Therapeutic Class Overview
Pulmonary Arterial Hypertension Agents

INTRODUCTION

- Pulmonary arterial hypertension (PAH), a subtype of pulmonary hypertension (PH), is a chronic, life-threatening disease that is characterized by increased resistance in the pulmonary circulation caused by progressive pulmonary artery remodeling and constriction of the pulmonary vasculature (Buckley et al, 2013; Wu et al, 2013).
  - PH is defined as a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg at rest. Normal pulmonary arterial systolic pressure ranges from 15 to 30 mmHg, diastolic pressure from 4 to 12 mmHg, and normal mPAP is ≤20 mmHg (UptoDate, 2016).
  - PAH often manifests with clinical symptoms such as shortness of breath and decreased functional capacity, and eventually leads to right heart failure and death (Gomberg-Maitland et al, 2011).
- Early recognition of PAH is essential and the gold standard for the clinical diagnosis of PAH is right heart catheterization (Buckley et al, 2013).
- The World Health Organization (WHO) classifies PH into 5 groups:
  - Group 1 – PAH
  - Group 2 – PH owing to heart disease
  - Group 3 – PH owing to lung diseases and/or hypoxia
  - Group 4 – Chronic thromboembolic PH (CTEPH)
  - Group 5 – PH with unclear or multifactorial etiologies
- WHO Group I encompasses PAH, including idiopathic PAH, heritable PAH, drug- and toxin-induced PAH, and PAH associated with other disorders such as connective tissue disease, portal hypertension, human immunodeficiency virus infection, congenital heart disease, and schistosomiasis (Simonneau et al, 2013).
- In addition to the diagnostic classification, patients may be stratified according to their WHO functional capacity, which was adapted from the New York Heart Association (NYHA) classification of left heart failure. A brief description of these functional classes (FC) is as follows (Stringham et al, 2010):
  - Class I: No limitation of physical activity
  - Class II: Slight limitation of physical activity
  - Class III: Marked limitation of physical activity
  - Class IV: Inability to carry out any physical activity without symptoms
- The prevalence of WHO Group 1 PAH has been estimated at seven to 26 cases per million adults (Pogue et al, 2016). The disease has a poor prognosis and an approximate mortality rate of 15% within one year on therapy (McLaughlin et al, 2009). The median survival in the 1980s was 2.8 years; this has improved to seven years in the late 2000s (Pogue et al, 2016).
- CTEPH (WHO Group 4) is a leading cause of severe PH that results from thrombus formation leading to fibrous stenosis or complete obliteration of pulmonary arteries.
  - The incidence of CTEPH is uncertain, but it occurs in up to 4% of patients after an acute pulmonary embolism (Simonneau et al, 2009).
- Specific agents to treat PAH primarily target three pathways critical to its pathobiology: the prostacyclin, endothelin, and nitric oxide pathways (Wu et al, 2013). There are currently 10 molecular entities within five therapeutic classes that are Food and Drug Administration (FDA)-approved for the treatment of PAH (Facts and Comparisons, 2016).
  - Drugs active within the prostacyclin pathway are the prostacyclin analogues (PCAs) or prostanoids, (intravenous [IV] epoprostenol; inhaled iloprost; and IV, subcutaneous [SC], inhaled, and oral treprostinil) and a prostacyclin receptor agonist (oral selexipag).
  - Drugs active within the endothelin pathway are the endothelin receptor antagonists (ERAs) (oral ambrisentan, oral bosentan, and oral macitentan).
  - Drugs active within the nitric oxide pathway are the phosphodiesterase-type-5 (PDE-5) inhibitors (IV and oral sildenafil and oral tadalafil) and a soluble guanylate cyclase (sGC) stimulator (oral riociguat).
- The goals of treatment include improvement in the patient's symptoms, quality of life (QOL), and survival. The optimal therapy for a patient should be individualized, taking into account many factors including severity of illness, route of administration, side effects, comorbid illness, treatment goals, and clinician preference (McLaughlin et al, 2009).
- Initial management of PAH includes the use of warfarin, diuretics, and/or oxygen depending on the patient's diagnosis and symptoms. Prior to the initiation of advanced therapy, patients with PAH should undergo a vasoreactivity test.

Oral calcium channel blockers (CCBs) are indicated only for patients who have a positive acute vasodilator response to testing (Galiè et al, 2015[b]; McLaughlin et al, 2009; Taichman et al, 2014).

- For patients who do not have a positive acute vasodilator response to testing and are considered low to moderate risk based on clinical assessment, oral mono- or combination therapy with certain agents are recommended. These include ERAs, PDE-5 inhibitors, an sGC stimulator, and a prostacyclin receptor (IP) agonist. In patients with high risk disease, continuous treatment with an IV PCA therapy (epoprostenol or treprostinil) would be recommended. Combination therapy may be considered if patients are not responding adequately to monotherapy or are not candidates for monotherapy (Barst, 2009; Galiè et al, 2015[b]; McLaughlin et al, 2009; Taichman et al, 2014).
- The PAH agents are FDA-approved for the treatment of patients with WHO Group I PAH; however, there are differences in the study populations for which their FDA-approvals were based (McLaughlin et al, 2009).
- ADEMPAS® (riociguat) is a first-in-class sGC stimulator with a dual mode of action involving endogenous nitric oxide that leads to increased generation of cyclic guanosine monophosphate (cGMP) with subsequent vasodilation. ADEMPAS (riociguat) has the additional FDA approval for treating adults with persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH. ADEMPAS is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy is curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment (Archer, 2013).
- In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation (McLaughlin et al, 2009). PCAs, iloprost and treprostinil, were developed as chemically stable alternatives to epoprostenol, which requires continuous IV infusion due to its lack of stability (Asaki et al, 2015). ORENITRAM™ (treprostinil) is the first FDA-approved oral PCA. It may represent a more convenient dosage form to the other treprostinil formulations (REMODULIN® and TYVASO®). However, patients with more severe PAH are likely to receive infused PCA rather than oral therapy (McLaughlin et al, 2009). Among these agents, epoprostenol IV is the only agent which has demonstrated improved patient survival in high risk PAH patients (Galiè et al, 2015[b]). UPTRAVI® (selexipag) works at the same pathway as the PCAs, but activates the IP receptor, also known as the prostacyclin receptor. ORENITRAM and UPTRAVI are the only orally administered agents that work within the prostacyclin pathway (Asaki et al, 2015).
- Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B. Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance. The ERAs (LETAIRIS® [ambrisentan], OPSUMIT® [macitentan], and TRACLEER® [bosentan]) competitively bind to both receptors with different affinities. LETAIRIS and OPSUMIT are highly selective for the ET_A receptor, while TRACLEER is slightly selective for the ET_A receptor over the ET_B receptor. In addition, OPSUMIT has a pharmacologically active metabolite and is considered “tissue-targeting” because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established (McLaughlin et al, 2009).
- In patients with PAH, there is also an impaired release of nitric oxide by the vascular endothelium, thereby reducing cGMP concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP. The PDE-5 inhibitors, REVATIO® (sildenafil) and ADCIRCA® (tadalafil), increase the concentrations of cGMP resulting in relaxation of the pulmonary vascular bed.
- Medispan class: Cardiovascular Agents, Miscellaneous – Prostaglandin Vasodilators; Pulmonary Hypertension: Endothelin Receptor Antagonists, Phosphodiesterase Inhibitors, Prostacyclin Receptor Agonist, and Soluble Guanylate Cyclase Stimulator

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ERAs			
LETAIRIS (ambrisentan)	Gilead	06/15/2007	-
OPSUMIT (macitentan)	Actelion	10/18/2013	-
TRACLEER (bosentan)	Actelion	11/20/2001	-
PDE-5 inhibitors			
ADCIRCA (tadalafil)	Eli Lilly	05/22/2009	-
REVATIO (sildenafil)	Pfizer	06/03/2005	✔ *
Prostacyclin receptor agonist			
UPTRAVI (selexipag)	Actelion Pharmaceuticals	12/21/2015	-
PCAs			
FLOLAN (epoprostenol)	GlaxoSmithKline	4/14/2000	✔
VELETRI (epoprostenol)	Actelion Pharmaceuticals	8/25/2010	-
ORENITRAM (treprostinil)	United Therapeutics	12/20/2013	-
REMODULIN (treprostinil)	United Therapeutics	5/21/2002	-
TYVASO (treprostinil)	United Therapeutics	7/30/2009	-
VENTAVIS (iloprost)	Actelion Pharmaceuticals	12/29/2004	-
sGC stimulator			
ADEMPAS (riociguat)	Bayer Healthcare	10/08/2013	-

*REVATIO tablet and IV formulations are currently available generically; however, the oral suspension is brand-only.

(Drugs@FDA, 2016; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2016)

INDICATIONS

Table 2. FDA-approved Indications

Indication	ADCIRCA (tadalafil)	ADEMPAS (riociguat)	FLOLAN (epoprostenol)	LETAIRIS (ambrisentan)	OPSUMIT (macitentan)	ORENITRAM (treprostinil)	REMODULIN (treprostinil)	REVATIO (sildenafil)	TRACLEER (bosentan)	TYVASO (treprostinil)	UPTRAVI (selexipag)	VELETRI (epoprostenol)	VENTAVIS (ioprost)
Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening				✔ *				✔ §	✔ †				
Treatment of PAH (WHO Group I) to improve exercise ability	✔ ¶		✔ ≠			✔ ¶¶	✔ ₴			✔ Ω		✔ ₳	
Treatment of PAH (WHO Group I) to delay disease progression and reduce hospitalization					✔ **						✔ ‡		
Treatment of PAH (WHO Group I) to improve exercise capacity, to improve WHO FC, and to delay clinical worsening		✔											✔ ¥

Indication	ADCIRCA (tadalafil)	ADEMPAS (riociguat)	FLOLAN (epoprostenol)	LETAIRIS (ambrisentan)	OPSUMIT (macitentan)	ORENITRAM (treprostinil)	REMODULIN (treprostinil)	REVATIO (sildenafil)	TRACLEER (bosentan)	TYVASO (treprostinil)	UPTRAVI (selexipag)	VELETRI (epoprostenol)	VENTAVIS (iloprost)
Treatment of persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO FC		✔											
Treatment of PAH (WHO Group I), in combination with ADCIRCA to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability				✔ *									

Abbrv: NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization, CTEPH=chronic thromboembolic pulmonary hypertension

*Studies establishing effectiveness included predominantly patients with WHO FC II to III symptoms and etiologies of idiopathic or heritable pulmonary arterial hypertension (PAH) (60%) or PAH associated with connective tissue diseases (34%).

†Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) FC II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

‡Studies included predominantly WHO FC II to III. Patients had idiopathic PAH (58%), PAH associated with connective tissue diseases (29%), and PAH associated with congenital systemic-to-pulmonary shunts (10%).

§Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

¶Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

¥Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).

ΩStudies included predominately patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

₳Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

≠Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%).

Ƨ Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) FC II to IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with connective tissue diseases (19%), and PAH associated with congenital systemic-to-pulmonary shunts (23%).** Disease progression included death, initiation of IV or SC prostacyclin vasodilators, or clinical worsening of PAH (decreased 6-minute walk distance (6MWD), worsened PAH symptoms, and need for additional PAH treatment).

¶¶The study that established effectiveness included predominantly patients with WHO FC II and III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). As the sole vasodilator, ORENITRAM has not been shown to add to other vasodilator therapy.

(Prescribing information: ADCIRCA, 2015; ADEMPAS, 2014; FLOLAN, 2016; LETAIRIS, 2015; OPSUMIT, 2016; ORENITRAM, 2016; REMODULIN, 2014; REVATIO, 2015; TRACLEER, 2016; TYVASO, 2016; UPTRAVI, 2015; VELETRI, 2016; VENTAVIS, 2013)

NOTE: Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

ADCIRCA (tadalafil)

- ADCIRCA was evaluated in the PHIRST study, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 405 patients with predominantly WHO FC II or III symptoms. Treatment with ADCIRCA significantly improved exercise capacity, as measured by the 6MWD and reduced clinical worsening compared to placebo (Galiè et al, 2009). In a 52-week extension trial, PHIRST-2, the improvements in 6MWD observed at the end of PHIRST appeared to be maintained through week 52 of PHIRST-2 (68 weeks total). In addition, 34% of patients enrolled in PHIRST-2 experienced an improvement in WHO FC compared to baseline of the PHIRST trial (Oudiz et al, 2012).

ADEMPAS (riociguat)

- The efficacy and safety of ADEMPAS were evaluated in CHEST-1, a multinational, multicenter, double-blind, 16-week trial in 261 adult patients with CTEPH. The majority of patients were WHO FC II (31%) or class III (64%). The primary endpoint of CHEST-1 was change from baseline in 6MWD after 16 weeks. Secondary endpoints included changes from baseline in pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP) level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. Improvements in walking distance occurred beginning at week two. At week 16, the placebo adjusted mean increase in 6MWD within the ADEMPAS group was 46 m (95% confidence interval [CI], 25 m to 67 m; P<0.001) (Ghofrani et al, 2013[a]).
    - An open-label, non-comparative, extension study (CHEST-2) included 237 patients who completed CHEST-1. CHEST-2 consisted of an eight-week, double-blind dose-adjustment phase, followed by an open-label study phase that continued until ADEMPAS received official approval and became commercially available. At the March 2013 cut-off date, 211 patients (89%) were receiving ongoing treatment, and 179 (76%) had received over one year of treatment. The safety profile of ADEMPAS in CHEST-2 was similar to CHEST-1, with no new safety signals. Improvements in 6MWD and WHO FC observed in CHEST-1 persisted for up to one year in CHEST-2. In the observed population at one year, mean±standard deviation (SD) 6MWD had changed by 51±62 m (n=172) versus CHEST-1 baseline (n=237), and WHO FC had improved, stabilized, or worsened in 47, 50, or 3% of patients (n=176) versus CHEST-1 baseline (n=236). Of patients treated for one year in CHEST-2, 145 (92%) out of 157 were continuing to receive monotherapy, and 12 (8%) patients were receiving additional PH-specific medication (eight [5%] were receiving ERAs and four [3%] were receiving prostanoids). No patient required additional treatment with both an ERA and prostanoid at one year (Simmoneau et al, 2015). An exploratory analysis noted a significant association with overall survival for 6MWD and NT-proBNP concentration at baseline (P=0.0199, and 0.0183, respectively), and at follow-up (P=0.0385, and 0.0068, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. At two years, the overall survival rate was 93% (95% CI, 89 to 96%) and the rate of clinical worsening-free survival was 82% (95% CI, 77 to 87%) (Simonneau et al, 2016). Due to lack of a control group and because certain outcomes were considered exploratory, data from this study must be interpreted cautiously.
- The efficacy and safety of ADEMPAS were also evaluated in PATENT-1, a multinational, multicenter, double-blind, 12-week trial in 443 adult patients with PAH as defined by PVR >300 dyn*sec*cm^{-5} and a PAP_{mean} >25 mmHg. In this study, 50% of the patients were treatment-naïve with respect to PAH therapy, 44% were pre-treated with an ERA, and 6% were pretreated with a PCA (inhaled, oral, or SC). Patients were randomized to one of three treatment groups: placebo (n=126), an exploratory capped titration arm of ADEMPAS 1.5 mg three times daily (n=63), or a capped maximum dose of ADEMPAS 2.5 mg three times daily (n=254). The primary endpoint of PATENT-1 was change from baseline in 6MWD after 12 weeks in the ADEMPAS 2.5 mg group compared to placebo. Secondary endpoints included changes from baseline in PVR, NT-proBNP level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. At week 12, the placebo-adjusted mean increase in 6MWD within the ADEMPAS 2.5 mg treatment group was 36 m (95% CI, 20 m to 52 m, P<0.001). The group receiving the capped dose at 1.5 mg was excluded from the efficacy analysis (Ghofrani et al, 2013[b]).
    - An open-label, non-comparative, extension study (PATENT-2) included 396 patients who completed PATENT-1. PATENT-2 consisted of an eight-week, double-blind dose-adjustment phase, followed by an open-label study phase that continues until all patients have transitioned to the commercially available drug. A total of 197 patients received ADEMPAS monotherapy and 199 received ADEMPAS in combination with an ERA or prostanoid, or both. The primary objective of the study was to assess the safety and tolerability of long-term ADEMPAS treatment. Assessments took place at entry to PATENT-2, at weeks two, four, six, eight, and 12, and every three months thereafter. At the March 2013 data cut-off, 324 patients (82%) were receiving ongoing treatment and 84% had received one year or more of treatment. Mean treatment duration was 95 weeks (median 91 weeks), and cumulative treatment exposure was 718 patient-years (Rubin et al, 2015). An exploratory analysis concluded that there was a significant association between overall survival and 6MWD, NT-proBNP concentration, and WHO FC

at baseline (P=0.0006, 0.0225, and 0.0191, respectively), and at follow-up (P=0.021, 0.0056, and 0.0048, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. The estimated survival rate was 97% (95% CI, 95 to 98%) and rate of clinical worsening-free survival was 88% (95% CI, 85 to 91%) at one year and 79% (95% CI, 74 to 82%) at two years (Ghofrani et al, 2016). Certain outcomes were considered exploratory, so data from this study must be interpreted cautiously.

FLOLAN (epoprostenol)

- The safety and efficacy of chronically-infused FLOLAN were evaluated in two similar, open-label, randomized trials of eight to12 weeks' duration comparing FLOLAN plus conventional therapy (eg. anticoagulants, oral vasodilators, diuretics, digoxin, oxygen) with conventional therapy alone in idiopathic or heritable PAH (NYHA Class II to IV) patients (N=106). The average FLOLAN dose was 9.2 ng/kg/min at the trials' end. A statistically significant improvement was observed in the 6MWD in patients receiving FLOLAN plus conventional therapy for eight to 12 weeks compared with those receiving conventional therapy alone. Improvements were noted as early as week one. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by the Chronic Heart Failure Questionnaire and the Dyspnea Fatigue Index, respectively.
- The efficacy of chronically-infused FLOLAN in PAH and scleroderma spectrum of diseases (NYHA Class II to IV) was evaluated in an open-label, randomized,12-week trial (N=111) comparing FLOLAN plus conventional therapy with conventional therapy alone. The mean FLOLAN dose was 11.2 ng/kg/min at the end of week 12. Statistically significant improvement was observed in the 6MWD in patients receiving continuous FLOLAN plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12, the NYHA FC improved in 41% of patients treated with FLOLAN plus conventional therapy compared to none of the patients treated with conventional therapy alone. However, the majority of patients in both treatment groups showed no change in FC, with 4% of the FLOLAN plus conventional therapy group and 27% of conventional therapy group alone worsening.

