques Benisty, MD, Raymond Benza, MD, and Jeffrey Edelman, MD.

We have seen significant progress in our effort to provide more hope to patients with pulmonary hypertension and I am honored to have been able to work with my colleagues and serve as Editor-in-Chief during the last 2 years. I also look forward to continued involvement with the journal and its outstanding educational program for more than 30,000 physicians engaged in pulmonary hypertension care.

I am sure I speak for all of our physicians and PHA staff in extending our best wishes for a joyous holiday season and a healthy and happy new year.

Vallerie V. McLaughlin, MD
Editor-in-Chief

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PH and Sickle Cell Disease

- Including basic epidemiology and pathophysiology in hemoglobinopathies
 - Sickle Cell diagnosis, screening
- Debates and controversies, cardiomyopathies, complications

For the treatment of pulmonary arterial hypertension (WHO Group I)
in patients with NYHA Class III or IV symptoms*

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If you treat patients with pulmonary arterial hypertension, it may be time to reexamine your options. What's changed? Ventavis—a potent prostacyclin analogue delivered through the lungs—is now in your armamentarium. By delivering prostacyclin benefits via inhalation, Ventavis is redefining prostacyclin therapy. The I-neb™ AAD® System is also redefining prostacyclin therapy by providing portable and precise delivery of Ventavis. For more information about Ventavis, please visit www.4VENTAVIS.com or call 1.877.4VENTAVIS (1.877.483.6828).



Ventavis®
(iloprost) Inhalation Solution

IMPORTANT SAFETY INFORMATION: In clinical studies, common adverse reactions due to Ventavis included: vasodilation (flushing, 27%), cough (39%), headache (30%), flu syndrome (14%), nausea (13%), trismus (12%), hypotension (11%), insomnia (8%), and syncope (8%); other serious adverse events reported with the use of Ventavis included congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, and kidney failure. Vital signs should be monitored while initiating Ventavis. Dose adjustments or a change in therapy should be considered if exertional syncope occurs. Ventavis should not be initiated in patients with systolic blood pressure lower than 85 mm Hg. Stop Ventavis immediately if signs of pulmonary edema occur. This may be a sign of pulmonary venous hypertension. Ventavis has not been evaluated in pediatric patients or patients with chronic obstructive pulmonary disease (COPD), severe asthma, or acute pulmonary infections.

*In controlled trials, Ventavis improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration.

Please see brief summary of prescribing information on the following page.

BRIEF SUMMARY

The following is a brief summary of the Full Prescribing Information for Ventavis (iloprost) Inhalation Solution. Please review the Full Prescribing Information prior to prescribing Ventavis.

INDICATIONS AND USAGE

Ventavis is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III or IV symptoms. In controlled trials, it improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration (see **CLINICAL PHARMACOLOGY, Clinical Trials** section of the Full Prescribing Information).

CONTRAINDICATIONS

There are no known contraindications.

WARNINGS

Ventavis is intended for inhalation administration only via either of two pulmonary drug delivery devices: the I-neb[™] AAD[®] System or the Prodose[®] AAD[®] System (See **DOSAGE AND ADMINISTRATION** section of the Full Prescribing Information). It has not been studied with any other nebulizers.

Vital signs should be monitored while initiating Ventavis. In patients with low systemic blood pressure, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mmHg. Physicians should be alert to the presence of concomitant conditions or drugs that might increase the risk of syncope. Syncope can also occur in association with pulmonary arterial hypertension, particularly in association with physical exertion. The occurrence of exertional syncope may reflect a therapeutic gap or insufficient efficacy, and the need to adjust dose or change therapy should be considered.

Should signs of pulmonary edema occur when inhaled iloprost is administered in patients with pulmonary hypertension, the treatment should be stopped immediately. This may be a sign of pulmonary venous hypertension.

PRECAUTIONS

General: Ventavis solution should not be allowed to come into contact with the skin or eyes; oral ingestion of Ventavis solution should be avoided.

Direct mixing of Ventavis with other medications in the I-neb[™] AAD[®] System or the Prodose[®] AAD[®] System has not been evaluated.

Ventavis has not been evaluated in patients with chronic obstructive pulmonary disease (COPD), severe asthma, or with acute pulmonary infections.

Information for Patients: 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** section of the Full Prescribing Information). Patients should be trained in proper administration techniques including dosing frequency, ampule dispensing, I-neb[™] AAD[®] System or Prodose[®] AAD[®] System operation, and equipment cleaning. Patients should be advised 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 a chair or bed. If fainting gets worse, patients should consult their physicians about dose adjustment.

Patients should be advised that Ventavis should be inhaled at intervals of not less than 2 hours and that the acute benefits of Ventavis may not last 2 hours.

Drug Interactions: In studies in normal volunteers, there was no pharmacodynamic interaction between intravenous iloprost and either nifedipine, diltiazem, or captopril. However, iloprost has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents. Since iloprost inhibits platelet function, there is a potential for increased risk of bleeding, particularly in patients maintained on anticoagulants. During clinical trials, iloprost was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, corticosteroids, and other medications. Intravenous infusion of iloprost had no effect on the pharmacokinetics of digoxin. Acetylsalicylic acid did not alter the clearance (pharmacokinetics) of iloprost.

