PDE-5 Inhibitors in Pulmonary Hypertension Monograph
April 2012

Introduction:

According to recent statistics, the total number of estimated hospitalizations of individuals with pulmonary hypertension (PH) at all ages was reported as 260,000 in 2002. The total number of Medicare hospitalizations for elderly persons (aged ≥65 years) with a diagnosis of all types PH was 87,205, which include 503 cases from Native Americans in 2002. There were 15,668 cases reported with PH as the contributing cause of death in the U.S.; American Indians/Alaska Natives accounted for 69 of these cases.[1]

Pulmonary arterial hypertension (PAH) is one of the classes in PH that is associated with chronic hardening of the pulmonary arteries and causing chronic hypertension in these arteries. This incurable disease is defined as a mean pulmonary artery pressure (PAPm) ≥ 25 mm Hg with a pulmonary capillary wedge pressure ≤ 15 mm Hg measured by cardiac catheterization.[2] Among the types of PH, the 4th World Symposium of PH defined PAH with the Dana Point classification as Group 1 and that includes idiopathic and heritable PAH, drug- and toxin-induced PAH, PAH associated with other cause (connective tissue diseases, HIV infection, portal hypertension, congenital heart diseases, schistosmoiasis, and chronic hemolytic anemia), and persistent pulmonary hypertension of the newborn.[3] Without appropriate treatment, various complications can occur including right ventricular dysfunction and impaired tolerance to physical activity, which may lead to right-heart failure and death. [4] New York Heart Association (NYHA) and World Health Organization (WHO) each published a functional classification that can be used in the disease progression assessment and the determination of treatment choices (Table 1).[5]

Table 1 New York Heart Association and World Health Organization PH functional classification[5]

A. New York Heart Association functional classification	
Class 1	No symptoms with ordinary physical activity.
Class 2	Symptoms with ordinary activity. Slight limitation of activity.
Class 3	Symptoms with less than ordinary activity. Marked limitation of activity.
Class 4	Symptoms with any activity or even at rest.

B. World Health Organization functional assessment classification		
	Description	**Pharmacologic Recommendations***
Class I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.	Oral calcium channel blocker (CCB) for IPAH or other PAH (B)
Class II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue,	Patients in functional class II who are not candidates for, or who have failed, CCB therapy, may benefit from treatment with:

	chest pain, or near syncope.	- Sildenafil (A) - Subcutaneous treprostinil (C) - IV treprostinil (C)
Class III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.	Patients in functional class III who are not candidates for, or who have failed, CCB therapy are candidates for long-term therapy with: - Endothelin receptor antagonists (bosentan), or sildenafil, in no order of preference (A) - IV epoprostenol (A) - Inhaled iloprost (A) - Subcutaneous treprostinil (B) - IV treprostinil (C)
Class IV	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.	PAH patients in functional class IV who are not candidates for, or who have failed, CCB therapy are candidates for long-term therapy with: - IV epoprostenol *(treatment of choice)* (A) Other treatments available for the treatment of functional class IV PAH patients include, in no order of preference: - Endothelin receptor antagonists (bosentan) (B) - Inhaled iloprost (B) - Subcutaneous treprostinil (B) - Sildenafil (C) - IV treprostinil (C)

Strength of Recommendation:
A - Strong recommendation; **B** - Moderate recommendation; **C** - Weak recommendation; **D** - Negative recommendation
* Badesch et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines.

There are several conditions that have been associated with the risk of developing PAH. These include: scleroderma, sickle-cell disease, thyroid dysfunction, chronic liver and renal disease.[6] The goals of treatment are to treat the underlying causes, reduce symptoms, improve quality of life, delay the growth of the smooth muscle cells and the development of blood clots, and increase cardiac perfusion while reducing cardiac workload. The recommended initial treatment options upon diagnosis include oral anticoagulants such as warfarin, oxygen, and diuretics such as hydrochlorothiazide and furosemide.

Note: Information within this document is current as of this writing and should not replace clinical judgment.

Currently, sildenafil (Revatio®) and tadalafil (Adcirca®) are the available phosphodiesterase-5 (PDE-5) inhibitors used to treat PAH.