LETAIRIS (ambrisentan)

- The safety and efficacy of LETAIRIS in the treatment of PAH were established in the ARIES trials. ARIES-1 and ARIES-2 were 12-week, randomized, double-blind, placebo-controlled trials that compared LETAIRIS to placebo in 394 patients. Compared to placebo, treatment with LETAIRIS resulted in a significant increase in exercise capacity as measured by 6MWD (Galiè et al, 2008). ARIES-E was the open-label extension study for ARIES-1 and ARIES-2. After one year of treatment, there was an improvement in 6MWD in the 2.5, 5 and 10 mg LETAIRIS groups (25, 28 and 37 m, respectively). After two years of treatment, the improvement was sustained in the 5 and 10 mg groups (23 and 28 m), but not the 2.5 mg group (7 m) (Oudiz et al, 2009).
- ARIES-3 was a long-term, open-label, single-arm, safety, and efficacy study of LETAIRIS in patients with PH receiving LETAIRIS 5 mg once daily for 24 weeks. The primary endpoint was change from baseline in 6MWD at week 24. Secondary efficacy endpoints included change in plasma NT-proBNP, Borg Dyspnea Index, WHO FC, time to clinical worsening of PAH, survival and adverse events (AEs). A total of 224 patients with PH due to idiopathic and familial PAH (31%), connective tissue disease (18%), chronic hypoxemia (22%), chronic thromboembolic disease (13%), or other etiologies (16%) were enrolled, and 53% of patients received stable background PAH therapies. After 24 weeks of therapy, there was an increase in 6MWD of 21 m (95% CI, 12 to 29), and a decrease in NT-proBNP of -26% (95% CI, -34 to -16%) observed in the overall population compared to baseline. However, increases in 6MWD were not observed in several non-Group 1 PH subpopulations. Peripheral edema, headache, and dyspnea were the most common AEs (Badesch et al, 2012).
- The AMBITION trial (n=610) was a double-blind, randomized, Phase 3/4 trial which compared combination treatment with LETAIRIS plus ADCIRCA to monotherapy with each in patients with WHO FC II or III symptoms. The study protocol was amended during the trial resulting in 17% of the initial protocol patients being excluded from the analysis, and treatment was administered significantly longer in the combination group vs. monotherapy groups (P=0.03). Results demonstrated that patients receiving combination therapy had significantly fewer clinical failure events (defined as death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response) compared to patients receiving individual monotherapy (combination vs. pooled-monotherapy group, hazard ratio [HR] 0.5; 95% CI, 0.35 to 0.72; P<0.001). Primary event outcomes were primarily driven by hospitalization. No significant differences were observed in terms of change in FC or all-cause death. The most common AEs that occurred more often with combination treatment included peripheral edema, headache, nasal congestion, anemia, and bronchitis (Galiè et al, 2015[a]). Based on results from the AMBITION trial, the FDA-

approved LETAIRIS in combination with ADCIRCA to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

OPSUMIT (macitentan)

- The efficacy and safety of OPSUMIT on progression of PAH were demonstrated in a multicenter, Phase 3, event-driven, placebo-controlled trial (SERAPHIN) in 742 patients with symptomatic PAH (WHO FC II, III, or IV) with or without concomitant use of oral PDE-5 inhibitors, oral or inhaled PCAs, CCBs, or L-arginine for the three month period prior to randomization. Patients were randomized to placebo (n=250), OPSUMIT 3 mg once daily (n=250), or OPSUMIT 10 mg once daily (n=242). The mean treatment durations were 85.3, 99.5, and 103.9 weeks in the placebo, OPSUMIT 3 mg, and OPSUMIT 10 mg groups, respectively. The primary study endpoint was time to the first occurrence of death, a significant morbidity event (defined as atrial septostomy, lung transplantation, initiation of IV or SC PCAs), or other worsening of PAH (defined as a sustained ≥15% decrease from baseline in 6MWD, worsening of PAH symptoms as determined by worsening of WHO FC, and need for additional treatment of PAH) during the double-blind treatment plus seven days. Pre-specified secondary endpoints included change from baseline to month six in the 6MWD and percentage of patients with improvement in WHO FC. Other critical pre-specified secondary endpoints were time to PAH death or PAH hospitalization. The primary endpoint occurred in 46.4%, 38%, and 31.4% of the patients in the placebo, OPSUMIT 3 mg, and OPSUMIT 10 mg groups, respectively. OPSUMIT 10 mg once daily therapy resulted in a 45% reduction compared to placebo (HR, 0.55; 97.5% CI, 0.39 to 0.76; P<0.001) in the occurrence of the primary endpoint to the end of the double-blind treatment. The beneficial effect of OPSUMIT 10 mg was primarily due to its reduction in clinical worsening (Pulido et al, 2013).
    - In a sub-group analysis of the effect of OPSUMIT on hospitalizations, there were 117 (46.8%), 104 (41.6%), and 90 (37.2%) patients in the placebo, OPSUMIT 3 mg and 10 mg groups, respectively, who were hospitalized for any cause at least once during double-blind treatment, and they experienced a total of 171, 159, and 135 all-cause hospitalizations, respectively. Compared with that of placebo, the risk of all-cause hospitalization with OPSUMIT 3 mg was reduced by 18.9% (HR, 0.811; 95% CI, 0.623 to 1.057; P=0.1208) and with OPSUMIT 10 mg by 32.3% (HR, 0.677; 95% CI, 0.514 to 0.891; P=0.0051). Compared with placebo, the rate of PAH-related hospitalization was reduced by 44.5% in the OPSUMIT 3 mg group (P=0.0004) and by 49.8% in the OPSUMIT 10 mg group (P<0.0001). The mean number of annual hospital days for PAH-related hospitalizations was reduced by 53.3% in the OPSUMIT 3 mg arm (P=0.0001) and by 52.3% in the OPSUMIT 10 mg arm (P=0.0003). Due to the exploratory nature of this endpoint and small population, data from this study must be interpreted cautiously (Channick et al, 2015).

REMODULIN (treprostinil)

- The safety and efficacy of REMODULIN were evaluated in two identical 12-week, multi-center, randomized, placebo-controlled, double-blind trials in a total of 470 patients with NYHA Class II, III, and IV PAH. REMODULIN was administered SC at an average dose of 9.3 ng/kg/min. The effect on the 6MWD was small and did not achieve statistical significance at 12 weeks. For the combined populations, the median change from baseline for patients on REMODULIN was 10 m and the median change from baseline on placebo was 0 m from a baseline of approximately 345 m. The Borg dyspnea score was significantly improved by REMODULIN during the 6-minute walk test. REMODULIN also consistently improved indices of dyspnea, fatigue, and signs and symptoms of PH. However, these results were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

ORENITRAM (treprostinil)

- The efficacy and safety of ORENITRAM were evaluated in three multi-center, randomized, placebo-controlled, double-blind trials in 349 patients (FREEDOM-M), 350 patients (FREEDOM-C), and 310 patients (FREEDOM-C2).
    - FREEDOM-M compared twice daily administration of ORENITRAM with placebo in patients newly diagnosed with PAH and not receiving any background PAH treatment. The dose titration was based on patient's clinical response and tolerability. The primary endpoint was change in 6MWD over 12 weeks. The ORENITRAM group showed a significant improvement in 6MWD of 23 m (P=0.0125). More than 50% of patients had an improvement of ≥20 m, and over 30% of patients had an improvement of >50 m (Jing et al, 2013). ORENITRAM demonstrated AEs typical of prostacyclin treatments (Waxman, 2013).
    - FREEDOM-C and FREEDOM-C2 failed to meet the primary endpoint of improved 6MWD (Tapson et al, 2012; Tapson et al, 2013).

REVATIO (sildenafil)

- The safety and efficacy of REVATIO were evaluated in the SUPER-1 study, a 12-week, randomized, double-blind, placebo-controlled trial consisting of 278 patients with predominantly WHO FC II or III symptoms. Compared to placebo, REVATIO significantly improved exercise capacity, as measured by the 6MWD, WHO FC symptoms and hemodynamics (Galiè et al, 2005). In a three-year extension study (SUPER-2), 46% of patients increased 6MWD relative to SUPER-1 baseline, 18% decreased 6MWD from baseline, 19% had died and 17% discontinued treatment or were lost to follow-up (Rubin et al, 2011). The addition of REVATIO to epoprostenol was evaluated in PACES, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 267 patients receiving epoprostenol with predominantly WHO FC II or III symptoms. REVATIO added to epoprostenol improved exercise capacity, hemodynamic measurements and time to clinical worsening more than epoprostenol plus placebo (Simonneau et al, 2008).

TRACLEER (bosentan)

- TRACLEER was originally FDA-approved in PAH patients with WHO FC III and IV symptoms based on the results from two randomized, double-blind, placebo-controlled trials in 32 (Study 351) and 213 (BREATHE-1) patients treated for 16 and 12 weeks, respectively. In both studies, significant increases in the 6MWD were observed in all TRACLEER groups compared to placebo. TRACLEER was also associated with a significant reduction in dyspnea during walk tests and a significant improvement in WHO FC symptoms (Channick et al, 2001; Rubin et al, 2002). The FDA-approved indication was subsequently expanded to include patients with WHO FC II symptoms based on the results of the EARLY study consisting of 168 patients. In this 26-week study, treatment with TRACLEER resulted in an increase in the 6MWD of 11.2 m compared to a decrease of 7.9 m in the placebo group; however, the difference was not statistically significant. The study did show a significant delay in clinical worsening and a lower incidence of worsening FC symptoms in the TRACLEER group compared to placebo (Galiè et al, 2008[b]; McLaughlin et al, 2006).
    - The results of an open-label extension phase of the EARLY trial suggested that the majority of patients exposed to long-term TRACLEER therapy maintained or improved their FC. Approximately 20% of patients discontinued treatment because of AEs which were most commonly PAH worsening (defined as death or initiation of IV or SC PCAs) and elevated liver enzymes. Due to lack of a control group, data from this study must be interpreted cautiously (Simmoneau et al, 2014).
- The COMPASS-2 trial (n=334) was a prospective, double-blind, randomized controlled trial consisting of symptomatic PAH patients ranging from WHO FC II to IV who were taking stable REVATIO doses (mean dose, 60 mg) for ≥3 months. Patients were randomized to TRACLEER 125 mg twice daily plus REVATIO or placebo plus REVATIO for 16 weeks. There was no difference in the primary endpoint, time to the first morbidity/mortality event (defined as time to all-cause death, hospitalization for worsening PAH, initiation of IV prostanoid, atrial septostomy, lung transplant, or worsening PAH). There were also no significant differences in the individual measures of the primary endpoint; however, observed benefits were seen in terms of the mean 6MWD test. A high drop-out rate was observed during the trial; therefore, study power was reduced (McLaughlin et al, 2015).

TYVASO (treprostinil)

- The safety and efficacy of TYVASO were evaluated in TRIUMPH I, a 12-week, multi-center, randomized, placebo-controlled, double-blind trial in WHO Group I PAH (98% NYHA Class III) patients who were receiving either TRACLEER or REVATIO (n=235) for at least three months prior to study initiation. Patients received either placebo or TYVASO in four daily treatments with a target dose of nine breaths (54 mcg) per session. The primary endpoint, 6MWD, was measured at peak exposure (10 to 60 minutes post dose) and three to five hours after TRACLEER or 30 to 120 minutes after REVATIO. Patients receiving TYVASO had a placebo-corrected median change from baseline in peak 6MWD of 20 meters (m) at week 12 ($P<0.001$). The 6MWD measured at trough exposure (measured 4 hours after dosing) improved by 14 m.
- In a long-term follow-up of patients who were treated with TYVASO in the pivotal study and the open-label extension (n=206), Kaplan-Meier estimates of survival at one, two, and three years were 97%, 91%, and 82%, respectively. Of note, these observations were uncontrolled and therefore cannot be compared to the control group to determine the long-term effect of TYVASO on mortality.