Although clinical studies have not been conducted, *in vitro* studies of iloprost indicate that no relevant inhibition of cytochrome P450 drug metabolism would be expected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Iloprost was not mutagenic in bacterial and mammalian cells in the presence or absence of extrinsic metabolic activation. Iloprost did not cause chromosomal aberrations *in vitro* in human lymphocytes and was not clastogenic *in vivo* in NMRI/SPF mice. There was no evidence of a tumorigenic effect of iloprost clathrate (13% iloprost by weight) in Sprague-Dawley rats dosed orally for up to 8 months at doses of up to 125 mg/kg/day (Cmax of 45 ng/mL serum), followed by 16 months at 100 mg/kg/day, or in CrI:CD-1@((ICR)BR albino mice dosed orally for up to 24 months at doses of up to 125 mg/kg/day (Cmax of 156 ng/mL serum). The recommended clinical dosage regimen for iloprost (5 mcg) affords a serum Cmax of 0.16 ng/mL. Fertility of males or females was not impaired in Han-Wistar rats at intravenous doses up to 1 mg/kg/day.

Pregnancy: Pregnancy Category C. In developmental toxicity studies in pregnant Han-Wistar rats, continuous intravenous administration of iloprost at a dosage of 0.01 mg/kg daily (serum levels not available) led to shortened digits 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 (Cmax of 90 ng/mL), in pregnant rabbits at intravenous dosages of up to 0.5 mg/kg/day (Cmax of 86 ng/mL), and in pregnant monkeys at dosages of up to 0.04 mg/kg/day (serum levels of 1 ng/mL), no such digital anomalies or other gross-structural abnormalities were observed 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 litters at an intravenous dosage of 1 mg/kg/day. 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.

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 dose of 250 mg/kg/day of iloprost clathrate (13% iloprost by weight). It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Ventavis, a decision to discontinue nursing 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 age 65 and older to determine whether they respond differently than 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, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Hepatic or Renal Impairment: Ventavis has not been studied in patients with pulmonary hypertension and hepatic or renal impairment, both of which increase mean AUC in otherwise normal subjects (see **CLINICAL PHARMACOLOGY, Special Populations** section of the Full Prescribing Information).

ADVERSE REACTIONS

Safety data on Ventavis were obtained from 215 patients with pulmonary arterial hypertension receiving iloprost in two 12-week clinical trials and two long-term extensions. Patients received inhaled Ventavis for periods of from 1 day to more than 3 years. The median number of weeks of exposure was 15 weeks. Forty patients completed 12 months of open-label treatment with iloprost.

The following table shows adverse events reported by at least 4 iloprost patients and reported at least 3% more frequently for iloprost patients than placebo patients in the 12-week placebo-controlled study.

Adverse Events in Phase 3 Clinical Trial

| Adverse Events | Iloprost (n=101) | Placebo (n=102) | Placebo subtracted % |
|-------------------------|---------------------|--------------------|----------------------------|
| Vasodilation (flushing) | 27 | 9 | 18 |
| Cough increased | 39 | 26 | 13 |
| Headache | 30 | 20 | 10 |
| Trismus | 12 | 3 | 9 |
| Insomnia | 8 | 2 | 6 |
| Nausea | 13 | 8 | 5 |
| Hypotension | 11 | 6 | 5 |
| Vomiting | 7 | 2 | 5 |
| Alk phos increased | 6 | 1 | 5 |
| Flu syndrome | 14 | 10 | 4 |
| Back pain | 7 | 3 | 4 |
| Abnormal lab test | 7 | 3 | 4 |
| Tongue pain | 4 | 0 | 4 |
| Palpitations | 7 | 4 | 3 |
| Syncope | 8 | 5 | 3 |
| GGT increased | 6 | 3 | 3 |
| Muscle cramps | 6 | 3 | 3 |
| Hemoptysis | 5 | 2 | 3 |
| Pneumonia | 4 | 1 | 3 |

In a small clinical trial (the STEP trial, see **CLINICAL TRIALS** section of the Full Prescribing Information), safety trends in patients receiving concomitant bosentan and iloprost were consistent with those observed in the larger experience of the Phase 3 study in patients receiving only iloprost.

Serious adverse events reported with the use of inhaled iloprost and not shown in the table above include congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, and kidney failure.

Adverse events with higher doses: In a study in healthy volunteers (n=160), 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 dose inhalations (total cumulative dose of 70 mcg) or up to the highest dose tolerated in a subgroup of 40 volunteers. There were 13 subjects (32%) who failed to reach the highest scheduled dose (20 mcg). Five were unable to increase the dose because of (mild to moderate) transient chest pain/discomfort/tightness, usually accompanied by headache, nausea, and dizziness. The remaining 8 subjects discontinued for other reasons.

OVERDOSAGE

In clinical trials of Ventavis, no case of overdose was reported. Signs and symptoms to be anticipated are extensions of the dose-limiting pharmacological effects, including hypotension, headache, flushing, nausea, vomiting, and diarrhea. A specific antidote is not known. Interruption of the inhalation session, monitoring, and symptomatic measures are recommended.

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FLOLAN®: Over a Decade of Experience in PAH



Survival*

Measured in Moments,
Proven in Years¹



FLOLAN is indicated for the long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy.

IMPORTANT SAFETY INFORMATION: Use of FLOLAN is contraindicated in patients with congestive heart failure due to severe left ventricular systolic dysfunction. FLOLAN should not be used in patients who develop pulmonary edema during dose initiation. FLOLAN is also contraindicated in patients with known hypersensitivity to the drug or structurally-related compounds. Abrupt withdrawal or reductions in delivery of FLOLAN, as well as overdoses, may result in hemodynamic instability, including rebound pulmonary hypertension or fatal hypotension. FLOLAN should be used only by clinicians experienced in the diagnosis and treatment of pulmonary hypertension.