Pharmacology/Pharmacokinetics: [7,8]

Mechanism of Action:

Revatio is the citrate salt of sildenafil. Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1 methyl-7-oxo-3-propyl-1H-pyrazolo [4,3- d] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate.[7]

The chemical designation of tadalafil is pyrazino[1' ,2' :1,6]pyrido[3,4–b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a- hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and slightly soluble in ethanol.[8]

Sildenafil and tadalafil inhibit PDE-5 in smooth muscle of pulmonary vasculature where PDE-5 is responsible for the degradation of cyclic guanosine monophosphate (cGMP). Increased cGMP concentration results in pulmonary vasculature relaxation; vasodilation in the pulmonary bed and the systemic circulation (to a lesser degree) may occur.

Pharmacokinetic/Pharmacodynamic Properties[7,8]

Drug	Absorption	Distribution	Metabolism	Excretion
Sildenafil	Rapid; slower with a high-fat meal Bioavailability: 41% (25% to 63%) Time to peak: 30-120 minutes; delayed by 60 minutes with a high-fat meal Onset of action: 60 minutes	Vd: 105 L Protein binding: 96%	Hepatic, via CYP3A4 (major) and CYP2C9 (minor route); forms N-desmethyl metabolite (active)	Half-life elimination: ~4 hours; the elderly and those with severe renal impairment have reduced clearance of sildenafil and its active N-desmethyl metabolite Excretion: feces (~80%); urine (~13%)
Tadalafil	Time to peak: 4 hours Onset of action: Within 1 hour	Vd: 77 L Protein binding: 94%	Hepatic, via CYP3A4 to catechol metabolites (inactive)	Half-life elimination: 35 hours Excretion: feces (~61%); urine (~36%)

FDA Approved Indications: [7-9]

Sildenafil (oral, IV) and tadalafil (oral) are both approved for the treatment of PAH (WHO Group I) to improve exercise ability. Sildenafil is also approved for delay in clinical worsening. Clinical studies of tadalafil included patients predominately from NYHA Functional Class II – III symptoms and those diagnosed with idiopathic or heritable PAH, or PAH associated with connective tissue diseases. Sildenafil was approved for use in PAH in 2005 and tadalafil was approved for use in PAH in 2009.

Current National Core Formulary Alternatives:

There are no alternatives within the PDE-5 inhibitor drug class on the IHS NCF.

Dosage and Administration: [7-9]

Sildenafil	Tadalafil
Injection: 10mg IV bolus 3 times/day Oral: 20mg 3 times/day, taken without regard to meals at least 4-6 hours apart.* Avoid grapefruit juice.	Oral: 40mg once daily without regard to meals. Dividing doses throughout the day is not advised.

**It should be noted that long-term data for sildenafil are available only at a dose of 80 mg po 3 times/day, while the dose approved by the FDA for the treatment of PAH is 20 mg 3 times/day.*

Dosage Adjustment in Special Populations: [7-9]

Population	Sildenafil	Tadalafil
Elderly >65 years	Use with caution. Refer to adult dosing. No adjustment necessary.	Refer to adult dosing. No adjustment necessary without renal or hepatic impairment.
Renal Impairment	No adjustment necessary.	Clcr>80 mL/minute:No adjustment. Clcr 31-80 mL/minute: Initial: 20 mg once daily; increase to 40 mg once daily based on individual tolerability. Clcr ≤30 mL/minute: Avoid use due to increased tadalafil exposure, limited clinical experience, and lack of ability to influence clearance by dialysis.
Hepatic impairment	Child-Pugh class A and B: No adjustment Child-Pugh class C: Not studied	Child-Pugh class A and B: Use with caution; consider initial dose of 20mg once daily Child-Pugh class C: Avoid use due to lack of studies.
Pediatric oral (unlabeled used)	Children ≥1 month: 0.25-2 mg/kg/dose every 4-6 hours. Most reports used 0.5 mg/kg/dose and titrated up to 2 mg/kg/dose	No recommendation
Concomitant use with other agents	Erythromycin: No adjustment Itraconazole, ketoconazole: Not recommended	Patient currently receiving atazanavir/ritonavir, darunavir/ritonavir, fosamprenavir, ritonavir, saquinavir/ritonavir, and/or tipranavir/ritonavir for at least 1 week when initiating tadalafil: - Initiate tadalafil at 20 mg once daily - Increase to 40 mg once daily based on individual tolerability Patient currently receiving tadalafil when