UPTRAVI (selexipag)

- The safety and efficacy of UPTRAVI were evaluated in the GRIPHON study (n=1,156), a randomized, double-blind, placebo-controlled trial consisting of patients with predominantly idiopathic PAH, and WHO FC II or III symptoms. The median duration of treatment varied from 1.2 to 1.4 years for placebo and UPTRAVI, respectively, and treatment end

was defined as seven days after the last day of treatment intake. Compared to placebo, UPTRAVI significantly reduced the composite endpoint signifying the time to progression of PAH, defined as all-cause death or a PAH complication (27% vs. 41.6%; HR, 0.6; 99% CI, 0.46 to 0.78; P<0.001); however, there were no differences in mortality between groups. The reduction in PAH complications was primarily driven by a reduction in disease progression (17.2% vs. 6.6%) and PAH-related hospitalization (18.7% vs. 13.6%). The safety of UPTRAVI compared to other agents in class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA which accounted for ~80% of patients within the placebo baseline group. Those AEs that occurred significantly more often with UPTRAVI treatment included headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing (P<0.001 for all AEs), anemia (P=0.05), and hyperthyroidism (P=0.004) (Sitbon et al, 2015).

VELETRI (epoprostenol)

- Please refer to the clinical efficacy summary for FLOLAN above.

VENTAVIS (iloprost)

- The efficacy of VENTAVIS was evaluated in a 12-week, randomized, multicenter, double-blind, placebo-controlled trial consisting of 203 patients with NYHA Class III PAH (majority), Class IV PAH, or CTEPH. Patients received 2.5 or 5 mcg of VENTAVIS six to nine times daily during waking hours. The difference in the primary composite endpoint (10% increase in 6MWD 30 minutes after dose, improvement by at least one NYHA class compared to baseline, and no death or deterioration of PH) was statistically significant (19% vs 4% placebo, P=0.0033). The results for the CTEPH patients were not included in the aforementioned results, since there was inadequate evidence of benefit in this patient population. The placebo-corrected difference in the 6MWD in VENTAVIS patients at 12 weeks was 40 m (P<0.01).
- The safety of VENTAVIS was evaluated in a prospective, two year, open-label study with 63 PAH patients. Patients received VENTAVIS 2 to 4 mcg six to nine times daily. Thirty-six patients completed at least 630 days of therapy, 19 patients dropped out prematurely, and eight patients died. AEs were mild to moderate, the most common of which were cough and flushing. Two-year survival was found to be 87% [95% CI, 76% to 98%] (Olschewski et al, 2010).

Meta-analyses and systematic reviews

- The results of a meta-analysis of 18 randomized controlled trials (n=4,363) suggested that all oral PAH therapies confer a therapeutic benefit. More specifically, the findings showed:
    - PDE-5 inhibitors were associated with a statically significant reduction in mortality (RR, 0.22; 95% CI, 0.07 to 0.71; P=0.011), while other drugs only showed a trend toward reducing mortality.
    - Compared with placebo, ERAs, PDE-5 inhibitors, and riociguat significantly reduced clinical worsening, ameliorated WHO function class, and increased 6MWD. Oral prostanoids only showed a mild effect on 6MWD (19.88 m; 95% CI, 10.12 to 29.64, P=0), and did not have any effect on reducing mortality and clinical worsening. Additionally, oral prostanoids significantly increased the incidence of treatment discontinuation due to AEs (relative risk [RR], 3.41; 95% CI, 2.06 to 5.63; P=0) (Zheng et al, 2014[a]).
- A meta-analysis of 14 randomized controlled trials (n=2,244) that evaluated the improvement in overall survival with use of oral, SC, IV, and inhaled PCAs, suggested the following:
    - Only IV PCAs showed a survival benefit (RR, 0.36; 95% CI, 0.16 to 0.79; P=0.011), while oral (RR, 0.73; 95% CI, 0.32 to 1.66; P=0.446), inhaled (RR, 0.28; 95% CI, 0.05 to 1.67; P=0.162), and SC administration (RR, 0.91; 95% CI, 0.38 to 2.20; P=0.837) did not show a benefit.
    - Overall mortality in the 14 studies was 3.30% (74 of 2,244 patients) with 2.52% (30 of 1,189 patients) mortality in the PCA-treated group and 4.17% (44 of 1,055 patients) mortality in the placebo group. The cumulative RR estimate of death showed a significant reduction of 44% (RR, 0.56; 95% CI, 0.35 to 0.88; P=0.01), and no heterogeneity (I^2=0.0%; P=0.84) was detected among studies (Zheng et al, 2014[b]).
- The results of a meta-analysis of 21 randomized controlled trials (n=5,105) suggested that there was a reduction in the number of combined clinical worsening events (defined as all-cause mortality, lung or heart-lung transplant, hospitalization for PAH, and escalation of treatment) in patients with PAH with oral treatments, but showed less favorable effects on life expectancy in the short-term follow-up. Results demonstrated:
    - All classes reduced clinical worsening compared to placebo, including oral prostanoids (odds ratio [OR], 0.616; 95% CI, 0.419 to 0.906; P=0.014), ERAs (OR, 0.504; 95% CI, 0.409 to 0.621; P<0.001), PDE-5 inhibitors (OR, 0.468; 95% CI, 0.329 to 0.664; P<0.001), and ADEMPAS (OR, 0.277; 95% CI, 0.098 to 0.782; P=0.015).

  - There were no significant reductions in mortality with any class versus placebo (Zhang et al, 2015).
- Several additional meta-analyses have been conducted evaluating ERAs, PDE-5 inhibitors, and PCAs. Notable observations in meta-analyses include the following:
  - Survival benefit was seen more with IV PCAs, especially in patients with more severe disease, compared with other routes such as oral and inhalation (Ryerson et al, 2010).
  - ERAs (LETAIRIS and TRACLEER) may have a somewhat lower effect on exercise tolerance in patients with connective tissue diseases, whereas PDE-5 inhibitors (REVATIO and ADCIRCA) and the PCA epoprostenol showed consistent effects regardless of the presence or absence of connective tissue diseases (Kuwana et al, 2013).
  - Combination therapy appears to improve exercise capacity and reduce the risk of clinical worsening in PAH patients compared with monotherapy (Zhu et al, 2012).
  - Favorable effects on clinical events were not predicted by changes in the 6MWD (Savarese et al, 2012). In addition, pulmonary hemodynamics correlated with exercise capacity, but not with clinical events (Savarese et al, 2013).
  - According to an Agency for Healthcare Research and Quality meta-analysis, prostacyclin analogues showed a statistically significant improvement in mortality. In addition, all drug classes improved 6MWD, but comparisons between agents were inconclusive. Combination therapy also improved 6MWD compared with monotherapy, but comparisons between specific regimens were inconclusive. Patients taking ERAs and PDE-5 inhibitors had a lower risk of hospitalization than those taking placebo, while the reduction in patients taking PCAs compared with placebo was similar, but not statistically significant (McCrory et al, 2013).

Treatment Guidelines

- Several recently published clinical guidelines on PAH are available.
  - The Chest Guideline and Expert Panel Report on pharmacologic therapy for PAH provides several options for initial and subsequent therapy (Taichman et al, 2014).
    - Initial therapy: For patients in WHO FC II or III, monotherapy with an ERA, PDE-5 inhibitor, or sGC stimulator is recommended. In WHO FC III patients with evidence of rapid progression or markers of poor prognosis, a parenteral prostanoid should be considered. For patients in WHO FC IV, a parenteral PCA is recommended; however, if patients are unable or unwilling to manage a parenteral product, an alternative is an inhaled PCA combined with an ERA.
    - Subsequent therapy: For patients in WHO FC III who have evidence of progression or markers of poor prognosis, addition of an inhaled or parenteral prostanoid should be considered. In patients in WHO FC III or IV, if clinical status is unacceptable, a second (and if needed, a third) class of PAH therapy can be added.
  - The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PH (Galiè et al, 2015[b]) provide several options for both monotherapy and combination therapy of PAH.
    - Monotherapy: For patients in WHO FC II, recommendations include an ERA, a PDE-5 inhibitor, an sGC stimulator, or a prostacyclin receptor agonist. For patients in WHO FC III, the same medications may be used, and another option is a PCA. PCAs (eg, epoprostenol) are generally preferred for patients in WHO FC IV.
    - Initial drug combination therapy: Only the combination of ADCIRCA and LETAIRIS has a category I recommendation for patients in WHO FC II and III; this combination also has a category IIb recommendation for patients in WHO FC IV. Other double- and triple-therapy combinations are also options, including other ERA and PDE-5 inhibitor combinations (WHO FC II, III, and IV) and some combinations of oral therapies with parenteral PCAs (WHO FC III and IV).
    - Sequential drug combination therapy: Several options are provided for sequential combination therapy. Oral combinations are commonly recommended for patients in WHO FC II and III, including OPSUMIT added to REVATIO, ADEMPAS added to TRACLEER, and UPTRAVI added to an ERA and/or a PDE-5 inhibitor. Other oral combinations and combinations of oral therapies with inhaled or parenteral agents may also be used in patients in WHO FC II, III, and/or IV, but in most cases these recommendations are not as strong.
  - Reputable society groups agree that evidence supporting pediatric treatment is lacking. The American Heart Association (AHA) and American Thoracic Society (ATS) recently published a guideline on pediatric PH. This guideline states that in pediatric patients with lower-risk PAH, oral therapy with either a PDE-5 inhibitor or an ERA is recommended, and in pediatric patients with higher-risk PAH, IV or SC PCAs should be initiated

without delay (Abman et al, 2015). A recent expert consensus statement from the European Pediatric Pulmonary Vascular Disease Network, the International Society of Heart and Lung Transplantation, and the German Society of Pediatric Cardiology reaffirm the AHA/ATS guideline. Additionally, early combination therapy with oral PAH drugs in treatment-naïve children who are FC II or III may be considered (Hansmann et al, 2016).

