

sitaxentan 100mg tablets (Thelin[®])
Encysive (UK) Ltd

No. (360/07)

9 March 2007

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

sitaxentan sodium (Thelin[®]) is accepted for restricted use within NHS Scotland for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.

Data suggest that sitaxentan 100mg daily has a benefit/risk ratio comparable to the other licensed endothelin receptor antagonist. Non-inferiority has not been formally demonstrated as sitaxentan is an orphan drug with limited clinical evidence. Where an endothelin receptor antagonist is indicated, sitaxentan provides an alternative.

It is restricted to initiation and prescribing by specialists in the Scottish Pulmonary Vascular Unit.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.

Dosing information

100mg daily

Product availability date

November 2006

Orphan drug

Summary of evidence on comparative efficacy

Pulmonary arterial hypertension (PAH) is characterised by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death. Endothelin-1 (ET-1) is a key mediator in the pathogenesis and progression of PAH. It acts via endothelin-A (ET-A) receptors in smooth muscle and endothelin-B (ET-B) receptors mainly on endothelial cells. Predominant actions of ET-1 at ET-A receptors are vasoconstriction and vascular remodelling, while binding with ET-B receptors results in ET-1 clearance, vasodilation and anti-proliferation effects, due in part to the release of nitric oxide and prostacyclin. Sitaxentan is a highly selective ET-A receptor antagonist.

A randomised, double-blind, placebo-controlled trial, incorporating an open-label observational bosentan arm, treated 245 patients of whom 59% had idiopathic PAH, 30% had PAH associated with connective tissue disease and 11% had PAH associated with congenital heart defects. Patients were in WHO functional class II, III, or IV, aged 12 to 78 years, had a 6 minute walk distance (6MWD) of 150-450m, and were symptomatic despite treatment with anticoagulants, vasodilators, diuretics, cardiac glycosides and supplemental oxygen (if required). Patients who had previously received bosentan were excluded. Seventy-eight percent of patients were female, reflecting the PAH population. Patients were randomised to receive 18 weeks' treatment with sitaxentan 50mg, 100mg, placebo once daily or open-label bosentan in the standard dose, (62.5mg twice daily for four weeks then 125mg twice daily thereafter).

The primary endpoint was mean change from baseline to week 18 in 6MWD. In the 240 evaluable patients, there were significant increases compared to placebo in 6MWD in the sitaxentan 100mg and bosentan groups but not in the sitaxentan 50mg group. Placebo-corrected mean increases were 31.4 metres(m) for sitaxentan 100mg and 29.5m for bosentan. (There was a mean decrease of 6.5m from baseline to week 18 in the placebo group). None of the secondary endpoints (time to clinical worsening and Borg dyspnoea score) were achieved except that change from baseline to week 18 in WHO functional class was better with sitaxentan 100mg compared to placebo, with 13% vs. 10% of patients having improved WHO functional class and 85% vs. 77% of patients remaining unchanged, in the respective groups (p=0.04). However, due to the observational nature of the bosentan arm it is not possible to make direct comparisons with the sitaxentan or placebo arms.

An earlier randomised, double-blind, placebo-controlled 12 week study in a similar population included patients with a specified peak oxygen uptake that was between 25% and 75% of predicted. One hundred and seventy-eight patients were randomised to once daily sitaxentan 100mg, 300mg or placebo. The primary endpoint of change from baseline to week 12 in percent of predicted oxygen uptake was described in the scientific discussion of the European Public Assessment Report (EPAR) as being of uncertain clinical relevance. The endpoint was achieved by the patients taking sitaxentan 300mg but not by those taking 100mg. Both the sitaxentan 100mg and 300mg doses significantly improved 6MWD at week 12 compared to placebo, with placebo-corrected increases from baseline of 35m and 33m respectively (there was a mean decrease of 13m from baseline to week 12 in the placebo group). Functional class and most haemodynamic measures significantly improved in the sitaxentan groups compared to placebo at week 12; however there were no significant differences compared to placebo for time to clinical worsening and quality of life.

In a blinded extension study, patients who had received sitaxentan in the core study continued the same treatment, while those who had received placebo, were randomised to either 100mg or 300mg sitaxentan daily. In all patients treated with active drug in the core and extension studies, (mean treatment duration of 26 weeks), improvement of at least one New York Heart Association functional class was demonstrated in 53% (n=42/79) of patients in the sitaxentan 100mg group and deterioration occurred in 5% (n=4/79). Safety concerns arose with the 300mg dose and its use was abandoned in subsequent studies.

Summary of evidence on comparative safety

In the 18 week trial described above, treatment-related adverse events were reported in 46% of sitaxentan 100mg patients, 56% of bosentan patients and 29% of placebo patients. Serious adverse events occurred most often in patients taking placebo. Discontinuations due to adverse events occurred in 10%, 3% and 10% of placebo, sitaxentan 100mg and bosentan groups respectively. The key safety issue is hepatotoxicity, the underlying mechanism of which is unclear. Symptomatic hepatitis has occurred in patients receiving sitaxentan 100mg daily. The limited data suggest that sitaxentan hepatotoxicity is at a comparable level to that of bosentan, although firm conclusions cannot be drawn on the basis of the available data. Similarly, the serious adverse event profile of sitaxentan appears to be comparable to that of bosentan, although the limited data do not permit robust conclusions. It may not be appropriate to compare rates of events between an open label arm and double blind arms of a study. The manufacturer intends that sitaxentan be distributed using a controlled access system with adverse events monitored in a post-marketing surveillance system.