		initiating one of these protease inhibitor regimens: - Discontinue tadalafil at least 24 hours prior to the initiation of the protease inhibitor regimen. - After at least 1 week of the protease inhibitor regimen, resume tadalafil at 20 mg once daily - Increase to 40 mg once daily based on individual tolerability Patient currently receiving with indinavir or nelfinavir when initiating tadalafil: - Initiate tadalafil at 20 mg once daily - increase to 40 mg once daily based on individual tolerability Patient receiving tadalafil when initiating indinavir/nelfinavir: - Adjust tadalafil to 20 mg once daily - Increase to 40 mg once daily based on individual tolerability

Efficacy:

Sildenafil

Clinical efficacy of sildenafil in primary pulmonary hypertension
Sastry et al conducted a randomized, double-blind, crossover design that compared the efficacy of sildenafil with placebo in patients with primary pulmonary hypertension.[10] The primary end point was the change in exercise time on treadmill using the Naughton protocol. Secondary end points were change in cardiac index and pulmonary artery systolic pressure as assessed by Doppler echocardiography and quality of life (QOL) as assessed by a questionnaire. After initial clinical evaluation, including Doppler echocardiography and treadmill exercise test, patients were randomized to placebo or sildenafil with dosages ranging from 25 to 100 mg thrice daily on the basis of body weight. The evaluation was repeated after six weeks. Then patients were crossed over to alternate therapy. Final evaluation was performed after another six weeks of treatment. Twenty-two patients completed the study. Exercise time increased by 44% from 475 ± 168 s at the end of placebo phase to 686 ± 224 s at the end of sildenafil phase ($p < 0.0001$). With sildenafil, cardiac index improved from 2.80 ± 0.9 l/m2 to 3.45 ± 1.1 l/m2 ($p < 0.0001$), whereas pulmonary artery systolic pressure decreased insignificantly from 105.23 ± 17.82 mm Hg to 98.50 ± 24.38 mm Hg. There was significant improvement in the dyspnea and fatigue components of the QOL questionnaire. During the placebo phase, one patient died and another had syncope. There were no serious side effects with sildenafil. The results of this study concluded that sildenafil significantly improved exercise tolerance, cardiac index, and QOL in patients with primary pulmonary hypertension.

Efficacy of oral sildenafil therapy in severe pulmonary artery hypertension
Singh et al conducted a randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension.[11] Twenty patients, 10 of each of idiopathic PAH and Eisenmenger syndrome, were randomized to receive placebo or sildenafil in a double-blind manner for 6 weeks and, after a washout period of 2 weeks, were crossed over. The primary end point of efficacy was the improvement in distance covered in 6-minute walk test. Secondary end points were reduction in pulmonary artery pressure as measured by Doppler echocardiography after 6 weeks of

treatment, improvement in clinical condition, New York Heart Association (NYHA) class, and exercise duration and metabolic equivalents (Mets) achieved on modified Bruce exercise protocol.
Results showed that there was significant improvement in primary and secondary end points. The primary end point of distance covered in 6-minute walk test improved from 262 +/- 99 to 358.9 +/- 96.5 m (P < .0001) after treatment with sildenafil. Pulmonary artery pressure, the secondary end point, improved from the baseline of 98.8 +/- 20.5 to 78.3 +/- 15.3 mm Hg (P < .0001), NYHA class improved from 2.65 +/- 0.59 to 1.55 +/- 0.51 (P < .0001), exercise duration from 6.4 +/- 3.1 to 10.2 +/- 2.05 minutes (P < .0001), and Mets achieved from 3.32 +/- 1.57 to 6.04 +/- 1.87 (P < .0001) after treatment with sildenafil. There was no significant fall in blood pressure with placebo and sildenafil, and no serious side effects of drug were observed in the study. This study showed that sildenafil significantly improved the symptomatic status, exercise capacity, NYHA class, and hemodynamic parameters of patients with severe PAH and can be safely used as a primary or adjunctive treatment of the same.

