Drug Use Research & Management Program
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Month/Year of Review: April 2012
PDL Classes: Pulmonary Arterial Hypertension Agents

Date of Last Review: September 2010
Source Document: Provider Synergies

Current Preferred Agents:	Current Non-Preferred Agents*:
Oral Agents Bosentan (Tracleer®) Sildenafil (Revatio®) Tadalafil (Adcirca®)	Oral Agents Ambrisentan (Letairis®) Inhalation Agents Iloprost (Ventavis®) Treprostinil (Tyvaso®)

Previous Recommendations:

1. There is no evidence found to support a difference in efficacy/effectiveness between members of this class.
2. There was no evidence found to support a difference in harms between members of this class.
3. Consideration should be given to including at least on medication from each dosage form (oral and inhalation).
4. Prior Authorization (PA) criteria should be considered for appropriate patient selection.

PA Criteria/QL: Prior Authorization is required for non preferred agents on PDL to ensure appropriate use for pulmonary arterial hypertension (Appendix 1). This requires the patient have a World Health Organization Functional Class (WHO-FC) of II-IV and the drug prescribed by a pulmonologist or cardiologist. Revatio and Adcirca have the FDA indication for pulmonary hypertension and should not be used for erectile dysfunction.

Methods:

A MEDLINE OVID search was conducted using all included oral and inhalation drugs in pulmonary arterial hypertension and limits for humans, English language, and controlled clinical trials or meta-analysis from 2010 to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Systematic Reviews:

A Meta -analysis was performed and reviewed by the Centre for Reviews and Dissemination and met their criteria for inclusion.[1] Twenty-four randomized controlled trials (RCTs) with 3,758 participants were included. This review concluded that prostanoids, endothelin receptor antagonists and phosphodiesterase type 5 (PDE5) inhibitors all had benefits in people with pulmonary arterial hypertension. Only intravenous prostanoids had a proven benefit on mortality, particularly in people with severe disease (RR 0.49, 95% CI 0.29 to 0.82; 10 trials). Compared to placebo, endothelin receptor antagonists (8 studies) and PDE5 inhibitors (3 trials) had no statistically significant effect on mortality. Endothelin receptor antagonists were associated with statistically significant improvements in six-minute walk distance (6MWD) based on seven trials (38 meters, 95% CI 27.2 to 48.7), functional class (six trials), Borg score (five trials) and most hemodynamic changes. PDE5 inhibitors were associated with statistically significant improvements in six-minute walk distance (33.7 meters, 95% CI 22.5 to 44.8; three trials) and all reported hemodynamic parameters (two trials). Available data was based on studies of short duration (12 -16 weeks) and authors agreed that longer term studies were needed to confirm results.

New Trials:
A total of 30 citations resulted from the initial MEDLINE search and after review for inclusion, four potentially relevant clinical trials were identified (Appendix 2). These trials are briefly described in Table 1.

Table 1: Study details

Study	Comparison	Population	Primary Outcome	Results
McLaughlin, 2010[2] DB, MC, PC, RCT TRIUMPH-1	Treprostinil inhaled four times daily vs. placebo in patients already on either bosentan or sildenafil therapy	Adults with PAH, baseline 6MWD between 200 and 450m, receiving bosentan 125mg daily or any prescribed dose of sildenafil for at least 3 months N=235	Change in 6MWD measured at peak (10 to 60 minutes after inhalation)	<u>Change in 6MWD at 12 weeks:</u> • Between-treatment median difference in change from baseline in peak 6MWD was 20 m (*P*=0.0004). • Between-treatment median difference in change in peak 6MWD was 25 m (*P*=0.0002) in patients receiving background bosentan therapy and 9 m in patients taking sildenafil background therapy (*P* value not significant). • There was no difference in time to clinical worsening between treatment groups
Barst, 2011[3] DB, PC	Tadalafil 2.5mg vs. 10mg vs. 20mg vs. 40mg vs. placebo stratified by background bosentan	Patients with PAH with the option of background bosentan	Change in 6-minute walk distance (6MWD)	<u>PBO-adjusted change in 6MWD from baseline at week 16 (meters)</u> *Bosentan background* 20mg: 22.6; 95 % CI (-0.5 to 45.7), p=NS 40mg: 22.7; 95% CI (-2.4 to 47.8), p=NS *Treatment-naïve* 20mg: 32.4; 95% CI (6.8 to 58.1), p=NS 40mg: 44.3; 95% CI (19.7 to 69.0), p<0.01
Sun, 2011[4] Open-label, uncontrolled, prospective	Low dose iloprost (2.5 ug per inhalation, 6 x daily) x 24 weeks	Adults patients with PAH (n=62), 95% in WHO-FC classes II and III	Change in 6-minute walk distance (6MWD)	<u>Change in 6MWD from baseline</u> + 57 meters; 95% CI (26.59-87.82), p<0.001 *The WHO_FC was improved significantly (p=0.006), no significant in change in systemic arterial oxygen saturation and systemic arterial pressure **14 patients (22.6%) discontinued the study prematurely
Barst, 2012[5] DB, PC, RCT	Low-dose vs. medium-dose vs. high-dose sildenafil vs. placebo	Treatment-naïve children, aged 1-17	% change from baseline in peak oxygen consumption (PVo2) to week 16	<u>% change from baseline inPVo2</u> Low: 3.8<u>+</u>5.0% [95% CI, -6.1% to 13.7%] Med: 11.3 <u>+</u> 4.8% [95% CI, 1.7–20.9%] high: 8.0 <u>+</u> 4.9% [95% CI, -1.6% to 17.6%] Combined sildenafil: 7.7 <u>+</u> 4.0% (95% CI, -0.2% to 15.6%);p=0.056

