Inhaled iloprost trometamol (Ventavis®) for the treatment of primary pulmonary hypertension

NICE MTA Submission

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Executive Summary

Inhaled iloprost (Ventavis®) is approved solely for the treatment of primary pulmonary hypertension (PPH) at New York Heart Association stage III (NYHA stage III). PPH is an incurable and progressive disease, and most patients will eventually need prostanoid treatment. Inhaled iloprost offers advantages over injectable prostanoids, such as epoprostenol, with respect to convenience, improved safety and tolerability, and avoidance of tachyphylaxis (large increases in dose, and hence cost, over time). Inhaled iloprost therefore offers a cost-saving therapy where oral treatment is contraindicated, has failed or not been tolerated but before continuous prostacyclin infusion is required. Due to the extremely rare occurrence of PPH, inhaled iloprost has been granted orphan drug status by the European Medicines Evaluation Agency (EMEA), and it meets the National Institute for Health & Clinical Excellence (NICE) definition of an ultra-orphan disease. There are approximately 24 patients treated with inhaled iloprost in England and Wales, and this number is not expected to change substantially over the next 5 years. The use of inhaled iloprost instead of intravenous epoprostenol in these patients will reduce costs to the NHS by £10.4 million over the next 5 years.

PPH is extremely rare, with an incidence of approximately 2 cases per million per year.[1] and the natural history is of relentless progression. Before the advent of targeted therapies for PPH, when only symptomatic treatments were available, the median survival after diagnosis was only 2.8 years.[2] The aims of drug therapy are therefore to control symptoms and, for targeted therapies, also to slow or stabilise progression. Drug treatment of PPH is based on the principles of maintaining oxygen saturation, reducing fluid retention, vasodilatation, anticoagulation, and prevention of vascular remodelling.[3] Anticoagulants, diuretics, oxygen, inotropes and simple vasodilators (such as calcium channel blockers) are commonly used. Licenced targeted pulmonary vascular therapies are vasodilators which may have effects on vascular remodelling as well as, in some cases, anti-platelet activity. These include sildenafil (a PDE-5 inhibitor), bosentan and sitaxentan (endothelin receptor antagonists), intravenous prostacyclin (epoprostenol) or prostacyclin analogues which may be inhaled (inhaled iloprost). Prostacyclin and its analogues are known collectively as 'prostanoids'.

Prostacyclin (prostaglandin I_2) is a naturally occurring, highly potent vasodilator affecting both the pulmonary and the systemic circulation as well as preventing clot formation.[4] In addition to immediate haemodynamic effects, prostanoid therapies are capable of preventing or delaying vascular remodelling.[5] However, systemically delivered prostanoids are not selective for the lung and can therefore lead to undesired systemic side effects limiting the beneficial effects. Tachyphylaxis (development of tolerance to the pharmacological effects of a drug) is also a problem with systemic prostanoids, requiring gradually increasing daily dose over time to maintain an adequate response. Intravenous and subcutaneous prostanoid treatments are also associated with administration-related side effects such as sepsis or painful local reactions. A syndrome described as rebound has also been noted to occur upon abrupt cessation of continuous systemic prostacyclin infusion leading to acute dyspnoea, pallor, weakness, dizziness, and in some cases death.[6]

The pulmonary selectivity of inhaled iloprost helps overcome many of the drawbacks of injectable prostanoids, notably systemic and administration-related side-effects. Rebound effects after overnight rest or following temporary interruption of dosing with inhaled iloprost have not been observed.[6] The inhaled route of administration also offers advantages over injectable prostanoids in terms of cost, convenience, safety/tolerability, and clinically significant tachyphylaxis is not seen. [7] Delivery of prostanoids by inhalation also ensures that vasodilatation occurs preferentially in those areas of the lung that are well ventilated, thus minimising the negative impact of ventilation-perfusion mismatch on the efficacy of therapy.[6]

Although intermittent inhalation of iloprost is associated with peak and trough pharmacodynamic effects compared to continuous prostanoid infusion, the demonstrated beneficial effects on exercise capacity when measured before inhalation, the improvement in NYHA class and the strong trend towards fewer patients with clinical deterioration, suggests that the overall positive clinical outcomes with iloprost inhalation do not require uniform and constant reduction in pulmonary pressure or resistance. The absence of tachyphylaxis and rebound may be due to the intermittent administration of inhaled iloprost with overnight breaks.[6] Alveolar deposition provides higher local concentrations of drug and will result in

pharmacodynamic effects persisting beyond the disappearance of iloprost from the systemic circulation.[8] [9] [10] Additionally, the therapeutic effect of iloprost in pulmonary hypertension is not believed to be due solely to its haemodynamic properties, but also to effects on platelet function, endothelin secretion, vascular wall remodelling and cytoprotective factors.