SAFETY SUMMARY

- sGC Stimulator
  - ADEMPAS has a boxed warning due to embryo-fetal toxicity. It is contraindicated in pregnancy (Pregnancy Category X) because it may cause fetal harm when administered to pregnant women.
  - Females can only receive ADEMPAS through the ADEMPAS REMS Program, a restricted distribution program that requires enrollment and certification of prescribers, patients, and pharmacies. The program also requires females of reproductive potential to comply with pregnancy testing and contraception requirements.
  - Additional contraindications for ADEMPAS include co-administration with nitrates or nitric oxide donors and PDE-inhibitors (specific and non-specific).
  - Warnings and precautions for ADEMPAS include symptomatic hypotension, bleeding, and pulmonary edema in patients with veno-occlusive disease (if confirmed, treatment should be discontinued).
  - The most common AEs associated with ADEMPAS include headache, dyspepsia and gastritis, dizziness, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux disease, and constipation.
- ERAs
  - The ERAs (LETAIRIS, OPSUMIT, and TRACLEER) have boxed warnings for embryo-fetal toxicity and/or risks of teratogenicity due to the potential for fetal harm when administered to women who are or may become pregnant.
  - The LETAIRIS and OPSUMIT REMS programs, respectively, are designed in the same manner as the ADEMPAS REMS program described above.
  - The TRACLEER Access Program (T.A.P.) program has been re-listed as the TRACLEER REMS program. As a requirement of the REMS, healthcare professionals who prescribe or dispense TRACLEER must enroll and comply with the requirements. Requirements include monthly reviews of pregnancy tests in women of reproductive potential, and liver enzymes and bilirubin in all patients. All patients must understand the risks and complete an enrollment form.
  - LETAIRIS has an additional contraindication for idiopathic pulmonary fibrosis.
  - TRACLEER has an additional boxed warning for risks of hepatotoxicity and birth defects. Throughout treatment and for one month after stopping TRACLEER, females of reproductive potential must use two reliable methods of contraception unless the patient has had a tubal sterilization or had an intrauterine device (IUD) inserted.
  - Warnings and precautions for ADCIRCA and REVATIO include prolonged erection (for more than four hours), hearing loss, and vision loss (in one or both eyes), all of which require immediate medical attention.
  - Pulmonary edema has been reported during postmarketing surveillance of LETAIRIS and TRACLEER. Pulmonary edema may occur within weeks after starting LETAIRIS and is more common when LETAIRIS is used in combination with ADCIRCA than with LETAIRIS or ADCIRCA alone.
  - Use of OPSUMIT and TRACLEER should be avoided in patients taking potent inhibitors or inducers of CYP3A.
  - Decreases in sperm count, decreased hemoglobin and hematocrit levels, and pulmonary edema (associated with pulmonary veno-occlusive disease (PVOD) have been observed in patients taking ERAs.
- PDE-5 Inhibitors
  - All PDE-5 inhibitor products have a contraindication for use in patients on nitrates as well as a warning with concomitant alpha blocker use due to resulting hypotension. The patient should allow 48 hours to elapse between the last dose of ADCIRCA and taking nitrates. Additionally, REVATIO and ADCIRCA are contraindicated for concomitant use with the sGC stimulator, ADEMPAS.
  - In August 2012, the prescribing information for REVATIO was updated with a warning stating that the use of REVATIO in pediatric patients is not recommended due to increased mortality associated with higher doses and noted that lower doses are not effective in improving exercise capacity. The FDA clarified the warning related to pediatric use of REVATIO in March 2014, stating it was not intended to suggest that REVATIO never be used in children. The FDA acknowledged there may be situations in which the benefit-to-risk profile may be acceptable in individual children, for example, when other treatment options are limited, in which case REVATIO can be used with close monitoring (FDA Drug Safety Communication, 2014).

- Co-administration of REVATIO or ADCIRCA with potent CYP3A4 inhibitors is not recommended. Co-administration of ADCIRCA with potent CYP3A4 inducers is not recommended.
- Blood pressure lowering effects are increased when ADCIRCA is taken with alcohol.
- REVATIO and ADCIRCA are generally well tolerated with headaches, myalgia, flushing, and dyspepsia being the most common AEs reported for both products.

- Prostacyclin Receptor Agonist
  - UPTRAVI has a warning/precaution to consider PVOD if acute pulmonary edema develops.
  - UPTRAVI is not recommended in patients with severe hepatic impairment (Child Pugh Class C) and has not been studied in dialysis patients (or with eGFR <15 mL/min/1.73m^2).
  - UPTRAVI should be avoided when concomitantly administered with strong inhibitors of CYP2C8.
  - The most common AEs reported with UPTRAVI are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing. These AEs are more frequent during the dose titration phase.
- PCAs
  - ORENITRAM is contraindicated for use in patients with severe hepatic impairment (Child Pugh Class C).
  - FLOLAN and VELETRI are contraindicated in patients with congestive heart failure due to severe left ventricular dysfunction. Additionally, VELETRI is contraindicated in patients with pulmonary edema
  - ORENITRAM and TYVASO both carry a warning/precaution related to an increased risk of bleeding, particularly in patients receiving anticoagulants. Additional warnings and precautions for TYVASO include symptomatic hypotension, possible TYVASO dose changes when inhibitors or inducers of CYP2C8 are added or withdrawn, and a possible increase in exposure or a decrease in tolerability with hepatic or renal impairment. ORENITRAM should be avoided in patients with blind-end pouches (diverticulosis).
  - The safety of TYVASO and VENTAVIS has not been established in patients with significant underlying lung disease (eg, asthma, chronic obstructive pulmonary disease, acute pulmonary infections). Patients with acute pulmonary infections who are taking TYVASO should be carefully monitored to detect any worsening of lung disease and loss of drug effect. VENTAVIS can induce bronchospasm.
  - Hypotension leading to syncope has been observed with VENTAVIS. It should not be administered in patients with a systolic blood pressure below 85 mmHg.
  - With FLOLAN, ORENITRAM, REMODULIN, and VELETRI, abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in the dose can worsen PAH symptoms (or cause rebound PH in patients taking FLOLAN).
  - FLOLAN carries additional warnings and precautions that include pulmonary edema, vasodilation reactions, and an increased risk of bleeding.
  - Both FLOLAN and REMODULIN are administered via an indwelling central venous catheter. This route of administration is associated with blood stream infections (BSI) and sepsis, which may be fatal. During long-term follow-up, sepsis was reported at a rate of 0.3 infections per patient per year in patients treated with FLOLAN. In an open-label study of IV REMODULIN (n=47), there were seven catheter-related line infections during approximately 35 patient years, or about one BSI event per five years of use. A Centers for Disease Control and Prevention survey of seven sites that used IV REMODULIN for the treatment of PAH found approximately one BSI event per three years of use. Continuous SC infusion (undiluted) is the preferred mode of administration of REMODULIN.
  - AEs reported with TYVASO include cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope. AEs with REMODULIN include infusion site pain, infusion site reaction, headache, diarrhea, nausea, rash, jaw pain, vasodilation, dizziness, edema, pruritus, and hypotension. The most common AEs reported with ORENITRAM include headache, diarrhea, nausea, and flushing.
  - AEs associated with VENTAVIS include vasodilation (flushing), increased cough, headache, trismus, insomnia, nausea, hypotension, vomiting, increased alkaline phosphatase, flu syndrome, back pain, tongue pain, palpitations, syncope, increased gamma-glutamyl transpeptidase, muscle cramps, hemoptysis, and pneumonia.
  - The most common AEs reported with FLOLAN and VELETRI include dizziness, jaw pain, nausea, vomiting, headache, hypotension, flushing, and musculoskeletal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ADCIRCA (tadalafil)	Tablet: 20 mg	40 mg once daily	Dividing the dose over the course of the day is not recommended. Use with Ritonavir: In patients receiving ritonavir for at least one week, ADCIRCA should be started at 20 mg once daily. Dose should be increased to 40 mg once daily based on tolerability. During the initiation of ritonavir, ADCIRCA should be avoided. ADCIRCA should be stopped at least 24 hours prior to starting ritonavir. After at least one week, ADCIRCA may be resumed at 20 mg once daily. Dose may be increased to 40 mg once daily based on tolerability.	With or without food
ADEMPAS (riociguat)	Tablet (film-coated): 0.5, 1, 1.5, 2, and 2.5 mg	Initial: 1 mg three times daily Maximum: 2.5 mg three times daily	Starting dose may be lowered to 0.5 mg three times daily in patients unable to tolerate the hypotensive effects and patients receiving strong CYP and P-gp/BCRP inhibitors. Dose increases should be no sooner than 2 weeks apart.	Patients who smoke may tolerate doses higher than 2.5 mg three times daily. If they stop smoking, dose decreases may be required.
FLOLAN (epoprostenol)	Powder for injection: 0.5, 1.5 mg	Initial: 2 ng/kg/min continuous infusion; dose may be increased in increments of 1 to 2 ng/kg/min every 15 minutes based on clinical response	If dose-limiting pharmacologic effects occur, the infusion rate should be decreased gradually until tolerated. Abrupt withdrawal or sudden large reductions in infusion rates should be avoided.	Continuous chronic infusion is administered through a central venous catheter. Temporary peripheral IV infusion may be used until central access is established.
LETAIRIS (ambrisentan)	Tablet: 5 and 10 mg	Initial, 5 mg once daily with or without ADCIRCA 20 mg once daily; at four-week intervals, the dose may be	Doses >10 mg once daily have not been studied.	With or without food. Tablets should not be split, crushed, or chewed.