New drugs:
None

New FDA safety alerts:
On March 4, 2011, the Food and Drug Administration removed a boxed warning about a potential for liver injury from the prescribing information for ambrisentan based on the review of post-marketing data; monthly liver function monitoring is no longer required.[6] Healthcare professionals should still order liver enzyme tests when they consider it clinically necessary. Bosentan, however, is still not recommended in patients with liver impairment.

Recommendations:
- No further research or review needed
- Evaluate comparative costs for further class decision making.

References:

1. Ryerson CJ, Nayar S, Swiston JR, Sin DD. Pharmacotherapy in pulmonary arterial hypertension: a systematic review and meta-analysis. *Respir. Res.* 2010;11:12.

2. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J. Am. Coll. Cardiol.* 2010;55(18):1915–1922.

3. Barst RJ, Oudiz RJ, Beardsworth A, et al. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. *J. Heart Lung Transplant.* 2011;30(6):632–643.

4. Sun Y-J, Xiong C-M, Shan G-L, et al. Inhaled Low-Dose Iloprost for Pulmonary Hypertension: A Prospective, Multicenter, Open-Label Study. *Clinical Cardiology*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22488211. Accessed April 20, 2012.

5. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. *Circulation*. 2012;125(2):324–334.

6. FDA Drug Safety Communication. Liver injury warning to be removed from Letairis (ambrisentan) tablets. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm245852.htm. Accessed April 24, 2012.

Appendix 1: Current PA

Pulmonary Arterial Hypertension

Goal(s): To ensure appropriate drug use for pulmonary arterial hypertension (PAH) by utilization in specified patient population.

Length of Authorization: 1 year

Preferred Alternatives: See PDL options: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

* Note: Revatio and Adcirca have the FDA indication for pulmonary hypertension and should not be used for Erectile Dysfunction (ED). Viagra® and Cialis® are FDA-approved for ED and not covered by OHP.

Requires PA:

GSN	Drug Name	Brand Name
	Bosentan	Tracleer
	Iloprost	Ventavis
	Treprostinil	Tyvaso

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code**.**	
2. Is this an OHP covered diagnosis?	**Yes:** Go to #3	**No**: Pass to RPh, DENY (Not covered by the OHP)
3. Does the patient have a diagnosis of pulmonary arterial hypertension (PAH)?	**Yes:** Go to #4	**No:** Pass to RPh. RPh go to #8
4. Is this renewal of current therapy?	Yes: Go to bottom section titled "renewal"	No: go to #5
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml. Approve for 1 year.	**No:** Go to #6
6. Does the patient have a WHO FC Classification of II-IV?	**Yes:** Go to #7	**No:** Deny (Medical Appropriateness)

7. Is the drug being prescribed by a pulmonologist or a cardiologist?	**Yes:** Approve for 1 year	**No:** Deny (Medical Appropriateness)

8. RPh Only; All other indications need to be evaluated as to whether they are above the line or below the line diagnosis.

- **If above the line or clinic provides supporting literature:** approve for length of treatment.
- **If below the line:** Deny, (Not Covered by the OHP).