SUPER-1 Study
Galie et al conducted a double-blind, placebo-controlled study, that randomly assigned 278 patients with symptomatic pulmonary arterial hypertension (either idiopathic or 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.[12] Upon initiation, 96% of patients were in WHO functional class II or III. The primary end point was the change from baseline to week 12 in the distance walked in six minutes. The change in mean pulmonary-artery pressure and WHO functional class and the incidence of clinical worsening were also assessed, but the study was not powered to assess mortality. The distance walked in six minutes increased from baseline in all sildenafil groups; the mean placebo-corrected treatment effects were 45 m (+13.0 percent), 46 m (+13.3 percent), and 50 m (+14.7 percent) for 20, 40, and 80 mg of sildenafil, respectively (P<0.001 for all comparisons). All sildenafil doses reduced the mean pulmonary-artery pressure (P=0.04, P=0.01, and P<0.001, respectively), improved the WHO functional class (P=0.003, P<0.001, and P<0.001, respectively), 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. Among the 222 patients completing one year of treatment with sildenafil monotherapy, the improvement from baseline at one year in the distance walked in six minutes was 51 m. This study identified the ability of sildenafil to significantly improve exercise tolerability and WHO functional class with a dose of 20mg three times daily, and it also demonstrated the hemodynamic benefits of sildenafil in patients receiving a dose of 80mg three times daily.

SUPER-2 Study
Rubin et al conducted a study that assessed the long-term safety and tolerability of sildenafil for the treatment of PAH. 259 of the 277 patients from the SUPER-1 study entered an open-label uncontrolled extension study (SUPER-2) that continued until the last patient completed 3 years of sildenafil treatment.[13] Patients titrated to sildenafil 80 mg three times a day; one dose reduction for tolerability was allowed during the titration phase. The median duration of sildenafil treatment across SUPER-1 and SUPER-2 was 1,242 days (range, 1-1,523 days); 170 patients (61%) completed both studies, and 89 patients discontinued from SUPER-2. After three years, 87% of 183 patients on treatment were receiving sildenafil 80 mg three times a day. Of patients remaining under follow-up, 3%, 10%, and 18% were receiving a second approved PAH therapy at 1, 2, and 3 years, respectively. At three years post-SUPER-1 baseline, 127 patients had an increased 6-min walk distance (6MWD); 81 improved and 86 maintained functional class. Most adverse events were of mild or moderate severity. At three years, 53 patients had died (censored, n = 37). Three-year estimated survival rate was 79%; if all censored patients were assumed to have died, three-year survival rate was 68%. No deaths were considered to be treatment related. Long-term treatment of PAH initiated as sildenafil monotherapy was generally well tolerated. After three years, the majority of patients (60%) who entered the SUPER-1 trial improved or maintained their functional status, and 46% maintained or improved 6MWD.

Tadalafil

PHIRST-1 Trial

In the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) study, tadalafil was evaluated the efficacy and safety as a treatment choice for pulmonary arterial hypertension.[14] This study was a 16-week, randomized, double-blind, double-dummy, placebo-controlled, trial occurred in 84 centers across the countries between August 2005 and August 2007. Subjects were randomized to receive tadalafil 2.5 mg, 10 mg, 20 mg, 40 mg, or placebo once daily. A total of 405 subjects were randomized and the baseline characteristics among 5 groups were similar. Most of the subjects in all groups were classified in WHO II and III, had idiopathic or familial PAH and 53% of subjects were already receiving bosentan prior to entering of the trial. Primary endpoint was the to assess the exercise capacity and the secondary endpoints included the changes in WHO functional class, the incidence of clinical worsening, the Borg dyspnea score, the quality of life and the hemodynamic parameters. The distance walked in 6 minutes was improved in a positive dose-dependent relationship with tadalafil 10, 20, and 40 mg at week 16 (20 m, 27 m, and 33 m, respectively), although only the result of tadalafil 40 mg was statistically significance ($p<0.01$). The tadalafil 40 mg group showed statistically significant improvement in the following measurements: the time to clinical worsening ($p=0.041$), the incidence of clinical worsening ($p=0.038$), the quality of life shown by the Medical Outcomes Study 36-item health survey ($p<0.01$) and by the EuroQol-5D questionnaire ($p<0.02$), the mean pulmonary arterial pressure ($p=0.01$), the pulmonary vascular resistance ($p=0.039$), and the cardiac index ($p=0.028$). There were no statistically significant differences in the changes in WHO functional class and the Borg dyspnea score. The common adverse events (reported ≥10% in tadalafil 40 mg group) were well-tolerated which included headache, diarrhea, nausea, back pain, dyspepsia, flushing and myalgia, flushing and pain in extremity.

