Scottish Medicines Consortium

iloprost trometamol nebuliser solution (Ventavis®) No. (219/05)
Schering Health Care

Scope of review: new medicine

4 November 2005

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

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.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

iloprost trometamol nebuliser solution (Ventavis®)

Indication

Treatment of patients with primary pulmonary hypertension, classified as New York Heart Association (NYHA) functional class III, to improve exercise capacity and symptoms.

Dosing information

The recommended dose per inhalation session is 2.5 or 5.0 micrograms (as delivered at the mouthpiece of the nebuliser) administered 6 to 9 times daily according to individual need and tolerability.

UK launch date

January 2004

Comparator medications

Licensed alternatives include oral bosentan and continuous intravenous infusion of epoprostenol. Unlicensed drugs are also in use.

Cost of relevant comparators

Drug	Dose	Annual cost (MIMS September 2005)
Iloprost nebulised (Ventavis®)	**2.5-5mcg 6-9 times daily****	**£30,895-£46,343**
Bosentan tablets (Tracleer®)	125mg twice daily	£20,995
Epoprostenol infusion (Flolan®)	20-40ng/kg/min*	£47,345-£94,691

* the dose of epoprostenol varies greatly between patients and also within patients over the course of treatment . The dose of 20-40ng/kg/min is suggested as the optimal dose for the majority of patients in the European guidelines on pulmonary hypertension. For a 60kg patient, this equates to 1.73-3.46mg/day. Costs assume 1-2 vials per day.

** one (20microgram) vial is used per inhalation session

These are drug costs only and do not include other likely associated costs e.g. infusion pumps and lines for epoprostenol and monitoring of liver function and haemoglobin levels for bosentan. Currently the cost of the nebulisers for iloprost is funded by the manufacturer.

Summary of evidence on comparative efficacy

Primary pulmonary hypertension is defined as an increased pulmonary artery pressure (>25mm Hg at rest or >30mm Hg during exercise) with no established secondary cause. Three factors are considered responsible for the increased pressure, namely vasoconstriction, pulmonary vascular remodelling and thrombosis in situ. There are one or two new cases reported per million per year. Although there are no known cures for this condition, several relatively recent treatment advances, including intravenous epoprostenol

and oral bosentan, have improved outcomes and/or symptoms and exercise capacity. Iloprost, a new treatment option, is a stable analogue of prostacyclin with a pharmacokinetic profile allowing nebulised administration. It has been granted orphan drug status and the clinical efficacy data are limited.

There is one pivotal phase III study (AIR) that enrolled 203 adults with primary pulmonary hypertension or selected forms of secondary (appetite-suppressant or scleroderma-associated or inoperable chronic thromboembolic) pulmonary hypertension. Eligible patients had NYHA class III or IV disease despite conventional therapy and were randomised to receive inhaled iloprost or placebo for 12 weeks in addition to their conventional therapy, which included anticoagulants, diuretics, digitalis, calcium channel blockers and/or oxygen. The iloprost dose was initially 5 micrograms nebulised and inhaled six times daily. If tolerated, the total daily dose was increased to 5 micrograms nine times daily within the first eight days. If single doses of 5 micrograms could not be tolerated, the dose per inhalation was reduced to 2.5 micrograms administered six times daily rising to nine times daily if tolerated.

The primary endpoint was a composite of an increase of ≥10% in the distance walked in 6 minutes plus an improvement in the NYHA class plus no clinical deterioration or death. After 12 weeks, this was achieved in 17% of iloprost and 4.9% of placebo patients (odds ratio of 3.97: 95% CI: 1.47, 10.75; p=0.007). In the subgroup of patients with primary pulmonary hypertension, the primary endpoint was achieved in 21% and 5.5% of patients respectively. While in the patient population defined in the product licence (primary pulmonary hypertension of NYHA class III), this was 15% and 5.6% respectively. The statistical significance of the latter two comparisons were not reported.