Renewal		
1. Does the patient have PAH with a WHO FC Classification of II-IV?	**Yes:** Go to #2	**No:** Deny (Medical Appropriateness)
2. Is the drug being prescribed by a pulmonologist or a cardiologist?	**Yes:** Approve for 1 year	**No:** Deny (Medical Appropriateness)

DUR Board Action: *9/16/10 (KS)*
Revision(s):

Appendix 2: Trial Abstracts

1. McLaughlin VV, Benza RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF, Robbins IM, Olschewski H, Rubenfire M, Seeger W. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol. 2010 May 4;55(18):1915-22.

OBJECTIVES: This study assessed the efficacy and safety of inhaled treprostinil in pulmonary arterial hypertension (PAH) patients receiving therapy with either bosentan or sildenafil. BACKGROUND: There is no cure for PAH, despite effective treatments, and outcomes remain suboptimal. The addition of inhaled treprostinil, a long-acting prostacyclin analog, might be a safe and effective treatment addition to other PAH-specific oral therapies. METHODS: Two hundred thirty-five PAH patients with New York Heart Association (NYHA) functional class III (98%) or IV symptoms and a 6-min walk distance (6MWD) of 200 to 450 m while treated with bosentan (70%) or sildenafil were randomized to inhaled treprostinil (up to 54 mug) or inhaled placebo 4 times daily. The primary end point was peak 6MWD at 12 weeks. Secondary end points included time to clinical worsening, Borg Dyspnea Score, NYHA functional class, 12-week trough 6MWD, 6-week peak 6MWD, quality of life, and PAH signs and symptoms. The biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) was assessed. RESULTS: Twenty-three patients withdrew from the study prematurely (13 treprostinil, 10 placebo). The Hodges-Lehmann between-treatment median difference in change from baseline in peak 6MWD was 19 m at week 6 ($p = 0.0001$) and 20 m at week 12 ($p = 0.0004$). Hodges-Lehmann between-treatment median difference in change from baseline in trough 6MWD at week 12 was 14 m ($p = 0.0066$). Quality of life measures and NT-proBNP improved on active therapy. There were no improvements in other secondary end points, including time to clinical worsening, Borg Dyspnea Score, NYHA functional class, and PAH signs and symptoms. Inhaled treprostinil was safe and well-tolerated. CONCLUSIONS: This trial demonstrates that, among PAH patients who remain symptomatic on bosentan or sildenafil, inhaled treprostinil improves exercise capacity and quality of life and is safe and well-tolerated. (TRIUMPH I: Double Blind Placebo Controlled Clinical Investigation Into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients With Severe Pulmonary Arterial Hypertension; NCT00147199).

2. Barst RJ, Oudiz RJ, Beardsworth A, Brundage BH, Simonneau G, Ghofrani HA, Sundin DP, Galiè N; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension.

BACKGROUND: Tadalafil 40 mg orally once daily, was shown to be well-tolerated and efficacious for pulmonary arterial hypertension in a 16-week, double-blind, placebo (PBO)-controlled trial. Inclusion criteria included the option for background bosentan. Analyses of tadalafil in treatment-naive patients and as add-on to bosentan were pre-specified. Objectives were to provide safety and efficacy data for both groups.METHODS: Groups analyzed included: treatment-naive + PBO; treatment-naive + tadalafil; background bosentan + PBO; and background bosentan + tadalafil. Patients randomized to tadalafil or PBO (N = 405) were analyzed by bosentan use (yes = 216, no = 189). Treatment differences in 6-minute walk distance (6MWD, PBO-adjusted), functional class (FC), clinical worsening (CW) and adverse events were assessed. Hazard ratios (HRs) with 95% confidence intervals (CIs) are presented for FC and CW.RESULTS: At Week 16, PBO-adjusted 6MWD increases were 44 m (CI: 20 to 69 m; n = 37) for tadalafil 40 mg in treatment-naive patients and 23 m (CI: -2 to 48 m; n = 42) for tadalafil 40 mg add-on to bosentan. The 6MWD for treatment-naive and background bosentan PBO patients decreased by 3 m and increased by 19 m, respectively, at Week 16 compared with baseline. Two (5%) treatment-naive patients had CW with tadalafil 40 mg vs 8 (22%) with PBO (HR = 3.3, CI: 1.1 to 10.0). Two (5%) background bosentan patients had CW with tadalafil 40 mg add-on vs 5 (11%) for PBO add-on (HR = 1.9, CI: 0.4 to 10.2). Adverse events for tadalafil monotherapy and as add-on were similar.CONCLUSION: Tadalafil 40 mg was well-tolerated and provided clinical benefit in patients as monotherapy. It was also well-tolerated when added to background bosentan, but data are insufficient to conclude additional benefit.