Excessive doses of FLOLAN may acutely result in systemic hypotension, tachycardia, jaw pain, headache, flushing, nausea and vomiting, diarrhea, flu-like symptoms, or anxiety; excessive doses administered chronically can lead to the development of a hyperdynamic state and high-output cardiac failure.

Although rare, serious adverse events have been reported during chronic infusion of FLOLAN. These include anemia, hypersplenism, thrombocytopenia, pancytopenia, splenomegaly, and hyperthyroidism.

Please see adjacent page for prescribing information.

*In patients with idiopathic pulmonary arterial hypertension (IPAH).

Reference: 1. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol.* 2002;40(4):780-788.



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for Injection
FLOLAN®
(epoprostenol sodium)

Proof of Survival

FLOLAN® (epoprostenol sodium) for Injection

The following is a brief summary only; see full Prescribing Information for complete product information.

INDICATIONS AND USAGE:

FLOLAN is indicated for the long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy.

CONTRAINDICATIONS:

A large study evaluating the effect of FLOLAN on survival in NYHA Class III and IV patients with congestive heart failure due to severe left ventricular systolic dysfunction was terminated after an interim analysis of 471 patients revealed a higher mortality in patients receiving FLOLAN plus conventional therapy than in those receiving conventional therapy alone. The chronic use of FLOLAN in patients with congestive heart failure due to severe left ventricular systolic dysfunction is therefore contraindicated.

Some patients with pulmonary hypertension have developed pulmonary edema during dose initiation, which may be associated with pulmonary veno-occlusive disease. FLOLAN should not be used chronically in patients who develop pulmonary edema during dose initiation.

FLOLAN is also contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds.

WARNINGS:

FLOLAN must be reconstituted only as directed using Sterile Diluent for FLOLAN. FLOLAN must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration.

Abrupt Withdrawal: Abrupt withdrawal (including interruptions in drug delivery) of sudden large reductions in dosage of FLOLAN may result in symptoms associated with rebound pulmonary hypertension, including dyspnea, dizziness, and asthenia. In clinical trials, one Class III PPH patient's death was judged attributable to the interruption of FLOLAN. Abrupt withdrawal should be avoided.

Sepsis: See ADVERSE REACTIONS: Adverse Events Attributable to the Drug Delivery System.

PRECAUTIONS:

General: FLOLAN should be used only by clinicians experienced in the diagnosis and treatment of pulmonary hypertension. The diagnosis of PPH or PH/SSD should be carefully established.

FLOLAN is a potent pulmonary and systemic vasodilator. Dose initiation with FLOLAN must be performed in a setting with adequate personnel and equipment for physiologic monitoring and emergency care. Dose initiation in controlled PPH clinical trials was performed during right heart catheterization. In uncontrolled PPH and controlled PH/SSD clinical trials, dose initiation was performed without cardiac catheterization. The risk of cardiac catheterization in patients with pulmonary hypertension should be carefully weighed against the potential benefits. During dose initiation, asymptomatic increases in pulmonary artery pressure coincident with increases in cardiac output occurred rarely. In such cases, dose reduction should be considered, but such an increase does not imply that chronic treatment is contraindicated.

During chronic use, FLOLAN is delivered continuously on an ambulatory basis through a permanent indwelling central venous catheter. Unless contraindicated, anticoagulant therapy should be administered to PPH and PH/SSD patients receiving FLOLAN to reduce the risk of pulmonary thromboembolism or systemic embolism through a patent foramen ovale. In order to reduce the risk of infection, aseptic technique must be used in the reconstitution and administration of FLOLAN as well as in routine catheter care. Because FLOLAN is metabolized rapidly, even brief interruptions in the delivery of FLOLAN may result in symptoms associated with rebound pulmonary hypertension including dyspnea, dizziness, and asthenia. The decision to initiate therapy with FLOLAN should be based upon the understanding that there is a high likelihood that intravenous therapy with FLOLAN will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a permanent intravenous catheter and infusion pump should be carefully considered.

Based on clinical trials, the acute hemodynamic response to FLOLAN did not correlate well with improvement in exercise tolerance or survival during chronic use of FLOLAN. Dosage of FLOLAN during chronic use should be adjusted at the first sign of recurrence or worsening of symptoms attributable to pulmonary hypertension or the occurrence of adverse events associated with FLOLAN (see DOSAGE AND ADMINISTRATION). Following dosage adjustments, standing and supine blood pressure and heart rate should be monitored closely for several hours.

Information for Patients: Patients receiving FLOLAN should receive the following information. **FLOLAN must be reconstituted only with Sterile Diluent for FLOLAN.** FLOLAN is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with FLOLAN requires commitment by the patient to drug reconstitution, drug administration, and care of the permanent central venous catheter. Sterile technique must be adhered to in preparing the drug and in the care of the catheter, and even brief interruptions in the delivery of FLOLAN may result in rapid symptomatic deterioration. A patient's decision to receive FLOLAN should be based upon the understanding that there is a high likelihood that therapy with FLOLAN will be needed for prolonged periods, possibly years. The patient's ability to accept and care for a permanent intravenous catheter and infusion pump should also be carefully considered.

ADVERSE REACTIONS:

During clinical trials, adverse events were classified as follows: (1) adverse events during dose initiation and escalation, (2) adverse events during chronic dosing, and (3) adverse events associated with the drug delivery system.

