PUBLIC SUMMARY DOCUMENT

Product: Sitaxentan sodium, tablet, 100 mg (base), Thelin®

Sponsor: Encysive Pharmaceuticals Inc.

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) listing for the treatment of primary pulmonary arterial hypertension (PAH) in patients with NYHA/WHO Functional Class III symptoms and primary pulmonary hypertension associated with connective tissue disease.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Sitaxentan was TGA registered on 15 March 2007 for the treatment of pulmonary arterial hypertension (PAH) in patients with NYHA/ WHO Functional Class III symptoms to improve exercise ability. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.

4. Listing Requested and PBAC's View

Section 100 – Public and private hospital authority required

The submission requested that the PBS restriction be the same as that for bosentan, taking into account the possible differences in the TGA approved indications and dosage recommendations of the two agents.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Primary, or unexplained, pulmonary arterial hypertension (PAH) is a rare lung disorder which is characterized by sustained elevations of pulmonary artery pressure without a demonstrable cause. The estimated incidence is 1-2 per million population. The natural history of PAH is usually progressive, intractable and often fatal, with treatment options aimed at relieving symptoms of the disease and returning the patient to a more functional lifestyle. These therapies include anticoagulants, vasodilators, antiplatelet agents, oxygen and anti-inflammatory therapies. Newer agents such as bosentan, iloprost, treprostinil, epoprostenol and sildenafil have been registered by the TGA for the treatment of more severe cases of PAH (Class III or IV) in the past few years.

Sitaxentan would be an alternative treatment for all agents currently used in PAH Class III patients.

6. Comparator

Appropriately, the submission nominated bosentan as the comparator.

7. Clinical Trials

The submission presented a direct randomised trial (STRIDE-2) of sitaxentan (50 mg/d, 100 mg/d), placebo and bosentan (unblinded; 62.5 mg bd for 4 weeks titrated to 125 mg bd), supplemented with an indirect meta-analysis of five randomised comparative trials (3 sitaxentan trials, inclusive of the direct randomised trial, above, and 2 bosentan trials) with placebo as the common reference.

These trials had been published at the time of submission, as follows:

Trial/First Author	Protocol title/Publication Title	Publication Citation
Direct randomised trial		
STRIDE-2 (FPH02) Barst RJ et al, 2006	Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxentan.	J Am Coll Cardiol. 47(10):2049-56.
Systematic reviews		
Liu & Chen, 2006	Endothelin receptor antagonists for pulmonary arterial hypertension.	Cochrane Database of Systematic Reviews. Issue 3. Art. No.: CD004434. DOI: 10.1002/ 14651858.CD004434.pub3.
Supplementary randomised trials for indirect meta-analysis (common reference – placebo)		
Sitaxentan		
Frost et al. (2005)	The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: demonstration of a ceiling effect.	Vascular Pharmacology; 43(1):36-9.
Horn et al. (2004)	Sitaxsentan, a selective endothelin-A receptor antagonist for the treatment of pulmonary arterial hypertension.	Expert Opinion on Investigational Drugs. 13(11):1483-92.
Langleben et al. (2004)	Sustained symptomatic, functional, and hemodynamic benefit with the selective endothelin-A receptor antagonist, sitaxsentan, in patients with pulmonary arterial hypertension: a 1-year follow-up study.	Chest. 2004; 126(4):1377-81.
Oudix et al. (2006)	Cardiopulmonary exercise testing and six-minute walk correlations in pulmonary arterial hypertension.	American Journal of Cardiology. 97(1):123-6.
Bosentan		
Channick et al (2001)	Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study.	Lancet. 358(9288):1119-23.
Rubin et al (2002)	Bosentan therapy for pulmonary arterial hypertension.	New England Journal of Medicine. 346(12):896-903.
Denton et al (2006).	Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions.	Annals of the Rheumatic Diseases.65(10):1336-40.
Galie et al. (2003)	Effects of the oral endothelin-receptor antagonist bosentan on echocardiographic and doppler measures in patients with pulmonary arterial hypertension.	Journal of the American College of Cardiology. 41(8):1380-6.

8. Results of Trials

The results of the key direct randomised trial and indirect meta-analyses of supplementary randomised trials are summarised in the tables below.