PHIRST-2 Trial

In the extension of 16 weeks PHIRST-1 trial, the same group of subjects had an option to enroll in a 52-week double-blinded PHIRST-2 trial to extend the study period to total of 68 weeks. 357 out of 405 subjects with PAH associated with connective tissue disease (PAH-CTD) and idiopathic/heritable PAH (I/H-PAH) from PHIRST-1 trial were included. Subjects in PHIRST-2 trial were assigned in one of the four groups:

- Received placebo in PHIRST-1 but received tadalafil 40 mg dose in PHIRST-2 (PBO/T40 group)
- Received tadalafil 2.5 – 20 mg in PHIRST-1 but received tadalafil 40 mg dose in PHIRST-2 (T2.5-T20/T40 group)
- Received tadalafil 40 mg in both PHIRST-1 and PHIRST-2 (T40/T40 group)
- Received tadalafil 20 mg in both PHIRST-1 and PHIRST-2 (T20/T20 group)

Baseline characteristics were similar among groups except the 6-minute walk distance (6MWD) for the tadalafil 40 mg group was slightly better than the other groups. Clinical outcomes included 6MWD, proportions of patients with clinical worsening, and treatment emergent adverse events were analyzed. Subjects in T20/T20 and T40/T40 maintained similar mean 6MWD while the mean 6MWD was improved in PBO/T40 and T2.5-T20/T40. The proportion of patients with clinical worsening was higher in the PAH-CTD subgroup than in the I/H-PAH subgroup across all treatment groups. Treatment emergent adverse events were similar between the two subgroups: 50% was recorded in the PAH-CTD subgroup and 48% was recorded in the I/H-PAH subgroups. The results of the treatment emergent adverse events were consistent with the observation from PHIRST-1.[15]

Meta-analyses & Systematic Reviews:

The Cochrane systematic review of PDE-5 inhibitors for PH was published in 2004 by Kanthapillai et al.[16] The authors conducted a meta-analysis in 2009 that focused on four clinical trials. Two of the studies examined the acute effects of sildenafil after an initial inhalation of nitric oxide. The first acute study compared oral sildenafil with inhaled iloprost and the second study compared oral sildenafil with IV epoprostenol. The other two trials examined longer-term effects of sildenafil use for two to six week periods compared to placebo, in addition to concomitant therapies including anticoagulants, digoxin and diuretics. Significantly-increased exercise tolerance (assessed by measuring distance covered during a six minute walk test; $P < 0.0001$, $P < 0.005$) and non-significant changes in NYHA functional class status were reported in the long-term studies. One of the long-term studies also noted a significant difference in cardiac index in favor of sildenafil ($P < 0.0001$).

There are no current recommendations for PAH treatments from the National Institute of Clinical Excellence (NICE), the Drug Effectiveness Review Project (DERP), or the Agency for Healthcare Research and Quality (AHRQ).

Head-to-Head Trial:
SITAR Trial (an ongoing study)
Frantz R, the principal investigator from Mayo Clinic, is conducting an observational study to assess the tolerability, transition method and clinical effects of the conversion from sildenafil to tadalafil for the treatment of PAH.[17] This ongoing clinical trial is titled as "Sildenafil to tadalafil in pulmonary arterial hypertension (SITAR)" Primary endpoint is to measure the tolerability and the secondary endpoints are to compare treatment satisfaction, N-terminal pro-BNP or brain natriuretic peptide levels, 6 minute walk distance, WHO functional class, and echo parameters before and after the transition of the two agents. The study also compares the methods of transition. The estimated population is about 100 subjects with the data collection from December 2009 and December 2011.

