# CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

## SITAXSENTAN
## (Thelin™ – Encysive Pharmaceuticals 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This product has been withdrawn from the Canadian market.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 that is indicated for the treatment of primary pulmonary arterial hypertension (PAH) or PAH secondary to connective tissue disease, in patients with WHO functional class III who have not responded to conventional therapy, and in patients with WHO functional class II who did not respond to conventional therapy and for whom no appropriate alternative can be identified.

### 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 clinically important outcomes such as survival, hospitalization rate, time to transplantation or quality of life. 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 clinical importance of this difference is uncertain.

2. There are a number of alternate treatment options for PAH, including sildenafil which is less costly than sitaxsentan, and there is insufficient evidence that sitaxsentan offers a therapeutic advantage over these agents.

### Summary of Committee Considerations:
The Committee considered a systematic review of randomized controlled trials (RCTs) evaluating sitaxsentan in patients with primary PAH or PAH secondary to connective tissue disease. Three double-blind, placebo controlled trials of 12-18 weeks duration and including a total of 521 patients, 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 6MWD in two of the three RCTs but the clinical importance of these differences (approximately 30-35 m on a baseline of 320 to 400 m) is uncertain. There were no statistically significant differences between sitaxsentan and placebo in the Borg dyspnea score in the two trials that reported on this outcome. One trial assessed the effect of sitaxsentan on quality of life and found no statistically significant difference versus placebo.

Sitaxsentan has the potential to cause hepatotoxicity and liver functions tests are recommended prior to initiation of therapy and monthly thereafter. Sitaxsentan has the potential to significantly inhibit the metabolism of warfarin, a drug commonly used in patients with PAH.

Sitaxsentan costs $126 per day which is similar to bosentan ($128 per day) but more than sildenafil ($31 per day), another oral agent approved for use in WHO class II or III PAH. The economic evaluation submitted by the manufacturer assumed that sitaxsentan resulted in improved quality of life compared to bosentan. Since no RCTs have been designed to compare the relative efficacy of these two agents, the incremental cost-effectiveness of sitaxsentan compared to bosentan is unknown.

## Of Note:

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

## 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.