

Recommendations and Reasons

Committee to Evaluate Drugs (CED)

Ambrisentan

Product:

AMBRISENTAN (Volibris®) 5mg and 10mg tablets

Class of drugs:

Endothelin receptor antagonist

Indication:

Treatment of pulmonary arterial hypertension

Manufacturer: Glaxosmithkline Inc.

Highlights of Recommendation:

- ◆ Ambrisentan is an oral drug used to treat pulmonary arterial hypertension (PAH), functional class II or III.
- ◆ The clinical trials demonstrated that ambrisentan improves exercise capacity when compared to placebo. One of the trials demonstrated statistically significant differences in clinically relevant outcomes such as reduction in clinical worsening, hospitalization, and quality of life, when compared to placebo.
- ◆ The risk of liver damage appears to be lower than that of bosentan. However, the trials excluded patients who have known intolerances to bosentan or a history of abnormal liver function tests. Thus, the true incidence of liver toxicities with ambrisentan is unknown.
- ◆ There appears to be no clinically significant drug interactions between ambrisentan and other drugs, such as warfarin, commonly used in patients with PAH. Drug-drug interactions have been noted with other drugs for the treatment of PAH.
- ◆ **Overall, the CED felt that ambrisentan demonstrated statistically significant differences in clinically relevant outcomes such as reducing clinical worsening and time spent in hospital, while improving quality of life, when compared to placebo.**

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).

Ambrisentan is approved in Canada for the treatment of PAH, WHO functional class II or III. Ambrisentan is an oral medication that is taken once daily.

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CED Recommendation-

The CED recommended that ambrisentan (Volibris®) be funded through the Exceptional Access Program (EAP), according to specific criteria, on the basis that the drug has demonstrated short-term clinical benefits and value for money in selected patients with pulmonary arterial hypertension.

Executive Officer Decision

Based on the CED's recommendation, the Executive Officer decided to fund ambrisentan (Volibris®) through the EAP for the treatment of pulmonary arterial hypertension, according to specific criteria.

Status

Funding available through the Ontario Public Drug Programs via the Exceptional Access Program (EAP).

Detailed Discussion:

- ◆ The CED considered two placebo-controlled, double-blind, randomized controlled trials in this review. ARIES-1 and ARIES-2 (Galie et al. *Circulation* 2008;117) trials were conducted in patients with idiopathic PAH or non-idiopathic PAH in functional class II or III.
- ◆ In both trials, ambrisentan demonstrated statistically significant improvement in the primary outcome (exercise capacity based on the six-minute walk distance) when compared to placebo. However, no difference in mortality was observed between ambrisentan and placebo.
- ◆ The ARIES-2 trial demonstrated significant differences in clinically relevant outcomes, such as reduction in clinical worsening, hospitalization, and quality of life.
- ◆ The two trials are short in duration (only 12 weeks) and the long-term effectiveness of ambrisentan is unknown.
- ◆ The most common adverse events include peripheral edema (fluid retention), dyspnea (laboured breathing), and right ventricular heart failure. However, it was difficult to determine whether these adverse events were due to the ambrisentan or to the disease itself.
- ◆ The incidence of abnormal liver function tests was less than 3 percent for patients on ambrisentan. The trials excluded patients with a known intolerance to endothelin Type A receptor antagonists and patients with a history of elevated liver function tests. The true incidence is not known.
- ◆ The CED noted that the American College of Chest Physicians guidelines (Badesch et al. *Chest* 2007 June;131:1917-1928) strongly recommends sildenafil as the drug of choice for patients with functional class II PAH who have failed standard therapy. For patients with functional class III PAH who have failed standard therapy, the guideline strongly recommends sildenafil or an endothelin type A receptor antagonist, with no order of preference.
- ◆ Ambrisentan costs less per day than bosentan and sitaxsentan, but more than sildenafil. Sildenafil has been shown to improve exercise capacity and quality of life compared to placebo. There are no trials comparing ambrisentan to sildenafil.

- ◆ **Overall, the CED noted that ambrisentan offers short-term clinical benefit in patients with functional Class II or III PAH. Because ambrisentan costs more than sildenafil but no data is available demonstrating its therapeutic advantage over sildenafil, the CED recommended that ambrisentan be funded for patients who have failed or are intolerant to sildenafil.**

EAP Funding Criteria:

Criteria for drugs used to treat PAH change often in response to evolving clinical evidence and on-going reviews. Therefore, please check http://www.health.gov.on.ca/english/providers/program/drugs/eap_criteria.html for the most up-to-date funding criteria.

CEDAC Recommendation:

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

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that ambrisentan (Volibris®) be listed according to specific criteria.



Ministry of
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