Adverse Events: [9]
Sildenafil
>10%:
Central nervous system: Headache (16% to 46%)
Gastrointestinal: Dyspepsia (7% to 17%; dose related)
2% to 10%:
Cardiovascular: Flushing (10%)
Central nervous system: Insomnia (≤7%), pyrexia (6%), dizziness (2%)
Dermatologic: Erythema (6%), rash (2%)
Gastrointestinal: Diarrhea (3% to 9%), gastritis (≤3%)
Genitourinary: Urinary tract infection (3%)
Hepatic: LFTs increased
Neuromuscular & skeletal: Myalgia (≤7%), paresthesia (≤3%)
Ocular: Abnormal vision (color changes, blurred vision, or increased sensitivity to light 3% to 11%; dose related)
Respiratory: Epistaxis (9% to 13%), dyspnea exacerbated (≤7%), nasal congestion (4%), rhinitis (4%), sinusitis (3%)

Tadalafil
>10%:
Cardiovascular: Flushing (1% to 13%; dose related)
Central nervous system: Headache (3% to 42%; dose related)
Gastrointestinal: Dyspepsia (1% to 13%), nausea (10% to 11%)
Neuromuscular & skeletal: Myalgia (1% to 14%; dose related), back pain (2% to 12%), extremity pain (1% to 11%)
Respiratory: Respiratory tract infection (3% to 13%), nasopharyngitis (2% to 13%)
2% to 10%:
Cardiovascular: Hypertension (1% to 3%)
Gastrointestinal: Gastroenteritis (viral; 3% to 5%), GERD (1% to 3%), abdominal pain (1% to 2%), diarrhea (1% to 2%)
Genitourinary: Urinary tract infection (≤2%)
Respiratory: Nasal congestion (≤9%), cough (2% to 4%), bronchitis (≤2%)
Miscellaneous: Flu-like syndrome (2% to 5%)

Precautions/Contraindications: [7-9]
Contraindications:
- Hypersensitivity to sildenafil or any component of the formulation
- Concurrent use (regularly/intermittently) of organic nitrates in any form
- Concurrent use with a protease inhibitor regimen

Warnings and Precautions:

- Vision: Vision loss or color discrimination; use caution in patients with retinitis pigmentosa
- Priapism
- Pulmonary edema
- Pulmonary veno-occlusive disease (PVOD): Pulmonary vasodilators may exacerbate the cardiovascular status in patients with PVOD; use is not recommended
- Cardiovascular disease: Use with caution in patients with hypotension (<90/50 mm Hg); uncontrolled hypertension (>170/110 mm Hg); left ventricular outflow obstruction (eg, aortic stenosis); life-threatening arrhythmias, stroke or MI within the last 6 months; cardiac failure or coronary artery disease causing unstable angina
- PAH: Sudden cessation of sildenafil monotherapy could result in an exacerbation of PAH
- Sickle cell anemia: Treatment of PH with sildenafil in this patient population may lead to more hospitalizations for management of vaso-occlusive crises; effectiveness of sildenafil has not been established in PH secondary to sickle cell disease

Tadalafil

Contraindications:

- Hypersensitivity to tadalafil or any component of the formulation
- Concurrent use (regularly/intermittently) of organic nitrates in any form

Warnings and Precautions:

- Angina pectoris
- Vision: Vision loss or color discrimination; use caution in patients with retinitis pigmentosa
- Priapism
- Pulmonary veno-occlusive disease (PVOD): Pulmonary vasodilators may exacerbate the cardiovascular status in patients with PVOD; use is not recommended
- Hepatic impairment: Use with caution in patients with mild-to-moderate hepatic impairment; dosage adjustment/limitation is needed. Use is not recommended in patients with severe hepatic impairment or cirrhosis.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment/limitation is needed.