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		increased up to LETAIRIS 10 mg or ADCIRCA 40 mg once daily		Treatment should be initiated in women of reproductive potential only after a negative pregnancy test. Monthly pregnancy tests should be conducted during treatment.
OPSUMIT (macitentan)	Tablet: 10 mg	10 mg once daily	Doses >10 mg once daily are not recommended.	-
ORENITRAM (treprostinil)	Extended-release tablet: 0.125, 0.25, 1, and 2.5 mg	Starting dose: 0.25 mg twice daily Maximum dose is determined by tolerability.	Dose should be titrated by 0.25 or 0.5 mg twice daily or 0.125 mg three times daily, not more than every three to four days as tolerated. Coadministration with CYP2C8 inhibitors (eg, gemfibrozil) requires a reduced starting dose of 0.125 mg twice daily and can be titrated in 0.125 mg twice daily increments every three to four days.	Should be taken with food Tablets should be swallowed whole When converting from SC/IV to oral routes, use the following equation to estimate the total daily oral dose: ORENITRAM total daily dose (mg) = 0.0072 x SC or IV dose (ng/kg/min) x weight (kg); decrease the SC/IV dose up to 30 ng/kg/min/day while increasing ORENITRAM dose up to 6 mg/day, as tolerated.
REMODULIN (treprostinil)	Multi-dose vials for injection: 20, 50, 100, 200 mg	Continuous infusion should be initiated at a rate of 1.25 ng/kg/min; dose may be reduced to 0.625 ng/kg/min if initial dose cannot be tolerated	The infusion rate should be increased by increments of 1.25 ng/kg/min for the first 4 weeks of treatment and then 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response	SC is preferred, although it can be administered by a central IV line if SC administration is not tolerated
REVATIO (sildenafil)	Tablet: 20 mg Powder for oral suspension: 10	Tablet and powder for oral suspension: 5 or 20 mg three times daily,	Doses above 20 mg three times daily are not recommended.	Should be administered four to six hours apart.

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	mg/mL Powder for injection: 10 mg	approximately four to six hours apart Injection: 2.5 mg or 10 mg as an IV bolus 3 times daily	A 10 mg dose of REVATIO injection is predicted to provide pharmacological effect of REVATIO and its metabolite equivalent to that of a 20 mg oral dose.	The expiration date of the reconstituted oral suspension is 60 days from the date of reconstitution.
TRACLEER (bosentan)	Tablet: 62.5 and 125 mg	Initial: 62.5 mg twice daily for four weeks Maintenance: 125 mg twice daily	Initial and maintenance dose is 62.5 mg twice daily for patients with body weight below 40 kg and over 12 years of age. In patients who have been receiving ritonavir for at least 10 days, TRACLEER should be started at 62.5 mg once daily or every other day based on tolerability. TRACLEER should be discontinued at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, TRACLEER should be resumed at 62.5 mg once daily or every other day based on tolerability.	Should be administered in the morning and evening, with or without food. Treatment should be initiated in women of reproductive potential only after a negative pregnancy test. Monthly pregnancy tests should be conducted during treatment.
TYVASO (treprostinil)	Inhalation solution: 0.6 mg/mL (1.74 mg per 2.9 mL)	Initial: Three breaths (18 mcg), per treatment session, four times a day (four hours apart) during waking hours. Maximum: Nine breaths per treatment session, four times daily.	If three breaths are not tolerated, the number of breaths may be reduced to one to two and subsequently increased to three breaths as tolerated. Dosage should be increased by an additional three breaths at approximately one to two week intervals, if tolerated, until the target dose of nine breaths (54 mcg) is reached per treatment session, four times daily.	The inhalation system consists of an ultrasonic, pulsed delivery device and its accessories.
UPTRAVI (selexipag)	Tablet: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg	Initial: 200 mcg orally twice daily. Dose should be titrated weekly in increments of 200 mcg twice daily.	If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous tolerated dose.	If treatment is missed for ≥ three days, UPTRAVI should be started at a lower dose and retitrated.

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		Maximum: 1600 mcg twice daily		
VELETRI (epoprostenol)	Powder for injection: 0.5, 1.5 mg	Initial: 2 ng/kg/min continuous infusion; dose may be increased in increments of 1 to 2 ng/kg/min every 15 minutes based on clinical response.	If dose-limiting pharmacologic effects occur, the infusion rate should be decreased gradually until tolerated. Abrupt withdrawal or sudden large reductions in infusion rates should be avoided.	Continuous chronic infusion is administered through a central venous catheter. Temporary peripheral IV infusion may be used until central access is established.
VENTAVIS (Iloprost)	Inhalation solution: 10, 20 mcg	Initial: 2.5 mcg via inhalation. Maintenance: 2.5 to 5 mcg, based on tolerability. VENTAVIS is administered six to nine times per day (no more than once every two hours) during waking hours, according to individual need and tolerability.	Vital signs should be monitored while initiating VENTAVIS	VENTAVIS is intended to be inhaled using the I-neb Adaptive Aerosol Delivery (AAD) System The 20 mcg/mL concentration is for patients who are maintained at the 5 mcg dose and who have repeatedly experienced extended treatment times, which could result in incomplete dosing.

Abbrv: CYP = cytochrome P450; IV = intravenous; P-gp/BCRP = P-glycoprotein/breast cancer resistance protein; SC = subcutaneous

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
ADCIRCA (tadalafil)	No dose adjustment is required in patients >65 years of age without renal or hepatic impairment. A greater sensitivity in some older patients should be considered.	Safety and efficacy have not been established.	Mild (CrCL 51 to 80 mL/min) or moderate (CrCL 31 to 50 mL/min): Start dose at 20 mg once daily. Increase to 40 mg daily based on individual tolerability. Severe (CrCL<30 mL/min and on	Mild or moderate (Child Pugh Class A or B): Consider starting dose of 20 mg once per day due to limited clinical experience. Severe (Child Pugh Class C): Not studied, avoid use.	Pregnancy category B Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
			hemodialysis): Avoid use**		
ADEMPAS (riociguat)	No dose adjustments required in older patients (65 years and older). A greater sensitivity in some older patients cannot be ruled out.	Safety and efficacy have not been established.	Not recommended in patients with CrCL <15 mL/min or on dialysis	Not recommended in patients with severe liver impairment (Child Pugh C)	Pregnancy category X Discontinue nursing or the drug.
FLOLAN (epoprostenol)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Safety and efficacy have not been established.	Not studied	Not studied	Pregnancy category B Unknown whether excreted in breast milk; use with caution.
LETAIRIS (ambrisentan)	The elderly (age ≥65years) showed less improvement in walk distances than younger patients. However no specific dose adjustments are needed.	Safety and efficacy have not been established.	Dose adjustment in patients with mild or moderate renal impairment is not required. There is no information for patients with severe renal impairment.	Not recommended in patients with moderate or severe hepatic impairment. Discontinue LETAIRIS if elevations of liver aminotransferases are >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.	Pregnancy category X Discontinue nursing or the drug.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
OPSUMIT (macitentan)	No dose adjustments required in patients ≥65 years.	Safety and efficacy have not been established.	Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15 to 29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.	Exposure to OPSUMIT was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.	Pregnancy category X Discontinue nursing or the drug.
ORENITRAM (treprostinil)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Safety and efficacy have not been established.	No dose adjustments are required.	Mild (Child Pugh Class A): Initial, 0.125 mg twice daily. Titrate by 0.125 mg every three to four days Moderate (Child Pugh Class B): Avoid use Severe (Child Pugh Class C): Contraindicated	Pregnancy category C Discontinue nursing or the drug.
REMODULIN (treprostinil)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Clinical studies did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients.	Not studied	Mild to moderate: Initial dose should be decreased to 0.625 ng/kg/min ideal body weight, and monitored closely Severe: Not studied	Pregnancy category B Unknown whether excreted in breast milk; use with caution.
REVATIO (sildenafil)	Clinical studies did not include a	Use of REVATIO,	No dosage adjustment	Mild to moderate: No dose	Pregnancy category B

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	particularly chronic use, is not recom-mended in children.	required (including with severe impairment CrCL <30 mL/min)	adjustment Severe: Not studied	 Unknown whether excreted in breast milk; use with caution.
TRACLEER (bosentan)	Clinical studies of TRACLEER did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.	Safety and efficacy have not been established.	No dosing adjustments required	Moderate to Severe (Child Pugh Class B and C): Avoid use.	Pregnancy category X Discontinue nursing or the drug.
TYVASO (treprostinil)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Safety and efficacy have not been established.	Not studied	Mild to moderate: Slow up-titration is recommended. Severe: Not studied	Pregnancy category B Unknown whether excreted in breast milk; use with caution.
UPTRAVI (selexipag)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	Safety and efficacy have not been established.	No dosing adjustments required in patients with eGFR >15 mL/min/1.73 m^2. Not studied in dialysis patients or in eGFR <15 mL/min/1.73 m^2.	Mild (Child Pugh Class A): No dose adjustment necessary Moderate (Child Pugh Class B): Starting dose of 200 mcg once daily; titrate weekly by 200 mcg once daily Severe (Child Pugh Class C): Not studied, avoid use.	No human studies; animal models show no clinically relevant effects on embryofetal development. Discontinue drug or breastfeeding.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
VENTAVIS (iloprost)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	Safety and efficacy have not been established.	Not studied	Not studied	Pregnancy category C Discontinue nursing, due to the importance of the drug to the mother.
VELETRI (epoprostenol)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	Safety and efficacy have not been established.	Not studied	Not studied	Pregnancy category B Unknown; use with caution.

Abbrv: CrCL = creatinine clearance; eGFR=estimated glomerular filtration rate; ULN = upper limit of normal
*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an AE on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from AE data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.
**Due to increased ADCIRCA exposure (AUC), limited clinical experience, and lack of ability to influence clearance by dialysis

CONCLUSION

- Pulmonary arterial hypertension (PAH) is a life-threatening disorder that is associated with a poor prognosis.
- There are five classes of drugs that are used in the management of PAH, including endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors, a prostacyclin analog (PCA), a prostacyclin receptor agonist, and a soluble guanylate cyclase (sGC) stimulator.
- All of the PAH agents have shown improved pulmonary hemodynamics and exercise capacity in PAH patients as compared to placebo. Their effects on mortality have not been adequately demonstrated.
- Most trials for PAH have been relatively short-term trials (12 to 18 weeks) that evaluated changes in exercise capacity using the 6-minute walk distance (6MWD) as a primary endpoint. However, recently there has been a preference toward longer, event-driven trials that evaluate composite clinical worsening events (LeVarge et al, 2015). Published event-driven trials include SERAPHIN, GRIPHON, AMBITION, and COMPASS-2 (Galiè et al, 2015[a]; McLaughlin et al, 2015; Pulido et al, 2013; Sitbon et al, 2015).
- Clinical trials have demonstrated the safety and efficacy of the individual PAH agents; however, there is limited data comparing the agents within classes or between classes. Data is conflicting regarding the benefits of combination vs. monotherapy (Barst, 2009; McLaughlin et al, 2009; Galiè et al, 2015[b]; Taichman et al, 2014). Two recent trials evaluating this include the AMBITION and COMPASS-2 trials. The AMBITION trial has demonstrated that combination treatment with LETAIRIS and ADCIRCA resulted in reduced disease progression and hospitalization in mainly FC II and III PAH patients compared to monotherapy (Galiè et al, 2015[a]). However, the COMPASS-2 trial

demonstrated no difference between TRACLEER plus REVATIO versus REVATIO monotherapy for most endpoints with the exception of the mean 6MWD test (McLaughlin et al, 2015).