Adverse Events During Dose Initiation and Escalation: During early clinical trials, FLOLAN was increased in 2-ng/kg/min increments until the patients developed symptomatic intolerance. The most common adverse events and the adverse events that limited further increases in dose were generally related to vasodilation, the major pharmacologic effect of FLOLAN. The most common dose-limiting adverse events (occurring in ≥1% of patients) were nausea, vomiting, headache, hypotension, and flushing, but also include chest pain, anxiety, dizziness, bradycardia, dyspnea, abdominal pain, musculoskeletal pain, and tachycardia. Adverse events reported in ≥1% of patients receiving FLOLAN (n = 391) during dose initiation and escalation in decreasing order of frequency are as follows: flushing 58%; headache 49%; nausea/vomiting 32%; hypotension 16%; anxiety, nervousness, agitation 11%; chest pain 11%; dizziness 8%; bradycardia 5%; abdominal pain 5%; musculoskeletal pain 3%; dyspnea 2%; back pain 2%; sweating 1%; dyspepsia 1%; hypesthesia/paresthesia 1%; and tachycardia 1%.

Adverse Events During Chronic Administration: Interpretation of adverse events is complicated by the clinical features of PPH and PH/SSD, which are similar to some of the pharmacologic effects of FLOLAN (e.g., dizziness, syncope). Adverse events probably related to the underlying disease include dyspnea, fatigue, chest pain, edema, hypoxia, right ventricular failure, and pallor. Several adverse events, on the other hand, can clearly be attributed to FLOLAN. These include headache, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like symptoms, and anxiety/nervousness.

Adverse Events During Chronic Administration for PPH: In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, the following is a listing of adverse events that occurred at a rate at least 10% different in the 2 groups [FLOLAN (n = 52), conventional therapy (n = 54)] in controlled trials for PPH (events are listed by body system with the incidence for FLOLAN followed by conventional therapy):

Occurrence More Common with FLOLAN: General: chills/fever/sepsis/flu-like symptoms (25%, 11%); **Cardiovascular:** tachycardia (35%, 24%), flushing (42%, 2%). **Gastrointestinal:** diarrhea (37%, 6%), nausea/vomiting (67%, 48%). **Musculoskeletal:** jaw pain (54%, 0%), myalgia (44%, 31%), nonspecific musculoskeletal pain (35%, 15%). **Neurological:** anxiety/nervousness/tremor (21%, 9%), dizziness (83%, 70%), headache (83%, 33%), hypesthesia, hyperesthesia, paresthesia (12%, 2%).

Occurrence More Common with Standard Therapy: **Cardiovascular:** heart failure (31%, 52%), syncope (13%, 24%), shock (0%, 13%). **Respiratory:** hypoxia (25%, 37%).

Thrombocytopenia has been reported during uncontrolled clinical trials in patients receiving FLOLAN.

Additional adverse events that occurred at a rate with less than 10% difference reported in PPH patients receiving FLOLAN plus conventional therapy (n = 52) compared to conventional therapy alone (n = 54) during controlled clinical trials are as follows (events are listed by body system with incidence for FLOLAN followed by conventional therapy): **General:** asthenia (87%, 81%). **Cardiovascular:** angina pectoris (19%, 20%), arrhythmia (27%, 20%), bradycardia (15%, 9%), supraventricular tachycardia (8%, 0%), pallor (21%, 30%), cyanosis (31%, 39%), palpitation (63%, 61%), cerebrovascular accident (4%, 0%), hemorrhage (19%, 11%), hypotension (27%, 31%), myocardial ischemia (2%, 6%). **Gastrointestinal:** abdominal pain (27%, 31%), anorexia (25%, 30%), ascites (12%, 17%), constipation (6%, 2%). **Metabolic:** edema (60%, 63%), hypokalemia (6%, 4%), weight reduction (27%, 24%), weight gain (6%, 4%). **Musculoskeletal:** arthralgia (6%, 0%), bone pain (0%, 4%), chest pain (67%, 65%). **Neurological:** confusion (6%, 11%), convulsion (4%, 0%), depression (37%, 44%), insomnia (4%, 4%). **Respiratory:** cough increase (38%, 46%), dyspnea (90%, 85%), epistaxis (4%, 2%), pleural effusion (4%, 2%). **Skin and Appendages:** pruritus (4%, 0%), rash (10%, 13%), sweating (15%, 20%). **Special Senses:** amblyopia (6%, 4%), vision abnormality (4%, 0%).

Adverse Events During Chronic Administration for PH/SSD: In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, the following is a listing of adverse events that occurred at a rate at least 10% different in the 2 groups [FLOLAN (n = 58) and conventional therapy (n = 55)] in the controlled trial for patients with PH/SSD (events are listed by body system with the incidence for FLOLAN followed by conventional therapy):

Occurrence More Common with FLOLAN: **Cardiovascular:** flushing (23%, 0%), hypotension (13%, 0%); **Gastrointestinal:** anorexia (66%, 47%), nausea/vomiting (41%, 16%), diarrhea (50%, 5%); **Musculoskeletal:** jaw pain (75%, 0%), pain/neck pain/arthritis (84%, 65%); **Neurological:** headache (46%, 5%); **Skin and Appendages:** skin ulcer (39%, 24%), eczema/rash/urticaria (25%, 4%).

Occurrence More Common With Conventional Therapy: **Cardiovascular:** cyanosis (54%, 80%), pallor (32%, 53%), syncope (7%, 20%); **Gastrointestinal:** ascites (23%, 33%), esophageal reflux/gastritis (61%, 73%); **Metabolic:** weight decrease (45%, 56%); **Neurological:** dizziness (59%, 76%); **Respiratory:** hypoxia (55%, 65%).