Look-alike/Sound-alike Error Risk Potential: [9]

- Revatio® may be confused with ReVia®, Revonto™
- Sildenafil may be confused with silodosin, tadalafil, vardenafil
- Tadalafil may be confused with sildenafil, vardenafil
- Adcirca® may be confused with Advair® Diskus®, Advair® HFA, Advicor®

The Institute for Safe Medication Practices (ISMP) does not list either medication on its list of confused drug name, FDA and ISMP list of drug names with tall man letters, high alert medications list, or the list of medications that should not be crushed or chewed.[18-21]

FDA Risk Evaluation and Mitigation Strategy (REMS): [22]

There are no REMS requirements for these medications.

Drug Interactions: [9]

Sildenafil

- Alpha1-blockers: May enhance hypotensive effect of alpha1-blockers
- Antihypertensives: May enhance the effect of antihypertensives
- Azole antifungal agents: May decrease the metabolism of sildenafil

- CYP3A4 inducers: May decrease the serum concentration of sildenafil; avoid use of sildenafil for PAH in patients receiving a strong CYP3A4 inducer
- CYP3A4 inhibitors: may increase the serum concentration of sildenafil
- PDE-5 inhibitors: May enhance the adverse/toxic effect of other PDE-5 inhibitors
- Erythromycin: May increase the serum concentration of sildenafil; when used for treatment of PAH, concurrent use with erythromycin is not recommended
- Etravirine: May decrease the serum concentration of PDE-5 inhibitors
- HMG-CoA reductase inhibitors: The metabolism of HMG-CoA reductase inhibitors may be decreased; exceptions: fluvastatin; pravastatin; rosuvastatin
- Protease inhibitors: Contraindicated if sildenafil being used for PA
- Vasodilators (organic nitrates): May enhance the effect of vasodilators; avoid combination

Tadalafil

- Alpha1-blockers: May enhance hypotensive effect of alpha1-blockers
- Antihypertensives: May enhance the effect of antihypertensives
- Azole antifungal agents: May decrease the metabolism of tadalafil
- CYP3A4 inducers: May decrease the serum concentration of tadalafil; avoid use of tadalafil for PAH in patients receiving a strong CYP3A4 inducer
- CYP3A4 inhibitors: may increase the serum concentration of tadalafil
- PDE-5 inhibitors: May enhance the adverse/toxic effect of other PDE-5 inhibitors
- Protease inhibitors: May increase the serum concentration of tadalafil; avoid combination
- Vasodilators (organic nitrates): May enhance the effect of vasodilators; avoid combination

Conclusions:

The progression and severity of pulmonary arterial hypertension is categorized based on the WHO functional assessment classifications of I-IV. Extended-release oral calcium channel-blockers (CCB) are recommended as first-line agents for patients in functional class I. However, if a patient exhibits a subclinical response to initial CCB therapy, oral PDE-5 inhibitor use is recommended as an alternative treatment. As severity progresses to functional classes II and III, clinical evidence supports PDE-5 inhibitor use as first-line treatment. Sildenafil and tadalafil are the two drugs from this class with FDA-approval for treatment of PAH. Treatment guidelines and much of the literature available refer to the use of sildenafil. The reasoning behind the recommendation of sildenafil can be deduced from the fact that sildenafil was approved four years prior to tadalafil for the use of PAH and much of the supporting literatures for PDE-5 inhibitor use were published before the approval of tadalafil. There are currently no data available that compares the efficacy of the two drugs head-to-head. Given the data from trials available thus far that have assessed the individual efficacy of sildenafil and tadalafil, it can be concluded that both drugs have been shown to be comparably effective in significantly improving exercise tolerability and delaying clinical worsening for patients with PAH.

Recommendations:

Based on the available information, it is recommended that the NPTC not add the PDE-5 inhibitor drug class to the IHS NCF. The addition of PDE-5 inhibitors would only offer benefit to a small subset of the AI/AN population. The initial treatment options such as CCBs, oral anticoagulants and diuretics are already on the IHS NCF and should be used before the initiation of the other treatment choices such as PDE-5 inhibitors. PDE-5 inhibitors are recommended when the first-line medication (CCB) inadequately controls disease progression or as one of the treatment choices for functional class II to IV.

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Note: Information within this document is current as of this writing and should not replace clinical judgment.

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