Indian Health Service

IHS National Pharmacy and Therapeutics Committee
Formulary Brief: Phosphodiesterase – 5 inhibitors In Pulmonary Hypertension
May 2012

Background:

The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the phosphodiesterase-5 (PDE-5) inhibitors for their use in the management of pulmonary arterial hypertension (PAH) at the April 2012 meeting. This presentation included a literature review of the PDE-5 inhibitors as well as the pharmacoeconomic and IHS utilization data for each agent. The NPTC did not add a PDE-5 inhibitor to the IHS National Core Formulary (NCF), however, it was felt that the development of a formulary brief to discuss the clinical use of these products in PAH.

Discussion:

Pulmonary arterial hypertension is a chronic disease state that if left untreated, can lead to significant physical impairment, right-heart failure and death.[1] Initial management of PAH includes the use of warfarin, diuretics and calcium channel blockers, then progresses to the use of prostanoids, edothelin receptor antagonists (ERA) and PDE-5 inhibitors. PDE-5 inhibitors have been used in the management of erectile dysfunction since 1998. Several trials have been published since 2004 regarding the use of PDE-5 inhibitors in the management of PAH.[2-7] Currently, there are two products that have been FDA approved for the management of PAH in the United States, sildenafil (Revatio®) and tadalafil (Adcirca®).

Dosage and Administration: [8-10]

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

Clinical trials for PAH focus on symptomatic improvement and quality of life in assessing the benefit of drug therapy. The six minute walk distance (6MWD) and the exercise treadmill time (ETT) are frequently used to assess exercise capacity. Time to clinical worsening is also frequently reported in clinical literature. Studies have shown that both of the approved agents improve the exercise capacity in patients with PAH. [2-7] Key clinical trials for sildenafil include the SUPER-1 and SUPER-2 trials and the PHIRST-1 and PHIRST-2 trials for tadalafil. Each product has been shown to delay time in clinical worsening. Sildenafil has been approved for use in combination with IV epoprostenol. However, the study that was used to achieve FDA approval used 80mg three times daily instead of the approved 20mg three times daily dose. There are no published clinical trials that compare sildenafil and tadalafil but the SITAR (sildenafil to tadalafil in pulmonary arterial hypertension) trial completed data collection phase and the publication of the trial will be eagerly anticipated.[11]

The ACCF/AHA guidelines from 2009 recommended the use of oral therapy with an ERA or a PDE-5 inhibitor as first line therapy.[12] The American College of Chest Physicians (ACCP) guidelines from 2007 provided similar recommendations with sildenafil being recommended for use in patietns with class II (grade A) and class III (grade A) and as an additive agent with IV ERA use in class IV patients (grade C).[13] It must be noted that tadalafil was not approved for use when the ACCP guidelines were released. The ERA agents (bosentan and ambrisentan) have FDA REMS associated with them with elements to assure safe use due to their potential for hepatotoxicity and teratogenicity.[14]

Findings:

There is compelling data to support the clinical use of PDE-5 inhibitors in PAH. The NPTC concluded that these agents are considered as standard of care. The NPTC did not feel that these agents would be used by a substantial proportion of the population. Therefore, the NPTC did not add a PDE-5 inhibitor to the IHS National Core Formulary. It was felt that these agents should be considered at the local level in patients who meet the requirements for use.

If you have any questions regarding this document, please contact the NPTC at nptc1@ihs.gov.

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