Additional adverse events that occurred at a rate with less than 10% difference reported in PH/SSD patients receiving FLOLAN plus conventional therapy (n = 56) or conventional therapy alone (n = 55) during controlled clinical trials are as follows (adverse events occurred in at least 2 patients in either treatment group and are listed by body system with the incidence for FLOLAN followed by conventional therapy): **General:** asthenia (100%, 98%), hemorrhage/hemorrhage injection site/hemorrhage rectal (11%, 2%), infection/rhinitis (21%, 20%), chills/fever/sepsis/flu-like symptoms (13%, 11%); **Blood and Lymphatic:** thrombocytopenia (4%, 0%); **Cardiovascular:** heart failure/heart failure right (11%, 13%), myocardial infarction (4%, 0%), palpitation (63%, 71%), shock (5%, 5%), tachycardia (43%, 42%), vascular disorder peripheral (96%, 100%), vascular disorder (95%, 89%); **Gastrointestinal:** abdominal enlargement (4%, 0%), abdominal pain (14%, 7%), constipation (4%, 2%), flatulence (5%, 4%); **Metabolic:** edema/edema peripheral/edema genital (78%, 67%), hypercalcemia (48%, 51%), hyperkalemia (4%, 0%), thirst (0%, 4%); **Musculoskeletal:** arthritis (52%, 45%), back pain (13%, 5%), chest pain (52%, 45%), cramps/leg (5%, 7%); **Respiratory:** cough increase (82%, 82%), dyspnea (100%, 100%), epistaxis (9%, 7%), pharyngitis (5%, 2%), pleural effusion (7%, 0%), pneumonia (5%, 0%), pneumothorax (4%, 0%), pulmonary edema (4%, 2%), respiratory disorder (7%, 4%), sinusitis (4%, 4%); **Neurological:** anxiety/hyperkinesia/nervousness/tremor (7%, 5%), depression/depression psychotic (13%, 4%), hyperesthesia/hypesthesia/paresthesia (5%, 0%), insomnia (9%, 0%), somnolence (4%, 2%); **Skin and Appendages:** collagen disease (82%, 84%), pruritus (4%, 2%), sweat (41%, 36%); **Urogenital:** hematuria (5%, 0%), urinary tract infection (7%, 0%).

Although the relationship to FLOLAN administration has not been established, pulmonary embolism has been reported in several patients taking FLOLAN and there have been reports of hepatic failure.

Adverse Events Attributable to the Drug Delivery System: Chronic infusions of FLOLAN are delivered using a small, portable infusion pump through an indwelling central venous catheter. During controlled PPH trials of up to 12 weeks' duration, up to 21% of patients reported a local infection and up to 13% of patients reported pain at the injection site. During a controlled PH/SSD trial of 12 weeks' duration, 14% of patients reported a local infection and 9% of patients reported pain at the injection site. During long-term follow-up in the clinical trial of PPH, sepsis was reported at least once in 14% of patients and occurred at a rate of 0.32 infections/patient per year in patients treated with FLOLAN. This rate was higher than reported in patients using chronic indwelling central venous catheters to administer parenteral nutrition, but lower than reported in oncology patients using these catheters. Malfunctions in the delivery system resulting in an inadvertent bolus of or a reduction in FLOLAN were associated with symptoms related to excess or insufficient FLOLAN, respectively (see ADVERSE REACTIONS: Adverse Events During Chronic Administration).

Observed During Clinical Practice: In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of FLOLAN. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to FLOLAN.

Blood and Lymphatic: Anemia, hypersplenism, pancytopenia, splenomegaly.

Endocrine and Metabolic: Hypertrophy/adipoidism.

OVERDOSAGE:

Signs and symptoms of excessive doses of FLOLAN during clinical trials are the expected dose-limiting pharmacologic effects of FLOLAN, including flushing, headache, hypotension, tachycardia, nausea, vomiting, and diarrhea. Treatment will ordinarily require dose reduction of FLOLAN.

One patient with secondary pulmonary hypertension accidentally received 50 mL of an unspecified concentration of FLOLAN. The patient vomited and became unconscious with an initially unrecordable blood pressure. FLOLAN was discontinued and the patient regained consciousness within seconds. In clinical practice, fatal occurrences of hypoxemia, hypotension, and respiratory arrest have been reported following overdosage of FLOLAN.

Single intravenous doses of FLOLAN at 10 and 50 mg/kg (2,703 and 27,027 times the recommended acute phase human dose based on body surface area) were lethal to mice and rats, respectively. Symptoms of acute toxicity were hypocoactivity, ataxia, loss of righting reflex, deep slow breathing, and hypothermia.

DOSAGE AND ADMINISTRATION:

Important Note: FLOLAN must be reconstituted only with STERILE DILUENT for FLOLAN. Reconstituted solutions of FLOLAN must not be diluted or administered with other parenteral solutions or medications (see WARNINGS).

Dosage: Continuous chronic infusion of FLOLAN should be administered through a central venous catheter. Temporary peripheral intravenous infusion may be used until central access is established. Chronic infusion of FLOLAN should be initiated at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established and further increases in the infusion rate are not clinically warranted (see Dosage Adjustments). If dose-limiting pharmacologic effects occur, then the infusion rate should be decreased to an appropriate chronic infusion rate whereby the pharmacologic effects of FLOLAN are tolerated. In clinical trials, the most common dose-limiting adverse events were nausea, vomiting, hypotension, sepsis, headache, abdominal pain, or respiratory disorder (most treatment-limiting adverse events were not serious). If the initial infusion rate of 2 ng/kg/min is not tolerated, a lower dose that is tolerated by the patient should be identified.

In the controlled 12-week trial in PH/SSD, for example, the dose increased from a mean starting dose of 2.2 ng/kg/min. During the first 7 days of treatment, the dose was increased daily to a mean dose of 4.1 ng/kg/min on day 7 of treatment. At the end of week 12, the mean dose was 11.2 ng/kg/min. The mean incremental increase was 2 to 3 ng/kg/min every 3 weeks.

