Pulmonary Arterial Hypertension Agents

Determining Efficacy

Efficacy in pulmonary arterial hypertension (PAH) drug trials is measured primarily with the 6-minute walking distance (6MWD) and a composite endpoint of time to clinical worsening (TTCW). Secondary measures include mortality, hospitalization due to PAH, improvement or worsening in functional class, requirement for surgery (atrial septostomy or lung transplant), measurement of right heart hemodynamics (pulmonary vascular resistance, pulmonary capillary wedge pressure, and mean arterial pressure) and N-terminal pro-brain natriuretic peptide.

Executive Summary

- The PAH Drug Class includes four subclasses: prostacyclins, endothelin receptor agonists (ERAs), soluble guanylate cyclase stimulator, and phosphodiesterase-5 (PDE-5) inhibitors. Individual agents are listed below in Tables 2–5.
- There are no head-to-head comparisons among the different agents; therefore, no evidence-based first line treatment can be proposed.
- In one systematic review (CHEST 2014), all agents increased the 6MWD (27.9m–39.9m) when compared to placebo. However, comparisons between agents are inconclusive (SOE = Moderate).[1,2]
  - ERA and PDE-5 monotherapy showed lower hospitalization rates but not with combination therapy (SOE = Moderate).[1,2]
  - There was no mortality benefit with combination therapy compared to monotherapy.[1,2]
- When used as monotherapy, Orenitram extended release (ER) increased the 6MWD significantly when compared to placebo.[3]
  - Combination therapy with an ERA or PDE-5 or both did NOT significantly increase the 6MWD.[3]
- Results of the SERAPHIN trial with macitentan showed a 30% reduction in the TTCW in the macitentan groups compared to placebo [HR 0.70 (0.52–0.96)].[4]
  - Worsening of PAH was the most frequent primary endpoint event.[4]
  - 6MWD decreased an average 9.4m (placebo group), increased 7.4m (3mg group), and 12.5mg (10mg group).[4]
- Riociguat increased 6MWD ~30m in the 2.5mg group and decreased ~6m in the placebo group.[5]
  - Riociguat significantly improved exercise capacity and secondary efficacy endpoints in patients with PAH.[5]
  - Patients in WHO functional class III or IV had a greater benefit than did those in functional class I or II.[5]
- Below are the most commonly assessed and reported ADEs with PAH agents:[1]
  - Headaches: PDE-5 and inhaled prostanoids
  - Cough: inhaled prostanoids
  - Jaw pain: inhaled prostanoids
  - Peripheral edema: PDE-5
  - Flushing: PDE-5 and prostanoids
- The ERAs and riociguat are pregnancy category X.
- Combination therapy is attractive because of different targets of therapy.
- Different mechanisms of action and safety profiles may differentiate one PAH agent from another depending on the clinical scenario.
- Choice of the drug depends on a variety of factors including approval status, labeling, route of administration, side effect profile, patient preference, physician experience, and cost.

Previous Formulary Decisions

- November 2005 (PDE-5 class)
  - Sildenafil (Revatio) placed on the Uniform Formulary
- November 2009 (PDE-5 for PAH)
  - Tadalafil (Adcirca) approved by FDA August 2009
  - There is insufficient evidence to conclude that there are relevant differences in clinical effectiveness or safety of PDE-5 inhibitors for PAH.
  - Tadalafil is nonformulary.
- November 2011 (review of PDE-5 class)
  - Sildenafil 20 mg (Revatio) prior authorization (PA) for primary pulmonary hypertension and Raynaud's Phenomenon
  - Tadalafil (Adcirca) PA for primary pulmonary hypertension

Table 1: Current Formulary Status

UF Status – PDE-5 Inhibitors for PAH	
BCF	None
UF	Sildenafil (Revatio, generics) – PA required
NF	Tadalafil (Adcirca) – PA required

Table 2: Prostacyclins[6-8]

Generic	Brand	Manufacturer	FDA Approval	Dose	Route	Generic	Patent
Epoprostenol	Flolan	GSK	10/20/1995	0.5mg, 1.5mg	IV	Yes	Orphan drug status
	Veletri	Actelion Pharms LTD	6/27/2008	0.5mg, 1.5mg	IV	No	
Treprostinil	Remodulin	United Therapeutics	5/21/2002	1mg, 2.5mg, 5mg, 10mg	IV / SQ	No	2014-2028 Orphan drug status
	Tyvaso	United Therapeutics	7/30/2009	18-54 mcg qid	Neb	No	2018-2028
	Orenitram ER	United Therapeutics	12/20/2013	0.25 mg q12h	PO	No	2024-2031
Iloprost	Ventavis	Actelion Pharms LTD	12/29/2004	2.5-45mcg q2h	Neb	No	Orphan drug status

Table 3: Endothelin Receptor Antagonists (ERAs)[9-11]

Generic	Brand	Manufacturer	FDA Approval	Dose	Patent
Bosentan	Tracleer	Actelion Pharms LTD	11/20/2001	62.5-125mg bid	2015 – Orphan drug status
Ambrisentan	Letairis	Gilead	6/15/2007	5-10mg qday	2015-2018 Orphan drug status
Macitentan	Opsumit	Actelion Pharms LTD	10/18/2013	10mg qday	2022

Table 4: Soluble Guanylate Cyclase Stimulator[12]

Generic	Brand	Manufacturer	FDA Approval	Dose	Route	Generic	Patent
Riociguat	Adempas	Bayer HealthCare	10/08/2013	2.5mg tid	PO	No	2019-2023

Table 5: Phosphodiesterase- 5 (PDE-5) Inhibitors[13,14]

Generic	Brand	Manufacturer	FDA Approval	Dose	Route	Generic	Patent
Sildenafil	Revatio	Pfizer	6/03/2005	20mg tid	PO	Yes	
Tadalafil	Adcirca	Eli Lilly & Co	5/22/2009	20mg tabs Dose: 40 mg qday	PO	No	2017-2020

References

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Abbreviations

The following abbreviations are used in this review:

6MWD	– 6-minute walking distance
ERAs	– endothelin receptor agonists
PA	– prior authorization
PAH	– pulmonary arterial hypertension
PDE-5	– phosphodiesterase-5
SOE	– strength of evidence
TTCW	– time to clinical worsening
WHO	– World Health Organization