



Canadian Agency for  
Drugs and Technologies  
in Health

# COMMON DRUG REVIEW

## CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

### AMBRISENTAN (Volibris™ – GlaxoSmithKline Inc.)

This document was originally issued on December 17, 2008. It was corrected on February 4, 2009. The references to the locations of the clinical studies have been corrected on page two in the second and third paragraphs, under the heading “Summary of Committee Considerations”. Improvements in the 6-minute walk distance have been clarified in paragraph one under the heading “Reasons for Recommendation” and in paragraph two under the heading “Summary of Committee Considerations”.

#### **Description:**

Ambrisentan is an endothelin A receptor antagonist (ETRA) indicated for treatment of idiopathic primary pulmonary arterial hypertension (PAH) or pulmonary hypertension associated with connective tissue disease in patients with WHO functional class II or III symptoms who have not responded to conventional therapy.

#### **Dosage Forms:**

5 mg and 10 mg tablets. The recommended initial dose is 5 mg taken once daily, which may be increased to 10 mg taken once daily.

#### **Recommendation:**

The Committee recommends that ambrisentan, in doses up to 10 mg daily, be listed for patients with at least WHO functional class III pulmonary arterial hypertension, either idiopathic or associated with connective tissue disease and confirmed by right heart catheterization.

Ambrisentan funding should be limited to patients who have failed to respond to sildenafil or who have contraindications to sildenafil.

Funding of ambrisentan given concomitantly with other ETAs, epoprostenol, treprostinil or sildenafil is not recommended.

#### **Reasons for the Recommendation:**

1. Compared with placebo, ambrisentan was associated with statistically significant differences in clinically relevant outcomes such as reduction in clinical worsening, decreased hospitalization and improved quality of life in one of the two RCTs included in the systematic review. There were also

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statistically significant improvements in the 6-minute walk distance compared with placebo (up to 50 and 60 metres for the 10 mg and 5mg dose, respectively).

2. There were no randomized controlled trials that compared the effects of ambrisentan with other drugs, or studied the effects of ambrisentan given as combination therapy.
3. Ambrisentan taken as 5 mg or 10 mg daily costs \$120 per day which is slightly less than other funded oral therapies such as bosentan (\$130 per day). The cost of ambrisentan is significantly higher than sildenafil (\$32 per day), which has been shown to improve exercise capacity and quality of life, relative to placebo.

### **Summary of Committee Considerations:**

The Committee considered a systematic review of two double-blind, randomized, placebo controlled trials evaluating the effects of ambrisentan in patients with class II or III PAH (N=394). The trials were both 12 weeks in duration. One trial was performed in Europe and South America and the second trial was performed in North America. The North American study results were deemed to have greater external validity for Canadian PAH patients, because the patients in this trial would have been treated in a manner approximating the Canadian treatment approach for PAH, compared to the European/South American study.

Compared to placebo, ambrisentan resulted in statistically significant improvements in the 6-minute walk distance for both the 5 mg and 10 mg treatment arms (up to 50 and 60 metres for the 10 mg and 5mg dose, respectively). Statistically significant differences between ambrisentan 5 mg and placebo in the Short Form-36 (SF36) physical function domain, Borg Dyspnea Index (BDI) or Clinical Worsening were not observed in the North American trial, but were observed for patients taking ambrisentan 5 mg daily compared to placebo in the European/South American trial. There were no statistically significant differences between ambrisentan and placebo for incidence of death, serious adverse events or lung transplantation. Hospitalization rate was lower in patients taking ambrisentan compared to placebo in the European/South American study, but not in the other trial.

Despite exclusion of patients with a previous intolerance to ETRAs or a history of elevated liver function tests, in the short term randomized trials, there was one death related to liver disease in an open-label extension phase in a patient taking ambrisentan. The exclusion of patients from these studies who had previous intolerance to ETRAs or elevated liver function tests reduces the ability to accurately discern the effects of ambrisentan on liver function. Peripheral edema was more common in patients taking ambrisentan than patients taking placebo in the trial performed in North America.

The manufacturer conducted a cost-minimization analysis in which the total costs of treatments (drug, administration, and monitoring) were compared over a one-year period. The manufacturer reported that the total annual costs per patient for ambrisentan (\$50,950) were substantially more compared to sildenafil (\$16,596) but less compared to bosentan (\$56,546), and treprostinil (\$87,275).

### **Of Note:**

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. The Committee noted the increase in the number of drugs indicated for PAH without clear evidence that they are disease modifying and suggests that drug plans consider a therapeutic class review of these agents to assess their relative effectiveness, harms, cost and place in therapy.

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**Background:**

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.

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The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial or federal government or the manufacturer.

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CEDAC Meeting – November 19, 2008

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