Dosage Adjustments: Changes in the chronic infusion rate should be based on persistence, recurrence, or worsening of the patient's symptoms of pulmonary hypertension and the occurrence of adverse events due to excessive doses of FLOLAN. In general, increases in dose from the initial chronic dose should be expected.

Increases in dose should be considered if symptoms of pulmonary hypertension persist or recur after improving. The infusion should be increased by 1- to 2-ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes. In clinical trials, incremental increases in dose occurred at intervals of 24 to 48 hours or longer. Following establishment of a new chronic infusion rate, the patient should be observed, and standing and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

During chronic infusion, the occurrence of dose-limiting pharmacological events may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment. Dosage decreases should be made gradually in 2-ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Abrupt withdrawal of FLOLAN or sudden large reductions in infusion rates should be avoided. Except in life-threatening situations (e.g., unconsciousness, collapse, etc.), infusion rates of FLOLAN should be adjusted only under the direction of a physician.

Administration: FLOLAN is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump. During initiation of treatment, FLOLAN may be administered peripherally.

To avoid potential interruptions in drug delivery, the patient should have access to a backup infusion pump and intravenous infusion sets. A multi-lumen catheter should be considered if other intravenous therapies are routinely administered.

To facilitate extended use at ambient temperatures exceeding 25°C (77°F), a cold pouch with frozen gel packs was used in clinical trials. Any cold pouch used must be capable of maintaining the temperature of reconstituted FLOLAN between 2° and 8°C for 12 hours.

Reconstitution: FLOLAN is stable only when reconstituted with STERILE DILUENT for FLOLAN. FLOLAN must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration.

GlaxoSmithKline
Research Triangle Park, NC 27709

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September 2002

RL-1139

In pulmonary arterial hypertension
WHO Class III or IV

Tracleer Stands Alone



*Clinical worsening defined as the combined endpoint of death, hospitalization for treatment related to PAH, discontinuation of therapy due to worsening PAH, or initiation of epoprostenol therapy.



Liver and pregnancy warnings Requires attention to two significant concerns: **Potential for serious liver injury** (including very rare cases of unexplained hepatic cirrhosis after prolonged treatment)—Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter. **High potential for major birth defects**—Pregnancy must be excluded and prevented by two forms of birth control; monthly pregnancy tests should be obtained.

In pulmonary arterial hypertension (PAH) WHO Class III or IV

Tracleer Stands Alone

The only oral therapy proven to reduce the risk of clinical worsening

- Clinical worsening is defined in bosentan clinical trials as the combined endpoint of death, hospitalization for treatment related to PAH, discontinuation of therapy due to worsening PAH, or initiation of epoprostenol therapy¹
- 71% relative risk reduction (26% absolute risk reduction) in clinical worsening data at 28 weeks in the BREATHE-1 pivotal trial. All patients (n=144, Tracleer group; n=69, control group) participated in the first 16 weeks; a subset (n=35, Tracleer group; n=13, control group) continued for up to 28 weeks¹

The only oral ERA with 2 years of follow-up data

- 93% and 84% of patients in the 2 Tracleer pivotal trials and their open-label extensions (N=235) were still alive at 1 year and 2 years, respectively, after the start of treatment with Tracleer²
- Without a control group, these data must be interpreted cautiously. These estimates may be influenced by the presence of epoprostenol treatment, which was administered to 43 of the 235 patients. Patients in the Tracleer trials may have also been receiving vasodilators (calcium channel blockers or ACE inhibitors), digoxin, anticoagulants, and/or diuretics²

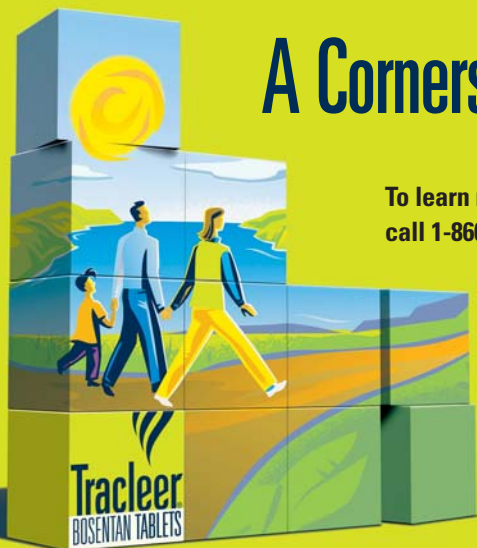
The only oral therapy prescribed to over 30,000 patients³

- Over 4 years of clinical experience and over 2 years of follow-up data in clinical trials

Liver and pregnancy warnings

Requires attention to two significant concerns: Potential for serious liver injury (including very rare cases of unexplained hepatic cirrhosis after prolonged treatment)—Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter. **High potential for major birth defects**—Pregnancy must be excluded and prevented by two forms of birth control; monthly pregnancy tests should be obtained.

Tracleer can be prescribed only through the Tracleer Access Program at 1-866-228-3546.



A Cornerstone of Oral Therapy

To learn more about Tracleer and PAH,
call 1-866-228-3546 or visit www.TRACLEER.com.



Please see brief summary of prescribing information and full reference list on following page.

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62.5 mg and 125 mg film-coated tablets

Brief Summary: Please see package insert for full prescribing information.

Use of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential damage to a fetus.

WARNING: Potential liver injury. TRACLEER® causes at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly (see WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION). In the post-marketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with TRACLEER® in patients with multiple co-morbidities and drug therapies. There have also been reports of liver failure. The contribution of TRACLEER® in these cases could not be excluded.