3. Sun YJ, Xiong CM, Shan GL, Gu Q, Zeng WJ, Lu XL, Zhu F, Liu ZH, Ni XH, He JG; on behalf of the Iloprost Therapy on Pulmonary Hypertension Study Group. Inhaled Low-Dose Iloprost for Pulmonary Hypertension: A Prospective, Multicenter, Open-Label Study. Clin Cardiol. 2012 Apr 9. doi: 10.1002/clc.21987. [Epub ahead of print]

BACKGROUND: Inhaled iloprost (average >30 μg/d) has been considered an effective treatment for severe pulmonary hypertension (PH). Further evidence also showed that low-dose iloprost given intravenously was equally effective as high-dose iloprost in the therapy of systemic sclerosis. HYPOTHESIS: Patients with pulmonary hypertension will benefit from inhalation of low-dose iloprost. METHODS: Sixty-two patients with PH were enrolled and initiated with neubulizedlow-dose iloprost (2.5 μg per inhalation, 6× daily) for 24 weeks in 13 medical centers in China. Efficacy endpoints included changes in 6-minute walk distance (6MWD), World Health Organization functional class (WHO-FC), and hemodynamic parameters.RESULTS: Fourteen patients (22.6%) prematurely discontinued the study: 8 due to clinical worsening (6 in WHO-FCIII-IV at baseline), 4 because of protocol change, and 2 patients lost during follow-up. In the remaining 48 patients, 6MWD was increased from 356 ± 98 meters to 414 ± 99 meters ($P < 0.001$) and WHO-FC improved significantly ($P = 0.006$) after 24-week inhalation therapy. Cardiac output, cardiac index, and mixed venous oxygen saturation improved significantly compared with baseline ($n = 34$, $P < 0.05$). Most of the hemodynamic parameters improved significantly in patients in WHO-FC II ($P < 0.05$) but not in patients in WHO-FCIII-IV. CONCLUSIONS: Low-dose iloprost inhalation significantly improved exercise capacity and functional status in patients with PH. It was well tolerated. The improvement of hemodynamics was confirmed in patients with WHO-FCI-II but not in patients with WHO-FCIII-IV, suggesting the importance of early treatment in patients with advanced disease stages. Clin. Cardiol. 2012 DOI: 10.1002/clc.21987 This study was supported by National Grant from the Ministry of Science and Technology (Beijing, China, project number 2006BAI01A07) and the Capital Development Scientific Fund (Beijing, China, project number 2005-1018). The authors have no other funding, financial relationships, or conflicts of interest to disclose.

4. Barst RJ, Ivy DD, Gaitan G, Szatmari A, Rudzinski A, Garcia AE, Sastry BK, Pulido T, Layton GR, Serdarevic-Pehar M, Wessel DL. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension.

BACKGROUND: Safe, effective therapy is needed for pediatric pulmonary arterial hypertension. METHODS AND RESULTS: Children (n=235; weight ≥8 kg) were randomized to low-, medium-, or high-dose sildenafil or placebo orally 3 times daily for 16 weeks in the Sildenafil in Treatment-Naive Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension (STARTS-1) study. The primary comparison was percent change from baseline in peak oxygen consumption (PV(O(2))) for the 3 sildenafil doses combined versus placebo. Exercise testing was performed in 115 children able to exercise reliably; the study was powered for this population. Secondary end points (assessed in all patients) included hemodynamics and functional class. The estimated mean±SE percent change in PV(O(2)) for the 3 doses combined versus placebo was 7.7±4.0% (95% confidence interval, -0.2% to 15.6%; P=0.056). PV(O(2)), functional class, and hemodynamics improved with medium and high doses versus placebo; low-dose sildenafil was ineffective. Most adverse events were mild to moderate in severity. STARTS-1 completers could enter the STARTS-2 extension study; patients who received sildenafil in STARTS-1 continued the same dose, whereas placebo-treated patients were randomized to low-, medium-, or high-dose sildenafil. In STARTS-2 (ongoing), increased mortality was observed with higher doses. CONCLUSIONS: Sixteen-week sildenafil monotherapy is well tolerated in pediatric pulmonary arterial hypertension. Percent change in PV(O(2)) for the 3 sildenafil doses combined was only marginally significant; however, PV(O(2)), functional class, and hemodynamic improvements with medium and high doses suggest efficacy with these doses. Combined with STARTS-2 data, the overall profile favors the medium dose. Further investigation is warranted to determine optimal dosing based on age and weight.