Summary of clinical effectiveness issues

Sitaxentan has been designated as an orphan drug and evidence of clinical efficacy and safety is limited.

Approximately one-third of the patients in the two main studies were in WHO functional class II which is not covered by the licensed indication.

Overall, the data suggest that sitaxentan 100mg daily has a benefit/risk ratio comparable to the non-selective endothelin receptor antagonist bosentan, although non-inferiority compared with bosentan has not been formally demonstrated.

The effect of sitaxentan on the outcome of PAH is unknown and there are no studies to demonstrate beneficial effects on survival.

The scientific discussion of the EPAR notes that non-selective blockade of endothelin receptors has proved to be a useful treatment strategy in primary and scleroderma-associated PAH, and that it has been postulated that relatively selective antagonism of the ET-A receptor may be more advantageous through blocking the deleterious vasoconstrictive effects of ET-1 on the pulmonary vasculature, while maintaining the vasodilator and clearance functions of the ET-B receptor. To date, the further clinical efficacy anticipated on the basis of this hypothesis remains to be proven.

Sitaxentan has the advantage of once-daily administration and there is no need for dose titration.

Summary of comparative health economic evidence

The manufacturer submitted a Markov model to compare the cost consequences of using sitaxentan and bosentan over a 12 month period in patients with pulmonary arterial hypertension (PAH) NYHA class III. The model assumed clinical equivalence between sitaxentan and bosentan. The cost of each drug is the same at £1,675 per month.

The base case used data from patients in a randomised placebo-controlled trial with an observational bosentan arm, and its extension study to model the number and timing of relevant clinical events. Such events included an adverse event, or hospitalisation, or clinical worsening. After any event a patient was assumed to switch to iloprost. Scottish hospitalisation and costs per test were applied. No other health benefits were modelled.

The results of the model indicated that sitaxentan was associated with lower costs and similar outcomes to bosentan. It is not clear however whether the study on which the model was based is fully representative of the difference between the two products, therefore no firm conclusion is possible.

There were no major weaknesses in the model. If clinical equivalence is accepted then the results and sensitivity analyses suggest using sitaxentan has similar cost consequences to bosentan in this indication.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: previous SMC advice

In March 2003, following a full submission, the Scottish Medicines Consortium (SMC) issued the following advice on bosentan (Tracleer): Recommended for restricted use within NHS Scotland. This medicine was approved by EMEA under the accelerated licensing process, thus evidence of its efficacy is limited. Bosentan may be a potentially useful alternative to epoprostenol for patients with Grade III pulmonary arterial hypertension. It offers major advantages over epoprostenol in its ease of administration. However, there are currently scant data on the effectiveness of these products on patient survival. The hepatotoxicity and teratogenicity of bosentan have led the EMEA to recommend post-marketing surveillance and the company operates this as a controlled release programme.

The cost-effectiveness of bosentan is impossible to estimate at present, and may be low. Bosentan should only be prescribed for patients who are treated in specialist centres run by physicians experienced in the management of these disorders.

In November 2005, following a full submission, the SMC advised that iloprost trometamol nebuliser solution (Ventavis) is accepted for restricted use within NHS Scotland for the treatment of patients with New York Heart Association Class III primary pulmonary hypertension as a second-line treatment where bosentan is ineffective or is not tolerated. It is an orphan product and efficacy data are very limited. Iloprost should also be restricted to use only as an alternative in patients receiving other forms of prostacyclin treatment. It is not recommended for patients who would not otherwise have received prostacyclin treatment because it is not cost effective in this situation. It is further restricted only to use by specialists working in the Scottish Pulmonary Vascular Unit.

In January 2006, following a full submission, the SMC advised that sildenafil citrate (Revatio) is accepted for restricted use within NHS Scotland for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. This is an orphan indication for sildenafil with limited clinical evidence from short-term clinical trials. It is restricted to initiation by specialists working in the Scottish Pulmonary Vascular Unit and by physicians experienced in the management of pulmonary vascular disease.

Additional information: comparators

Alternative drugs include the only other licensed endothelin receptor antagonist, bosentan, (oral tablet); sildenafil (oral tablet), iloprost (nebulised solution) and epoprostenol (continuous intravenous infusion). A substantial proportion of this small patient population receives unlicensed medicines often through involvement in clinical trial programmes.

Cost of relevant comparators

Doses are shown for general comparison and do not imply therapeutic equivalence.

Product	Regimen	Cost per year (£)
sitaxentan (Thelin)	100mg orally once daily	20,020
epoprostenol (Flolan)	20-40 nanograms/kg/minute by continuous intravenous infusion	*94,691-142,036
iloprost (Ventavis)	2.5-5micrograms nebulised 6-9 times daily	30,940 - 46,358
bosentan (Tracleer)	125mg orally twice daily	20,033
sildenafil (Revatio)	20mg orally three times daily	4,532

epoprostenol,sildenafil costs accessed from evadis on 3/1/07; bosentan, iloprost costs from MIMS; sitaxentan costs from manufacturer.

* costs assume daily use of 2 or 3 vials based on suggested optimal dose in a published paper by the European Society of Cardiology and bodyweight range of 60-80kg.

Additional information: budget impact

Other data were also assessed but remain commercially confidential.*

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 16 February 2007.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk/>*

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Barst J, Langleben D, Badesch D et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxentan. J Am Coll Cardiol. 2006; 47 (10): 2049-5.

Barst J, Langleben D, Frost A et al. Sitaxentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 2004; 169: 441-447