In at least one case the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of TRACLEER®. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping TRACLEER® with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction. (see DOSAGE AND ADMINISTRATION).

Elevations in aminotransferases require close attention (see DOSAGE AND ADMINISTRATION). TRACLEER® should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring liver injury may be more difficult. 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 should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances.

CONTRAINDICATION: Pregnancy. TRACLEER® (bosentan) is very likely to produce major birth defects if used by pregnant women. This effect has been seen consistently when it is administered to animals (see CONTRAINDICATIONS). Therefore, pregnancy must be excluded before the start of treatment with TRACLEER® and prevented thereafter by the use of a reliable method of contraception. 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® (see Precautions: Drug Interactions). Therefore, effective contraception through additional forms of contraception must be practiced. Monthly pregnancy tests should be obtained.

Because of potential liver injury and in an effort to make the chance of fetal exposure to TRACLEER® (bosentan) as small as possible, TRACLEER® may be prescribed only through TRACLEER® Access Program by calling 1 866 228 3546. Adverse events can also be reported directly via this number.

INDICATIONS AND USAGE: TRACLEER® is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.

CONTRAINDICATIONS: TRACLEER® is contraindicated in pregnancy, with concomitant use of cyclosporine A, with administration of glyburide, and in patients who are hypersensitive to bosentan or any component of the medication.

Pregnancy Category X. TRACLEER® is expected to cause fetal harm if administered to pregnant women. The similarity 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. There are no data on the use of TRACLEER® in pregnant women. TRACLEER® should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescription for TRACLEER® should not be issued by the prescriber unless the patient assures the prescriber that she is not sexually active or provides negative results from a urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking TRACLEER®. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, she must notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the pregnancy and to the fetus.

WARNINGS: Potential Liver Injury: Elevations in ALT or AST by more than 3 x ULN were observed in 11% of bosentan-treated patients (N = 658) compared to 2% of placebo-treated patients (N = 280). The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 3 x ULN) is a marker for potential serious liver injury. Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and to date have been reversible after treatment interruption or cessation. These aminotransferase elevations may reverse spontaneously while continuing treatment with TRACLEER®. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. 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 should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances. **Pre-existing Liver Impairment:** TRACLEER® should generally be avoided in patients with moderate or severe liver impairment. In addition, TRACLEER® should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) because monitoring liver injury in these patients may be more difficult.

PRECAUTIONS: Hematologic Changes: Treatment with TRACLEER® caused a dose-related decrease in hemoglobin and hematocrit. 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 of hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 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 of < 11 g/dl) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. In patients with pulmonary arterial hypertension treated with doses of 125 and 250 mg b.i.d., 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 29% of placebo-treated patients. In 80% of cases, the decrease occurred during the first 6 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained within normal limits in 68% 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. 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. **Fluid retention:** In a placebo-controlled trial of patients with severe chronic heart failure, there was an increased incidence of hospitalization for CHF associated with weight gain and increased leg edema during the first 4-8 weeks of treatment with TRACLEER®. 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.

Information for Patients: Patients are advised to consult the TRACLEER® Medication Guide on the safe use of TRACLEER®. The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases and urine or serum pregnancy testing and of avoidance of pregnancy. The physician should discuss options for effective contraception and measures to prevent pregnancy with their female patients. Input from a gynecologist or similar expert on adequate contraception should be sought as needed.

Drug Interactions: Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these isoenzymes will likely increase the plasma concentration of bosentan. Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes will be decreased when TRACLEER® is co-administered. Contraceptives: Co-administration of bosentan and the oral hormonal contraceptive Ortho-Novum® produced decreases of norethindrone and ethinyl estradiol levels by as much as 56% and 66%, respectively, in individual subjects. Therefore, hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when TRACLEER® is co-administered. Women should practice additional methods of contraception and not rely on hormonal contraception alone when taking TRACLEER®. Cyclosporine A: During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A (see CONTRAINDICATIONS). Tacrolimus: Co-administration of tacrolimus and bosentan has not been studied in man. 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. Glyburide: An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide (see CONTRAINDICATIONS). Alternative hypoglycemic agents should be considered. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A4. The possibility of worsened glucose control in patients using these agents should be considered. Ketconazole: Co-administration of bosentan 125 mg b.i.d. and ketconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold. No dose adjustment of bosentan is necessary, but increased effects of bosentan should be considered. Simvastatin and Other Statins: Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A4 substrate), and its active β-hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that have significant metabolism by CYP3A4, eg, lovastatin and atorvastatin. The possibility of reduced statin efficacy

should be considered. Patients using CYP3A4 metabolized statins should have cholesterol levels monitored after TRACLEER® is initiated to see whether the statin dose needs adjustment. Warfarin: Co-administration of bosentan 500 mg b.i.d. for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 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, and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. Digoxin, Nimodipine and Losartan: Bosentan has been shown to have no pharmacokinetic interactions with digoxin and nimodipine, and losartan has no effect on plasma levels of bosentan.