The components of the primary composite included the percentage of patients with an increase of ≥10% in the 6 minute walking distance. This was not significantly differently between the treatment groups (38% versus 26%, p=0.06). The absolute change in the distance walked in 6 minutes was 36 metres further in the iloprost than the placebo group (p=0.004) and 59 metres further in the subgroup with primary pulmonary hypertension. The NYHA class improved in 25% of iloprost patients compared with 13% of placebo patients; remained unchanged in 65% and 66% and worsened in 5.9% and 7.8% of patients respectively. There were no significant differences between the two treatments in the numbers of patients with clinical deterioration or death.

Other secondary endpoints included haemodynamic parameters and gas exchange, which were improved in the iloprost group compared to baseline when measured at peak effect (post inhalation). However, trough drug effects were largely unchanged from baseline. There was a significant difference between iloprost and placebo in the Mahler dyspnoea index transition score but not the focal score. Only one quality of life measure, the EuroQoL visual analogue scale, found a significant difference between the treatment groups (p=0.026).

There is an additional supportive study, not yet published in full, which was designed primarily to assess safety. This was an open-label study with patients randomised to receive iloprost plus conventional therapy or conventional therapy alone. Efficacy was measured by a composite response criterion where patients were deemed responders if they met each of the following: no death and improvement in at least one NYHA class and an increase ≥10% in the 6-minute walking distance. After 12 weeks of therapy, there was a significantly larger number of responders in the iloprost than the control group when assessed before inhalation (4/30 iloprost versus 0/33 control patients, p=0.046).

Summary of evidence on comparative safety

Nebulised iloprost was associated with a number of local inhalation effects, such as increased cough, along with systemic effects common to prostacyclin therapy. During clinical studies the most commonly reported adverse events were headache, jaw pain, nausea and vasodilation. In the pivotal study, flushing and jaw pain were significantly more common in the iloprost group than in the placebo group. Although the incidence of syncope was similar in both groups (7.9% versus 4.9%), it was more frequently reported as serious in the iloprost group (5% versus 0, p=0.03).

Inhaled iloprost avoids the need for central venous access and the increased risk of infection associated with this, as is necessary for intravenous epoprostenol. Inhaled iloprost is also free from the dose-dependent abnormalities in liver function associated with bosentan.

Summary of clinical effectiveness issues

Common to treatments of rare conditions, the clinical trial data on iloprost remain limited. Epoprostenol is the only treatment to offer survival benefit. As yet, there are no data on survival with iloprost. The long-term effects of the lack of continuous drug administration remain to be assessed.

Although the pivotal study demonstrated a statistically significant advantage in terms of the primary composite response with iloprost compared with placebo, the majority of patients (83%) treated with iloprost failed to achieve a response. Moreover, the change from baseline in the 6-minute walking distance failed to reach the threshold considered to be clinically significant (40metres) in the whole study population, although it did reach this threshold in the subgroup of patients with primary pulmonary hypertension. The main driver of the overall treatment effect was the improvement in NYHA class. The assignment of patients to an NYHA class is considered to be subject to the bias of the investigators, which has been noted to limit its usefulness as an endpoint. The EPAR comments that most of the patients who were categorised as NYHA class IV (41% of study population) seem to have been less limited in exercise capacity than such patients from other published comparative studies or those encountered in practice.

Despite the limited data, iloprost offers an alternative to oral bosentan, which has been associated with hepatotoxicty, and intravenous epoprostenol, which has problems associated with central venous access. Since there are no directly comparative clinical trials, drug choice is often dependent on other factors including approval status, route of administration, tolerability, patient preference and physician experience.

Summary of comparative health economic evidence

A cost utility analysis is presented. This compares iloprost with epoprostenol. The economic case places iloprost as second line to bosentan in NYHA III patients for whom bosentan is either ineffective or not tolerated.

The source of the clinical effectiveness and drug usage data for iloprost is based upon the pivotal study. Clinical effectiveness is estimated for the primary pulmonary hypertension NYHA III AIR patient subset.

