ambrisentan, 5mg and 10mg tablets (Volibris®) No. (511/08)
GlaxoSmithKline

10 October 2008

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

ambrisentan (Volibris®) is accepted for restricted use within NHS Scotland for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

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

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

The treatment of patients with pulmonary arterial hypertension (PAH) classified as World Health Organisation functional class (WHO FC) II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

Dosing information

Orally, 5 mg once daily. Some additional efficacy has been observed with 10 mg ambrisentan in patients with Class III symptoms however an increase in peripheral oedema has also been observed. Patients with PAH associated with connective tissue disease may require 10 mg ambrisentan for optimal efficacy. Confirm that the 5 mg dose is well tolerated before considering an increase in dose to 10mg ambrisentan in these patients.

Treatment must be initiated by a physician experienced in the management of PAH.

Product availability date

23rd June 2008

Ambrisentan has been designated as an orphan drug in this indication.

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. It may be idiopathic (primary) or secondary to other conditions. 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, vasodilatation and anti-proliferation effects, due in part to the release of nitric oxide and prostacyclin. Ambrisentan is a selective non-sulphonamide endothelin receptor antagonist (ERA), selective for ET_A.

Two randomised, double-blind, placebo-controlled trials were identical in design except for ambrisentan doses used: in the first, patients were randomised to receive 12 weeks' treatment with placebo or ambrisentan 5 mg or 10 mg while in the second, the ambrisentan doses were 2.5 mg and 5 mg. Ambrisentan or placebo was added to patients existing supportive/background medication which could include digoxin, anticoagulants, diuretics, oxygen and vasodilators. A combined analysis included 393 patients from the intention to treat (ITT) populations of whom 64% had idiopathic PAH and the remaining 36% had PAH associated with connective tissue disease, appetite suppressant use or human immunodeficiency virus (HIV) infection. Entry was not restricted according to WHO functional class, but most patients were in Class II (38%) or Class III (55%). Mean age standard deviation (SD) was 50.5 (15.2) years and mean (SD) six-minute walk distance (6MWD) was 345 (80) metres (m). They met haemodynamic criteria for PAH despite stable therapy. Patients who had previously received bosentan, a phosphodiesterase type 5 inhibitor, or a chronic prostanoid therapy within four weeks prior to the screening visit were excluded. Seventy-nine percent of patients were female, reflecting the PAH population.

The primary endpoint was mean change from baseline to week 12 in 6MWD in the ITT population with last observation carried forward for missing values. In the 261 evaluable patients in the combined analysis, there were significant increases compared to placebo in 6MWD in all dosing groups including a combined ambrisentan group. Placebo-corrected

mean increases were 31 m (95% confidence interval (CI): 5.6 to 57) for ambrisentan 2.5 mg, 45m (95% CI: 24 to 65) for 5 mg, 52m (95% CI: 29 to 76) for 10 mg and 43m (95% CI: 26 to 60) for combined ambrisentan. (There was a mean decrease of 9.0m from baseline to week 12 in the placebo group). Placebo-controlled comparisons were also significant for all ambrisentan doses in each of the individual trials.

Ambrisentan was also significantly superior to placebo for time to clinical worsening and Borg dyspnoea score in all treatment arms in the combined analysis. Overall, when both trials were combined, there was a significant improvement in terms of change in WHO FC at 12 weeks compared with the placebo group for the combined ambrisentan group and the 5 mg and 10 mg groups, mainly due to a lower rate of deterioration with ambrisentan. For example 22% of patients in the combined ambrisentan group and 20% in the placebo group improved by at least one class, while 3.5% and 17% respectively deteriorated. The primary quality of life measure was the physical functioning scale of the SF36 questionnaire, and there was significant improvement over placebo in all ambrisentan groups in the combined analysis.

Summary of evidence on comparative safety

In the combined analysis of the 12-week trials described above, treatment-related adverse events were reported in 40% of patients for all doses of ambrisentan combined and 33% of placebo patients. Serious adverse events occurred most often in patients taking placebo. Discontinuations due to adverse events occurred in 3.8% and 7.6% of ambrisentan and placebo groups respectively. The most commonly reported adverse events with both ambrisentan and placebo were headache and peripheral oedema.

No cases of elevated liver enzymes (ALT/AST $\geq$3 x ULN) were observed with ambrisentan in either of the pivotal studies while three cases were observed in the placebo arm across both studies. There was also a low incidence of abnormalities in a study which recruited patients with a history of hepatotoxicity from other endothelin receptor antagonists (ERAs). The European Medicines Agency states that this indicates that ambrisentan may lack the hepatotoxicity associated with other members of this class, although firm conclusions cannot be drawn on the basis of the available data.

A number of drug-drug interactions which are common with other ERAs have not been observed with ambrisentan.

Summary of clinical effectiveness issues

Ambrisentan has been designated as an orphan drug in this indication and evidence of clinical efficacy and safety is limited. There are no studies to demonstrate an effect on survival or other long-term outcomes. It is the first disease-specific agent to be licensed for treatment of patients with WHO functional class II disease, although the bosentan licence now also notes that some improvement has also been shown in patients with PAH WHO functional class II.

Over one-third of the patients in the two main studies were in WHO functional class II and the European Medicines Agency considered this group to be sufficiently well represented to grant a licence for Class II and Class III patients. The trials did not restrict entry on the basis of WHO functional status, but very few Class I or Class IV patients were recruited.

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. Ambrisentan is intermediate in selectivity between sitaxentan and bosentan, however there are no direct comparative data to assess clinical efficacy anticipated from ambrisentan selectivity.