Sildenafil: In healthy subjects, co-administration of multiple doses of 125 mg b.i.d. bosentan and 80 mg t.i.d. sildenafil resulted in a reduction of sildenafil plasma concentrations by 63% and increased bosentan plasma concentrations by 50%. A dose adjustment of neither drug is necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses about 8 times the maximum recommended human dose (MRHD) of 125 mg b.i.d., on a mg/m² basis. In the same study, doses greater than about 32 times the MRHD were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses about 16 times the MRHD. Impairment of Fertility/Testicular Function: Many endothelin receptor antagonists have profound effects on the histology and function of the testes in animals. These drugs have been shown to induce atrophy of the seminiferous tubules of the testes and to reduce sperm counts and male fertility in rats when administered for longer than 10 weeks. Where studied, testicular tubular atrophy and decreases in male fertility observed with endothelin receptor antagonists appear irreversible. In fertility studies in which male and female rats were treated with bosentan at oral doses of up to 50 times the MRHD on a mg/m² basis, no effects on sperm count, sperm motility, mating performance or fertility were observed. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as about 4 times the MRHD for two years but not at doses as high as about 50 times the MRHD for 6 months. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to about 75 times the MRHD or in dogs treated up to 12 months at doses up to about 50 times the MRHD. There are no data on the effects of bosentan or other endothelin receptor antagonists on testicular function in man.

Pregnancy, Teratogenic Effects: Category X

SPECIAL POPULATIONS: Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding while taking TRACLEER® is not recommended. Pediatric Use: Safety and efficacy in pediatric patients have not been established. Use in Elderly Patients: Clinical experience with TRACLEER® in subjects aged 65 or older has not included a sufficient number of such subjects to identify a difference in response between elderly and younger patients.

ADVERSE REACTIONS: Safety data on bosentan were obtained from 12 clinical studies (8 placebo-controlled and 4 open-label) in 777 patients with pulmonary arterial hypertension, and other diseases. Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (5%; 8/165 patients) than on placebo (3%; 2/80 patients). In this database the only cause of discontinuations > 1%, and occurring more often on bosentan was abnormal liver function. In placebo-controlled studies of bosentan in pulmonary arterial hypertension and for other diseases (primarily chronic heart failure), a total of 677 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The duration of treatment ranged from 4 weeks to 6 months. For the adverse drug reactions that occurred in ≥ 3% of bosentan-treated patients, the only ones that occurred more frequently on bosentan than on placebo (≥ 2% difference) were headache (16% vs. 13%), flushing (7% vs. 2%), abnormal hepatic function (6% vs. 2%), leg edema (5% vs. 1%), and anemia (3% vs. 1%). Additional adverse reactions that occurred in > 3% of bosentan-treated pulmonary arterial hypertension patients were: nasopharyngitis (11% vs. 8%), hypertension (7% vs. 4%), palpitations (5% vs. 1%), dyspepsia (4% vs. 0%), edema (4% vs. 3%), fatigue (4% vs. 3%), and pruritus (4% vs. 0%). Post-marketing experience: hypersensitivity, rash, angiodema.

Special Considerations: Patients with Congestive Heart Failure (CHF): Based on the results of a pair of studies with 1613 subjects, bosentan is not effective in the treatment of CHF with left ventricular dysfunction.

OVERDOSAGE: Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 and 1000 mg b.i.d. of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed. There is no specific experience of overdose with bosentan beyond the doses described above. Massive overdose may result in pronounced hypotension requiring active cardiovascular support.

DOSAGE AND ADMINISTRATION: TRACLEER® treatment should be initiated at a dose of 62.5 mg b.i.d. for 4 weeks and then increased to the maintenance dose of 125 mg b.i.d. Doses above 125 mg b.i.d. 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 Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

| ALT/AST levels | Treatment and monitoring recommendations |
|-------------------|---|
| > 3 and ≤ 5 x ULN | Confirm by another aminotransferase test; if confirmed, reduce the daily dose 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). |
| > 5 and ≤ 8 x ULN | 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). |
| > 8 x ULN | 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. |

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. 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 should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances. Use in Women of Child-bearing Potential: See CONTRAINDICATIONS and Drug Interactions. **Dosage Adjustment in Renally Impaired Patients:** The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment. **Dosage Adjustment in Geriatric Patients:** Clinical studies of TRACLEER® did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. 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. **Dosage Adjustment in Hepatically Impaired Patients:** The influence of liver impairment on the pharmacokinetics of TRACLEER® has not been evaluated. Because there is *in vivo* and *in vitro* evidence that the main route of excretion of TRACLEER® is biliary, liver impairment would be expected to increase exposure to bosentan. There are no specific data to guide dosing in hepatically 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. **Dosage Adjustment in Children:** Safety and efficacy in pediatric patients have not been established. **Dosage Adjustment in Patients with Low Body Weight:** In patients with a body weight below 40 kg but who are over 12 years of age the recommended initial and maintenance dose is 62.5 mg b.i.d. **Discontinuation of Treatment:** There is limited experience with abrupt discontinuation of TRACLEER®. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg b.i.d. for 3 to 7 days) should be considered.

HOW SUPPLIED: 62.5 mg film-coated, round, biconvex, orange-white tablets, embossed with identification marking "62.5" NDC 66215-101-06; Bottle containing 60 tablets. 125 mg film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125" NDC 66215-102-06; Bottle containing 60 tablets.

Rx only.

STORAGE: Store at 20°C – 25°C (68°F – 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature].

References for previous pages: 1 Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med.* 2002;346:896-903. 2 Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals US, Inc. 2005. 3. Data on file, Actelion Pharmaceuticals.

To learn more: Call 1-866-228-3546 or visit www.TRACLEER.com

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\$30,000 stipend support per year for two years/
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- Genetics
- Molecular biology of pulmonary vascular endothelium
- Development of new pharmacologic agents to treat PH
- Development of innovative techniques for early diagnosis
- Pathophysiology of right heart failure
- Epidemiology of risk factors for developing PH

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Brian Hawkins, PhD
University of Pennsylvania, PA
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Project: "Sphingosine-1-Phosphate and
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