The source of the clinical effectiveness data for epoprostenol is a placebo-controlled randomised trial with dosing at 9.2ng/kg/min by the end of the twelve weeks treatment. It is noted that the submission uses a dose rate of 20ng/kg/min to cost epoprostenol, claiming this as a better reflection of current practice as communicated by expert opinion.

A Markov model was used to compare the use of iloprost with epoprostenol in NYHA III patients. These patients may improve their NYHA status to NYHA II, or deteriorate to NYHA IV. In the base case, all patients who progress to NYHA IV are transferred to treatment with epoprostenol. NYHA IV patients may also progress to transplant. Twelve-week effectiveness data are used in the first 3-month cycle of the model. Natural history data are used to extrapolate thereafter, with a 15-year time horizon.

The main result is that, in a cohort of 100 patients, iloprost saves a total of £6.7 million over 15 years. A minor patient gain of eight QALYs is also reported for the cohort, though the manufacturer recognises that this is of limited impact.

Questions remain around the cost effectiveness as estimated by the manufacturer. It is recognised that for an orphan drug effectiveness data will be more limited than would ideally be the case. This notwithstanding, it is unclear whether the estimates of clinical effectiveness from the trials will apply to those NYHA III patients who are intolerant of bosentan; the market position sought by the manufacturer.

Significant doubts also remain around the comparability of the placebo arms of the trials of Iloprost and epoprostenol. As a consequence, the robustness of the bridging analysis performed in order to populate the model is uncertain. This applies with particular force to the estimate of those likely to worsen during epoprostenol treatment.

Within the modelling it also appears that a second-round treatment effect occurs within the iloprost arm when patients worsen and transfer to treatment with epoprostenol. The clinical effectiveness assumed for this is arbitrary and without any apparent evidence base. Only one round of clinical effectiveness is assumed within the epoprostenol arm.

The analysis also assumes that all NYHA III patients intolerant of bosentan would be treated with epoprostenol, and similarly that all patients coming off iloprost would be treated with epoprostenol.

The ICER for iloprost compared to no treatment is around £250,000 per QALY. In patients who would otherwise not have received treatment, prescribing iloprost would also result in a substantial additional cost to NHSScotland.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

No estimate of the budget impact is presented. The manufacturer estimates the annual cost of iloprost to be £41,500 per patient, as compared with £66,000 per patient for epoprostenol. The five-year cost per patient within the modelling is stated as £180,000 for iloprost followed by epoprostenol as compared with £240,000 for epoprostenol. Over a five-year period the saving from initially using iloprost is estimated to be around £60,000.

Guidelines and protocols

European Guidelines on the diagnosis and treatment of pulmonary arterial hypertension recommend inhaled iloprost as one of the treatment options for patients with NYHA class III disease. In patients with class III disease, the options include inhaled iloprost, oral bosentan and intravenous epoprostenol. Although the latter tends to be used in patients refractory to bosentan or iloprost, some physicians still use epoprostenol first-line in these patients because of the demonstrated survival benefit.

Additional information

SMC issued advice in March 2003 on bosentan (Tracleer®). This stated that “this medicine was approved by the 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 artery 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.”

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 14 October 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Humbert MH, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med 2004; 351: 425-36.

Goldsmith DR, Wagstaff AJ. Inhaled iloprost in primary pulmonary hypertension. Drugs 2004; 64:763-73.

Galiè N, Torbicki A, Barst R et al Guidelines on diagnosis and treatment of pulmonary arterial hypertension: task force on diagnosis and treatment of pulmonary arterial hypertension of the European Society of Cardiology. European Heart Journal 2004; 25: 2243-2278

Olschewski H, Simmoneau G, Nazzareno G et al Inhaled iloprost for severe pulmonary hypertension N Eng J Med 2002; 347:5; 322 – 329

Ventavis European Public Assessment Report (EPAR) December 2003 http://www.emea.eu.int/

*Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The primary pulmonary hypertension study group. N Engl J Med 1996;**334**:296-302*