CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

SITAXSENTAN RESUBMISSION (Thelin™ – Encysive Canada Inc.)

This product has been withdrawn from the Canadian market.
Date of notification was December 15, 2010.

Description:

Sitaxsentan is an endothelin-A receptor antagonist (ETRA) indicated for treatment of primary pulmonary arterial hypertension (PAH) or pulmonary hypertension secondary to connective tissue disease, in patients with WHO functional class III who have not responded to conventional therapy. Sitaxsentan is also indicated in patients with WHO functional class II who did not respond to conventional therapy and for whom no appropriate alternative can be identified. The Canadian Expert Drug Advisory Committee (CEDAC) had previously recommended that sitaxsentan not be listed (see Notice of CEDAC Final Recommendation issued on January 30, 2008). A new confidential price was the basis of this resubmission.

Dosage Forms:

100 mg tablets. The recommended dose is 100 mg taken once daily.

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that sitaxsentan not be listed.

Reasons for the Recommendation:

1. Sitaxsentan has not been shown to improve important outcomes such as survival, hospitalization rate, time to transplantation or quality of life and did not improve dyspnea scores. Sitaxsentan has been shown to have a statistically significant treatment effect on surrogate outcomes such as the six-minute walk distance (6MWD) when compared to placebo but the overall difference was small, not attained in all trials and of uncertain clinical importance.

2. There are a number of alternate treatment options for PAH, including sildenafil, which is much less costly than sitaxsentan. While a confidential lower price was submitted for sitaxsentan, there remains insufficient evidence that sitaxsentan is cost effective.

Summary of Committee Considerations:

The basis of this resubmission was a lower price of [redacted] per 100 mg tablet, which is a [redacted] price reduction, compared to the original submitted price. This price is slightly less than bosentan ($130 per

day) but considerably more than sildenafil ($32 per day), another oral agent approved for use in WHO class II or III PAH. Since no RCTs have been designed to compare the relative efficacy of sitaxsentan to other agents for PAH, the incremental cost-effectiveness of sitaxsentan compared to other agents is unknown.

There have been no new randomized controlled trials (RCTs) since the original sitaxsentan submission. In the original sitaxsentan submission, the Committee considered a systematic review of RCTs evaluating sitaxsentan in patients with primary PAH or PAH secondary to connective tissue disease. Three double-blind, placebo controlled trials of 12 to 18 weeks duration and including a total of 305 patients treated with sitaxsentan, and a randomized open-label extension study of one of these trials, met the inclusion criteria for the systematic review. While one of the trials also included an open-label bosentan treatment group, no statistical comparisons were performed between the sitaxsentan and bosentan arms. Compared to placebo, sitaxsentan resulted in statistically significant improvements in the 6MWD in two of the three RCTs but the clinical importance of these differences is uncertain (approximately 24 to 35 m from a baseline of 320 to 400 m). There were no statistically significant differences between sitaxsentan and placebo in the Borg dyspnea score in the two trials that reported on this outcome. Only one trial assessed the impact of sitaxsentan on quality of life, which was not improved compared to placebo.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

2. The Committee considered the results of a post-hoc subgroup analysis of patients with WHO functional class III PAH (including 67 patients taking sitaxsentan). The Committee thought that the results of this subgroup analysis were of uncertain significance, given the small sample size and post-hoc nature of the subgroup.

3. The Committee noted the increase in the number of drugs for PAH and suggests that drug plans consider a class review of these agents to assess their relative effectiveness, harms, cost and place in therapy.

4. The Committee will be interested in the results of an additional Phase III study for sitaxsentan which was requested by the FDA. The "Sitaxsentan Efficacy and Safety Trial With a Randomized Prospective Assessment of Adding Sildenafil" (SR-PAAS) is expected to be completed by June 2010.

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.