Summary of results from the direct randomised trial (STRIDE 2)

Measure	Sitaxentan 50mg	Sitaxentan 100mg	Open label bosentan
Primary End-point (placebo-corrected for -6.5m)			
Change from baseline in 6MWD at week 18	24.2 metres p=0.07	31.4 metres p=0.03	29.5 metres p=0.05

The PBAC noted that the STRIDE-2 trial was not designed or powered to detect non-inferiority or equivalence between sitaxentan and the open label bosentan arm. A post-hoc review, calculated the mean difference in the 18 week change from baseline (sitaxentan 100 mg/d – bosentan 125 mg bd) was 1.89 m (95% CI -22.7, 26.5; p=0.9).

Summary of results from the supplementary indirect meta-analyses of randomised trials

Change from baseline in 6MWT to:	Estimate Sitaxentan – Bosentan	SE	95% CI	*P*-value
12 weeks, ITT populations	-18.0m	22.4	-61.9, 25.9	0.4
Endpoint, ITT populations	-14.6m	20.0	-53.7, 24.6	0.5
12 weeks, Equivalent groups	10.9m	26.2	-40.5, 62.2	0.7
Endpoint, Equivalent groups	11.2m	23.9	-35.5, 58.0	0.6

negative values = favours bosentan

The PBAC noted that based on the point estimates, the indirect meta-analysis favours bosentan for the intention to treat (ITT) population and favours sitaxentan for the PBS equivalent subgroup. The PBS equivalent subgroup analysis includes only data from patients in Functional Class III/IV, with a baseline six minute walk test (6MWT) <450 m, and without congenital heart disease. The confidence intervals are very wide and the point estimates may not be reliable.

In STRIDE-2, sitaxentan 100 mg-treated patients had a lower rate of liver function test (LFT) increases (> 3 x upper limit of normal (ULN)) than bosentan treated patients (3% vs 11%).

The PBAC noted that sitaxentan 100 mg/d (the TGA approved dose) appeared to have comparable nature (i.e. class-related) and frequency of adverse events to bosentan 125 mg bd based on the presented trial based evidence.

9. Clinical Claim

The submission claimed that sitaxentan is non-inferior in term of effectiveness and toxicity to bosentan.

The PBAC considered sitaxentan is no worse than bosentan on the basis of an indirect comparison of the results of the 6-minute walk test. The PBAC noted the supplementary meta-analyses supported this conclusion.

10. Economic Analysis

The cost-minimisation approach taken by the submission was accepted as valid.

The equi-effective doses in the context of cost-minimisation were sitaxentan 100 mg/d and bosentan 125 mg bd (62.5 mg bd for 4 weeks titrated to 125 mg bd). This was based on the TGA approved dose regimen and relevant dose arms in the presented randomised trials.

The drug cost/patient/year was estimated to be in the range $45,000 – $75,000. The proposed price was identical to the current special supply arrangement for bosentan.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed/year accounting for market share as necessary was estimated by the submission to be < 10,000 in Year 5 (2012).

Sitaxentan was expected to take market share directly from bosentan at no additional cost to the PBS.

12. Recommendation and Reasons

The PBAC recommended sitaxentan be listed on the PBS for the treatment of primary pulmonary arterial hypertension in patients with NYHA/WHO Functional Class III symptoms, and primary pulmonary hypertension associated with connective tissue disease on a cost-minimisation basis compared to bosentan.

The PBAC accepted that bosentan was the appropriate comparator to sitaxentan, noting that the two drugs belong to the same therapeutic class and bosentan is the drug most likely to be the replaced by sitaxentan.

The PBAC considered sitaxentan is no worse than bosentan on the basis of an indirect comparison of the results of the 6-minute walk test. The PBAC noted the supplementary meta-analyses supported this conclusion. The equi-effective doses are sitaxentan 100 mg daily and bosentan 125 mg twice daily.

The PBAC recalled that the November 2006 meeting recommended the listing of sildenafil on a cost-minimisation basis with bosentan. Sildenafil was listed from 1 March 2007 at a considerably lower cost than bosentan, and the PBAC understood that a price reduction would flow on to bosentan, and hence to sitaxentan.

The PBAC recommended the eligibility and continuation criteria should take account of the TGA approved indications and dosage recommendations for sitaxentan, as should the clinical interchangeability arrangements specified in the PBS restrictions for the agents used in these conditions.

Recommendation

SITAXENTAN, tablet, 100 mg, Thelin®, Encysive Pharmaceuticals Inc.
Restriction:
To be finalised.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the

medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no comment.