- ADEMPAS is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy can be curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment. ADEMPAS is dosed three times daily, which is more frequent than several other oral treatments for PAH.
- The ERAs (LETAIRIS, OPSUMIT, and TRACLEER) competitively bind to both receptors with different affinities. LETAIRIS and OPSUMIT are highly selective for the ET_A receptor, while TRACLEER is slightly selective for the ET_A receptor over the ET_B receptor. In addition, OPSUMIT has a pharmacologically active metabolite and is considered "tissue-targeting" because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established.
- The PDE-5 inhibitors (ADCIRCA and REVATIO) are generally well tolerated; the most common side effects include headache, myalgia, flushing, dizziness, and gastrointestinal upset. Both products are contraindicated for use in patients on nitrates and have warnings about their use in patients on alpha-adrenergic inhibitors. Use of ADCIRCA with potent CYP3A4 inhibitors or inducers may significantly alter serum levels of ADCIRCA and is not recommended. Use of ADCIRCA in patients who are using a sGC stimulator may potentiate the hypotensive effects of sGC stimulators and is not recommended. Use of REVATIO with potent CYP3A4 inhibitors is not recommended as they may significantly alter serum levels of REVATIO.
- In addition to the oral formulation, REVATIO is available in an oral suspension formulation and an intravenous formulation. Currently, REVATIO tablets are available generically.
- ADCIRCA is taken just once a day compared to three times a day with REVATIO.
- ORENITRAM is the first oral PCA approved by the FDA. The PCAs are frequently reserved for more severe forms of PAH. As the first oral option in this subclass for treatment of PAH, ORENITRAM may offer a more convenient alternative dosage form leading to earlier PCA initiation in treatment. ORENITRAM is dosed twice daily and requires dosage titration every 3 to 4 days. ORENITRAM did not demonstrate added benefit when added to other vasodilator therapy.
- UPTRAVI is a first-in-class prostacyclin receptor agonist, which works within the same pathway as ORENITRAM. Based on results from the GRIPHON trial, UPTRAVI has reduced disease progression and hospitalization. This is in contrast to ORENITRAM, which has only improved exercise tolerability. Unlike ORENITRAM, UPTRAVI has also demonstrated efficacy when combined with a PDE-5 inhibitor and/or an ERA. The safety of UPTRAVI compared to other oral agents in class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA throughout the trial. Background treatment was used by ~80% of patients within the placebo baseline group. Those AEs reported significantly more often with UPTRAVI treatment include headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing, anemia, and hyperthyroidism (Sitbon et al, 2015). Based on indirect trial evidence, the proportion of patients discontinuing UPTRAVI vs. placebo (14% vs. 7%) due to AEs in the GRIPHON trial was higher than those within the ORENITRAM labeling vs. placebo (4% vs. 3%) (ORENITRAM prescribing information, 2014; Sitbon et al, 2015). Overall, it is not clear how the UPTRAVI safety profile compares to other agents in class due to different study populations. Head-to-head trials are needed to confirm safety risks and differences.
- The 2014 CHEST Guideline and Expert Panel Report update identifies PDE-5 inhibitors, ERAs, the oral PCA, and the sGC stimulator as viable alternatives in treating PAH adults with varying severity levels (FC II to IV) based primarily on consensus opinions (Taichman et al, 2014).
- The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines stratifies PAH treatment by low or intermediate risk or high risk patients. In adult patients with low or intermediate risk (FC II to III), initial monotherapy or initial oral combination therapy is recommended. Based on the AMBITION trial, guidelines state that initial combination treatment with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure. In adult patients with high risk (FC IV), initial combination therapy including IV PCAs are recommended with epoprostenol IV considered first-line due to the mortality benefits in trials (Galiè et al, 2015[b]).
- Reputable society group guidelines agree that there is a lack of randomized trials in pediatric patients, making it difficult to deliver strong guidelines (Abman et al, 2015; Galiè et al, 2015[b]; Hansmann et al, 2016). The 2015 American Heart Association and American Thoracic Society guidelines recommend oral therapy with either a PDE-5 inhibitor or an ERA in lower risk PAH pediatric patients. In pediatric patients with higher-risk PAH, IV and SC PCAs should be initiated immediately with a goal to transition patients to oral or inhaled therapy after the patient is asymptomatic and stable (Abman et al, 2015). The 2015 ESC/ERS guidelines recommend that pediatric treatment follows adult guidelines taking in account risks (Galiè et al, 2015[b]). The European Pediatric Pulmonary Vascular

Disease Network, the International Society of Heart and Lung Transplantation, and the German Society of Pediatric Cardiology reaffirm much of the aforementioned guidance, but also stipulate that early combination therapy with two oral PAH drugs in treatment-naïve children who are FC II or III may be considered (Hansmann et al, 2016).

Table 5. Advantages and Disadvantages of PAH Agents

Drug	Advantages	Disadvantages
ERAs		
LETAIRIS (ambrisentan)	• Highly selective potent ET_A receptor antagonist • Indicated for treatment of PAH in patients with WHO Class II or III symptoms, to improve exercise capacity and to delay clinical worsening • Administered once daily with or without food (may require titration)	• Boxed warning for embryo-fetal toxicity and required REMS restricted distribution program • Contraindication in patients with IPF, including IPF patients with pulmonary hypertension (WHO Group III) • Not recommended for use in patients with moderate or severe hepatic impairment
OPSUMIT (macitentan)	• Newest ERA indicated to delay disease progression • "Tissue-targeting" in human pulmonary arterial smooth muscle cells • Administered once daily with or without food (no titration required)	• Boxed warning for embryo-fetal toxicity and required REMS restricted distribution program • Requires baseline and periodic lab tests prior to treatment initiation
TRACLEER (bosentan)	• First oral agent to be approved for PAH • Efficacy demonstrated as both monotherapy and in combination treatment	• Administered twice daily • Non-selectively blocks both ET_A and ET_B receptors • Boxed warning for teratogenicity with required participation in REMS restricted distribution program • Additional boxed warning related to hepatotoxicity • Use in patients with moderate to severe hepatic impairment should be avoided • Contraindication in patients receiving either cyclosporine A or glyburide • Potential teratogenic effects • Multiple drug interactions
PDE-5 inhibitors		
ADCIRCA (tadalafil)	• Administered once daily with or without food • Efficacy demonstrated as both monotherapy and in combination treatment	• Contraindicated with concomitant organic nitrates and sGC stimulator • Dose reductions needed in patients with mild and moderate renal and hepatic impairment
REVATIO (sildenafil)	• Available in multiple formulations (tablets, injection, and oral suspension) • Generic availability	• Administered three times daily • Contraindicated with concomitant organic nitrates and sGC stimulator
Prostacyclin receptor agonist		
UPTRAVI (selexipag)	• First in class, prostacyclin receptor agonist • Efficacy demonstrated as both monotherapy and in combination treatment (with an ERA and/or	• Administered twice daily • Requires dose titration between 200 mcg and 1600 mcg twice daily • Requires dose reduction in moderate hepatic impairment; not recommended for

Drug	Advantages	Disadvantages
	PDE-5 inhibitor)	use in severe hepatic impairment
PCAs		
FLOLAN (epoprostenol)	• First approved drug for the treatment of PAH, so more data and experience with this drug • Generic availability	• Risk of BSI due to use of an indwelling central venous catheter • Requires use of complex delivery system • Risk of rebound PH with abrupt discontinuation or large dose decreases • Vials must be refrigerated and infusion must be kept cool with ice packs (unless reconstituted solution was prepared with pH 12 sterile diluent for FLOLAN, in which case it is stable for 72 hours at a room temperature of up to 77°F)
ORENITRAM (treprostinil)	• First FDA-approved oral PCA	• Administered twice daily • Contraindicated in patients with Child-Pugh Class C hepatic impairment • Tablets must be swallowed whole and taken with food • Has not demonstrated benefit in combination therapy. • Abruptly lowering the dose or withdrawing the drug should be avoided
REMODULIN (treprostinil)	• Can be administered SC as an alternative to IV administration • Longer half-life compared to FLOLAN • Vials and solution are stable at room temperature (no need for ice packs), regardless of which compatible diluent is used	• Risk of BSI due to use of an indwelling central venous catheter with IV administration • Pain associated with SC administration
TYVASO (treprostinil)	• Administered via inhalation	• Must be administered 4 times daily, at equally spaced intervals • Safety and efficacy of have not been established in patients with significant underlying lung disease (eg, asthma or chronic obstructive pulmonary disease)
VELETRI (epoprostenol)	• Vials and solution are stable at room temperature (no need for ice packs), regardless of which compatible diluent is used • Reconstitution easier and more flexible	• Risk of BSI due to use of an indwelling central venous catheter • Requires use of complex delivery system • Risk of rebound PH with abrupt discontinuation or large dose reductions
VENTAVIS (iloprost)	• Administered via inhalation	• Frequent administration is required (6 to 9 times daily). • May cause bronchospasm, especially in patients with a history of hyperreactive airway disease
sGC stimulator		
ADEMPAS (riociguat)	• First in class, sGC stimulator • First FDA-approved treatment for CTEPH (WHO Group IV)	• Administered three times daily • Requires lower initial doses in patients with intolerable hypotensive effects • Requires higher doses in patients who smoke • Boxed warning for embryo-fetal toxicity and