Ambrisentan has the advantage of once-daily administration at both 5mg and 10mg doses. Some additional efficacy has been demonstrated with 10mg ambrisentan in patients with Class III PAH, however an increase in peripheral oedema has also been observed in these patients. The SPC notes the need to confirm the 5mg dose is well tolerated before an increase to the 10mg dose is considered in such patients.

Summary of comparative health economic evidence

The manufacturer submitted a discrete event simulation model to estimate a cost per quality adjusted life year (QALY) over a five year time horizon. The patients had PAH, classified as WHO functional class II and III. The comparators were bosentan and sitaxentan. The model used patient level data from the two pivotal ambrisentan studies and relied on an indirect comparison to provide information on the comparator treatments. The simulation involved updating the 6MWD for each patient commencing treatment. This was then used to estimate the risk of various clinical worsening events which in turn determined the next stage after accruing the appropriate event costs, to include for adverse events, and utilities. The equations mainly adopted a logistic regression format, with changes over time modelled using parabolic equations.

The results reported that ambrisentan was dominant (i.e. resulted in both lower total cost and greater health benefits) compared with bosentan and sitaxentan. In all the sensitivity analyses ambrisentan remained dominant. Ambrisentan was £20,987 cheaper than bosentan and produced 0.15 more QALYs. The corresponding figures for the comparison with sitaxentan were a saving of £3,966 and a QALY gain of 0.06.

The main concerns with the submission include:

- the comparators have a narrower indication than the patients included in the model
- the resources required to manage clinical worsening events represent best practice and may overstate those used in typical Scottish settings
- some lack of clarity on utility values used
- no validation of model structure and no sensitivity analyses to test the sensitivity of the results to this aspect.

Despite these concerns, the conclusion is that ambrisentan is cost-effective compared to bosentan and sitaxentan.

Summary of patient and public involvement

A Patient Interest Group submission was not made.

Additional information: guidelines and protocols

European Society of Cardiology guidelines published in 2004 recommend bosentan for Grade III PAH within a number of complex sequential options for treatment. No grade of recommendation is given for ambrisentan or sitaxentan as these drugs had not received regulatory approval at the time that the guidelines were developed.

A United Kingdom and Ireland consensus statement from the national PAH centres published in 2008 provides one algorithm for idiopathic, familial and anorexinogen-induced PAH and a second for PAH associated with connective tissue disease (CTD). Both algorithms incorporate bosentan as first-line in some situations and sitaxentan as second-line, with no reference to other ERAs.

A Cochrane review of ERAs for PAH published in 2008 concluded that ERAs in conjunction with conventional therapy over 12 to 16 weeks can improve exercise capacity, Borg dyspnoea score and several cardiopulmonary haemodynamics variables in patients mainly with idiopathic PAH. The data on mortality do not currently show a benefit of this class of drugs on this endpoint and studies with longer follow up are required. The review did not consider any trials with ambrisentan. Ambrisentan was not included in the consensus statement as it had not received regulatory approval at the time the consensus statement was being developed.

Additional information: previous SMC advice

Following a full submission the Scottish Medicines Consortium (SMC) issued advice in May 2007: 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 100 mg 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.

Following a full submission the Scottish Medicines Consortium (SMC) issued advice in February 2006: 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.

Following a full submission the Scottish Medicines Consortium (SMC) issued advice in December 2005: 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.

Following a full submission the Scottish Medicines Consortium (SMC) issued advice in March 2003: bosentan (Tracleer) is 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.

Additional information: comparators

Bosentan and sitaxentan are alternative ERAs while disease-specific therapies for PAH also include the prostacyclin analogues epoprostenol and iloprost and the phosphodiesterase-type-5 inhibitor sildenafil.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
ambrisentan (Volibris)	**5-10 mg orally once daily**	**20,033**
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**	30,904 - 46,355
bosentan (Tracleer)	125mg orally twice daily	20,033
sitaxentan (Thelin)	100mg orally once daily	20,020
sildenafil (Revatio)	20mg orally three times daily	4,532

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 7th August 2008 or from Monthly Index of medical Specialities August 2008.

* the dose of epoprostenol varies greatly between patients and also within patients over the course of treatment. The dose of 20-40 mg/kg/min is suggested as the optimal dose for the majority of patients in European Society of Cardiology guidelines on PAH. For a 70kg patient this equates to 2.02 to 4.03 mg/day, and costing is based on the use of 2-3 vials per day.

** One ampoule is used per administration

Additional information: budget impact

The three drugs ambristentan, bosentan and sitaxentan have similar acquisition costs so the drug budget impact is expected to be cost neutral. The manufacturer assumed that an estimated120 patients in 2009 would have PAH, falling to about 100 in 2013, and that 40% of these patients would be treated with a prostacyclin. Of the remaining patients, it was assumed that one third would be prescribed ambrisentan. This represented 24 patients in 2009, falling to 20 in 2013.

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 15 September 2008.

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 reference was supplied with the submission. The one shaded grey is additional to the reference supplied with the submission.

Galie N, Torbicki A, Barst R et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension: The Task Force on diagnosis and treatment of pulmonary arterial hypertension of the European Society of Cardiology. Eur Heart J. 2004; 25:2243-78.

European Medicines Agency Assessment Report. Volibris. EMEA/123999/2008. www.emea.europa.eu

Liu C, Chen J. Endothelin receptor antagonists for pulmonary arterial hypertension (Review). The Cochrane Collaboration. 2008 Issue 3. www.the cochranelibrary.com