

Recommendations and Reasons

Committee to Evaluate Drugs (CED)

Sitaxsentan sodium

Product:

SITAXSETAN SODIUM (Thelin®) 5mg and 10mg tablets

Class of drugs:

Endothelin receptor antagonist

Indication:

Treatment of pulmonary arterial hypertension

Manufacturer: Pfizer Canada Inc.

On December 15, 2010, Pfizer Canada announced that it is voluntarily withdrawing THELIN® (sitaxsentan sodium) from the market due to concerns about hepatotoxicity. For details, please see: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2010/thelin_2_hpc-cps-eng.php.

Highlights of Recommendation:

- ◆ Sitaxsentan is an oral drug used to treat pulmonary arterial hypertension (PAH).
- ◆ The clinical trials demonstrated that sitaxsentan improves exercise capacity based on the six-minute walk distance when compared to placebo. However, sitaxsentan has not been shown to improve clinically important outcomes (such as survival, hospitalization rate, time to transplantation or quality of life).
- ◆ The CED had concerns with the potential of sitaxsentan for liver toxicities and drug-interactions with warfarin.
- ◆ The cost of sitaxsentan is similar to bosentan but is more than sildenafil. There are no direct comparison randomized controlled trials to demonstrate that sitaxsentan is better than bosentan or sildenafil to support the price premium.
- ◆ **Overall, the CED had concerns with the lack of robust clinical efficacy data for sitaxsentan. As there is no data demonstrating the therapeutic or safety advantage of sitaxsentan over other drugs in the same class, the CED recommended that sitaxsentan not be funded**

Background:

Pulmonary arterial hypertension (PAH) is a disabling and typically progressive disease that occurs when dangerously high blood pressure builds up in the blood vessels that lead from the heart to the lungs. The small blood vessels in the lungs narrow and their walls thicken, causing the pressure to build. The heart is unable to keep up with the extra work needed to pump blood through the lungs, resulting in right-sided heart failure. Symptoms include fatigue, dizziness, shortness of breath, chest pain and, eventually, heart failure and death.

PAH can occur on its own, due to unknown causes (idiopathic), or as a complication of congenital heart disease, HIV or connective tissue diseases such as scleroderma (a collagen vascular disease). A right heart catheterization is required for a definitive diagnosis by a specialist. PAH is classified according to clinical status and functional capacity.

The goals of treatment are to prevent disease progression, prevent blood clots, relieve symptoms, improve exercise capacity and prolong survival. Standard treatment for PAH includes lifestyle modifications, conventional non-specific medications (such as oral anticoagulants, digoxin, calcium channel blockers, diuretics) and supplemental oxygen therapy. Exercise can be an important part of treatment for some patients if used cautiously and with close monitoring; however, it is not an alternative for patients who have more severe disease.

Disease specific medications have become available in the last several years. There are several classes of disease specific medications: prostanoids (epoprostenol, treprostinil), endothelin type A receptor antagonists (bosentan, ambrisentan, sitaxsentan) and phosphodiesterase inhibitors (sildenafil, tadalafil).

CED Recommendation

The CED recommended that sitaxsentan (Thelin®) not be funded through the Exceptional Access Program (EAP), on the basis that the drug does not have a therapeutic or safety advantage over other treatments already funded.

Executive Officer Decision

Based on the CED's recommendation, the Executive Officer decided to not fund sitaxsentan (Thelin®).

Status

No funding available through the Ontario Public Drug Programs.

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Detailed Discussion:

- ◆ The CED considered funding sitaxsentan in February 2008 and December 2008.
- ◆ The Committee considered two published double-blinded, randomized controlled trials:
 - ◆ Barst RJ et al for STRIDE-1 Study Group. *Am J Respir Crit Care Med* 2004; 169(4):441-7.
 - ◆ Barst RJ et al for STRIDE-2 Study Group. *J Am Coll Cardiol* 2006;47(10):2049-56.
- ◆ Both trials were placebo-controlled and were 12 to 18 weeks in duration, respectively.
- ◆ The trials demonstrated that improvements from baseline on the six-minute walk distance, a surrogate outcome often used in trials for PAH, was statistically significant for sitaxsentan when compared to placebo.
- ◆ The STRIDE-2 trial included an open-label bosentan arm, but no statistical comparisons were performed.
- ◆ The STRIDE-1 trial indicated no statistical difference in the quality of life measure, SF-36, for sitaxsentan versus placebo.
- ◆ Sitaxsentan has not been shown to improve clinically important outcomes such as survival, hospitalization rate, time to transplantation or quality of life.
- ◆ The CED noted that the US Food and Drug Administration (FDA) concluded there is an insufficient level of evidence on effectiveness required for approval, thus, sitaxsentan is not approved for sale in the United States.
- ◆ Liver toxicities are the main safety concerns for all endothelin type A receptor antagonists. In the trials, there was a higher incidence of elevated liver function tests in patients receiving sitaxsentan 300mg. This dose was not approved. Across all studies, the same number of patients on sitaxsentan 100mg had abnormal liver function tests when compared to placebo. The manufacturer has issued an advisory to health care professionals informing them of this safety issue (http://www.hc-sc.gc.ca/dhp-mpps/medeff/advisories-avis/prof/2007/thelin_hpc-cps-eng.php).
- ◆ The daily cost of sitaxsentan is slightly less than bosentan but more expensive than ambrisentan and sildenafil 20mg three times daily. The manufacturer submitted a cost utility analysis comparing sitaxsentan to bosentan on the basis that sitaxsentan is superior to

bosentan. However, there is no direct comparison trial that demonstrates sitaxsentan is therapeutically superior to bosentan or to ambrisentan.

- ◆ Overall, the CED has concerns over the lack of robust clinical efficacy data; as such cost-effectiveness, regardless of price, is a secondary issue. Since there are no randomized controlled trials comparing the relative efficacy of the three available endothelin type A receptor antagonists, the therapeutic advantage and cost-effectiveness of sitaxsentan are unknown.

CEDAC Recommendation:

(<http://www.cadth.ca/index.php/en/cdr/recommendations>)

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that sitaxsentan sodium (Thelin®) not be listed.



Ministry of
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