Drug	Advantages	Disadvantages
		required REMS restricted distribution program

REFERENCES

- Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015 Nov 24;132(21):2037-99.
- ADCIRCA prescribing information. Eli Lilly and Company. Indianapolis, IN. April 2015.
- ADEMPAS prescribing information. Bayer Healthcare Pharmaceuticals. Whippany, NJ. September 2014.
- Archer, SL. Riociguat for pulmonary hypertension – a glass half full. *N Engl J Med*. 2013;369(4):386-88.
- Asaki T, Kuwano K, Morrison K, et al. Selexipag: An oral and selective IP prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. *J Med Chem*. 2015 Sep 24;58(18):7128-37.
- Badesch DB, Feldman J, Keogh A, et al. ARIES-3: Ambrisentan therapy in a diverse population of patients with pulmonary hypertension. *Cardiovasc Ther.* 2012 Apr;30(2):93-9.
- Barst RJ, Gibbs US, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009; 54:S78.
- Buckley MS, Staib RL, Wicks LM. Combination therapy in the management of pulmonary arterial hypertension. Int J Clin Pract Suppl. 2013;(179):13-23.
- Channick RN, Delcroix M, Ghofrani HA, et al. Effect of macitentan on hospitalizations: results from the SERAPHIN trial. *J Am Coll Cardiol HF*. 2015;3:1-8.
- Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo-controlled study. *Lancet*. 2001 Oct 6;358(9288):1119-23.
- DRUGS@FDA.com: Approved drug products with therapeutic equivalence evaluations. Available at: http://www.accessdata.fda.gov/scripts/cder/daf/ . Accessed December 10, 2016.
- Flolan prescribing information. GlaxoSmithKline. Research Triangle Park, NC. June 2016.
- Food and Drug Administration (FDA) Drug Safety Communication: FDA recommends against use of Revatio (sildenafil) in children with pulmonary hypertension. August 30, 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm317123.htm. Accessed December 10, 2016.
- Food and Drug Administration (FDA) Drug Safety Communication: FDA clarifies warning about pediatric use of Revatio (sildenafil) for pulmonary arterial hypertension. March 31, 2014. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm390876.htm. Accessed December 10, 2016.
- Galiè N, Barberà JA, Frost AE, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension (AMBITION). *N Engl J Med.* 2015 Aug 27 [a];373(9):834-44.
- Galiè N, Brundage BH, Ghofrani HA, et al. Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009 Jun 9;119(22):2894-903.
- Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005 Nov 17;353(20):2148-57.
- Galiè N, Humbert M, Vachiery JL, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC), International Society of Heart and Lung Transplantation (ISHLT). *Eur Respir J*. 2015 Oct [b];46(4):903-75.
- Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation*. 2008 Jun 10[a];117(23):3010-9.
- Galiè N, Rubin LJ, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet*. 2008 Jun 21[b];371(9630):2093-100.
- Ghofrani HA, D'Armini AM, et al. Riociguat for the treatment of Chronic Thromboembolic Pulmonary Hypertension. *N Engl J Med*. 2013[a];369:319-29.
- Ghofrani HA, Galiè N, et al. Riociguat for the treatment of Pulmonary Arterial Hypertension. *N Engl J Med*. 2013[b];369:330-40.
- Ghofrani HA, Grimminger F, Grunig E, et al. Predictors of long-term outcomes in patients treated with riociguat for pulmonary arterial hypertension: data from the PATENT-2 open-label, randomized, long-term extension trial. *Lancet Respir Med*. 2016;4:361-71.
- Gomberg-Maitland M, Dufton C, Oudiz RJ, Benza RL. Compelling evidence of long-term outcomes in pulmonary arterial hypertension? A clinical perspective. J Am Coll Cardiol. 2011;57(9):1053-61.
- Hansmann G, Apitz C; for the European Paediatric Pulmonary Vascular Disease Network. Treatment of children with pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. Endorsed by the International Society of Heart and Lung Transplantation (ISHLT) and the German Society of Paediatric Cardiology (DGPK). *Heart*. 2016;102:ii67-85.
- Jing XC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized controlled trial (FREEDOM-M). *Circulation*. 2013;127:624-33.
- Kuwana M, Watanabe H, Matsuoka N, Sugiyama N. Pulmonary arterial hypertension associated with connective tissue disease: meta-analysis of clinical trials. *BMJ Open*. 2013;3(8):e003113.
- LETAIRIS prescribing information. Gilead Sciences. Foster City, CA. October 2015.
- LeVarge BL, Channick RN. The changing paradigm in pulmonary hypertension trials: longer duration, new endpoints. *Curr Opin Pulm Med.* 2015;21:438-445.
- McCrory DC, Coeytaux RR, Schmit KM, et al. Pulmonary arterial hypertension: screening, management, and treatment. Comparative Effectiveness Review No. 117. Rockville, MD: Agency for Healthcare Research and Quality. 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
- McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration

with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation*. 2009 Apr 28;119(16):2250-94.
- McLaughlin VV, Channick RN, Ghofrani HA, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension (COMPASS-2). *Eur Respir J.* 2015 Aug;46(2):405-13.
- McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. A*m J Respir Crit Care Med*. 2006 Dec 1;174(11):1257-63.
- Olschewski H, Hoeper M, Behr J, et al. Long-term therapy with inhaled iloprost in patients with pulmonary hypertension. *Respir Med*. 2010;104(5):731-40.
- OPSUMIT prescribing information. Actelion Pharmaceuticals. South San Francisco, CA. February 2016.
- ORENITRAM prescribing information. United Therapeutics. Research Triangle Park, NC. January 2016.
- Oudiz RJ, Brundage BH, Galiè N, et al. Tadalafil for the treatment of pulmonary arterial hypertension: a double-blind 52-week uncontrolled extension study. *J Am Coll Cardiol.* 2012 Aug 21;60(8):768-74.
- Oudiz RJ, Galiè N, Olschewski H, et al. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009 Nov 17;54(21):1971-81.
- Pogue KT, Walter CP. Pulmonary Arterial Hypertension. In: Murphy JE, Lee MW, eds. Pharmacotherapy Self-Assessment Program, 2016 Book 1. Cardiology. Lenexa, KS: American College of Clinical Pharmacy, 2016:61-81.
- Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369:809-18.
- REMODULIN prescribing information. United Therapeutics Corporation. Research Triangle Park, NC. December 2014.
- REVATIO prescribing information. Pfizer. NY, NY. April 2015.
- Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002 Mar 21;346(12):896-903.
- Rubin LJ, Badesch DB, Fleming TR, et al. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: the SUPER-2 study. *Chest*. 2011 Nov;140(5):1274-83.
- Rubin LJ, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension: a long-term extension study (PATENT-2). *Eur Respir J*. 2015;45:1303-13.
- Rubin LJ, Hopkins W. Overview of pulmonary hypertension in adults. UpToDate Web site. 2016. www.uptodate.com. Accessed December 9, 2016.
- Ryerson CJ, Nayar S, Swiston JR, Sin DD. Pharmacotherapy in pulmonary arterial hypertension: a systematic review and meta-analysis. *Respir Res*. 2010;11:12.
- Savarese G, Musella F, D'Amore C, et al. Haemodynamics, exercise capacity and clinical events in pulmonary arterial hypertension. *Eur Respir J*. 2013;42(2):414-24.
- Savarese G, Paolillo S, Costanzo P, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *J Am Coll Cardiol*. 2012;60(13):1192-201.
- Simonneau G, D'Armini AM, Ghofrani H, et al. Predictors of long-term outcomes in patients treated with riociguat for chronic thromboembolic pulmonary hypertension: data from the CHEST-2 open-label, randomized, long-term extension trial. *Lancet Respir Med*. 2016; 4:372-80.
- Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34-41.
- Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2009 Jun 30;54(1 Suppl):S43-54.
- Simonneau G, Rubin LJ, Galiè N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med*. 2008 Oct 21;149(8):521-30.
- Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension (GRIPHON). *N Engl J Med.* 2015 Dec 24;373(26):2522-33.
- Stringham R, Shah NR. Pulmonary arterial hypertension: an update on diagnosis and treatment. *Am Fam Physician*. 2010;82(4):370-377.
- Taichman DB, Ornelas J, Chung L, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST Guideline and Expert Panel Report. *Chest*. 2014;146(2):449-75.
- Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (The FREEDOM-C Study). *Chest*. 2012; 142(6):1383-90.
- Tapson VF, Jing ZC, Xu KF, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (The FREEDOM-C2 Study). *Chest*. 2013; 144(3):952-8.
- TRACLEER prescribing information. Actelion Pharmaceuticals. South San Francisco, CA. October 2016.
- TYVASO prescribing information. United Therapeutics Corporation. Research Triangle Park, NC. June 2016.
- UPTRAVI prescribing information. Actelion Pharmaceuticals. South San Francisco, CA. December 2015.
- VELETRI prescribing information. Actelion Pharmaceuticals. South San Francisco, CA. July 2016.
- VENTAVIS prescribing information. Actelion Pharmaceuticals. South San Francisco, CA. November 2013.
- Waxman AB. Oral prostacyclin therapy for pulmonary arterial hypertension: another step forward. *Circulation*. 2013;127:563-5.
- Wu Y, O'Callaghan DS, Humbert M. An update on medical therapy for pulmonary arterial hypertension. Curr Hypertens Rep. 2013;15(6):614-22.
- Zhang HD, Zhang R, Jiang X, et al. Effects of oral treatments on clinical outcomes in pulmonary arterial hypertension: a systematic review and meta-analysis. *Am Heart J.* 2015;170:96-103.e14.
- Zheng YG, Ma H, Hu EC, et al. Oral targeted therapies in the treatment of pulmonary arterial hypertension: a meta-analysis of clinical trials. *Pulm Pharmacol Therap*. 2014 [a];29:241-49.
- Zheng Y, Yang T, Chen G, et al. Prostanoid therapy for pulmonary arterial hypertension: a meta-analysis of survival outcomes. *Eur J Clin Pharmacol.* 2014 [b];70(1):13-21.
- Zhu B, Wang L, Sun L, Cao R. Combination therapy improves exercise capacity and reduces risk of clinical worsening in patients with pulmonary arterial hypertension: a meta-analysis. *J Cardiovasc Pharmacol.* 2012;60(4):342-6.

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