The extreme rarity of PPH resulted in the EMEA granting orphan drug status to inhaled iloprost (Ventavis®), and inhaled iloprost also meets the NICE definition of an ultra-orphan disease (a prevalence of <1 per 50,000 population i.e. fewer than 1000 affected people in the UK)[11]. Evidence from two randomised controlled trials in severe PPH demonstrates that inhaled iloprost produces statistically and clinically significant improvements in exercise capacity, severity of heart failure, quality of life and haemodynamic values at 3 months.[12] [13] The combined primary endpoint in the phase III study (improvement in exercise capacity at 12 wks by at least 10% AND improvement by at least 1 NYHA class at 12 weeks AND no deterioration or death before 12 weeks) was met by 14.7% of the PPH NYHA III patients receiving iloprost, compared to 5.6% of the placebo group. This combined primary endpoint encompassed improvements in walking distance of 37.8% and in NYHA class of 24.8% (both vs. placebo). The overall patient population also improved significantly as measured by the Mahler dyspnoea index (MDI) transition score which assesses the dyspnoea related symptoms, as well as in health-related quality of life (HRQL) measured by the EQ5D-VAS. Numerical trends in favour of iloprost were found with respect to MDI focal score, need for transplantation, deterioration and mortality. Longer-term follow up data (up to 5 years) show continued effect and greater survival compared to natural history and comparable to those seen with other targeted therapies.[13] [14] [15] [16] [17] [18]

Inhaled iloprost occupies a very specific niche in the treatment of PPH in UK clinical practice. This is reflected in the 2004 European Society of Cardiology (ESC) Guidelines for the treatment of PAH[3] and the 2001 British Cardiac Society (BCS) Guidelines.[19]

The BCS guidelines predate the launch of iloprost, but state that : 'Prostaglandins may also be administered by nebuliser and have been shown to have a beneficial acute effect. Nebulised iloprost appears to be safe and produces sustained improvement in exercise capacity and haemodynamics after 12 months. It may be effective in severely ill patients when administered chronically. [……] The high pH of epoprostenol makes it unsuitable for long term inhaled therapy.'[19]

The more recent ESC guidelines recommend inhaled iloprost as an alternative to bosentan for NYHA class III. 'Inhaled iloprost is likely to be used in a minority of PAH patients at NYHA III whose disease, whilst still in class III, is no longer controlled by oral therapy alone, who are unable to tolerate bosentan (e.g. due to liver toxicity) or are primarily unresponsive to oral therapy'.[3]

Inhaled iloprost treatment is not intended to replace oral therapy with sildenafil or endothelin antagonists. Current UK clinical practice follows the ESC guidelines[3], using inhaled iloprost as the next step after oral therapy in PPH patients at NYHA stage III who have failed or not tolerated oral therapy but do not yet require continuous intravenous or subcutaneous prostanoid infusion. The main advantage of inhaled iloprost is to delay progression to continuous infused prostanoid therapy, with its inconvenience, inherent risks (relating to the need for an indwelling cannula) and escalating costs (secondary to tachyphylaxis and steadily increasing dose requirements), which are not seen with inhaled prostanoid therapy.

When considering the clinical and cost effectiveness of inhaled iloprost compared to licensed alternatives, the only appropriate comparator is epoprostenol, since this would be the drug treatment of choice for this patient population if inhaled iloprost was not available. On the basis of restricted specialist use in PPH at NYHA stage III when oral treatments are contraindicated, have failed or are ineffective and patients are suitable for prostacyclin treatment, iloprost has been recommended by both the Scottish Medicines Consortium in December 2005 and the All Wales Medicines Strategy Group in March 2007.

A systematic review of the cost effectiveness literature did not identify any UK specific economic evaluations relating to the use of inhaled iloprost in PPH. A Markov model was therefore built to estimate the incremental cost per quality adjusted life year (QALY) of the prostanoid treatments. This aimed to compare, for patients with PPH NYHA class III, where oral treatments were contraindicated, ineffective or no longer tolerated, a strategy of initiating treatment with inhaled iloprost followed by epoprostenol on progression to NYHA class IV, with the use of epoprostenol in stages III and IV.

The model took a lifetime (20-year) time horizon, composed of three monthly cycles, and discounted future costs and benefits at 3.5%. The model allocated patients to states according to NYHA functional classification and whether or not the patient is receiving therapy. Transition probabilities in the model differ between the first cycle of each active therapy received and subsequent cycles of treatment. The evidence of effectiveness during the initial cycles is based on evidence from two RCTs that directly compare the treatments considered to a control group,[12 20] identified through a systematic review of the clinical literature. Beyond the randomised phase the model uses evidence from long term studies to model the survival associated with each treatment. [13 14 21 22 23 24 25 26 27]

Costs associated with treatment and ongoing medical management were based on expert interviews with 5 clinicians experienced in the management of PPH. Health related quality of life data collected in the pivotal AIR study showed a correlation between quality of life and NYHA class. On this basis QALY estimates were calculated based on an analysis of utility data collected in the clinical trial, multiplied by the expected time in each of the states. Extensive one way sensitivity analysis and a probabilistic sensitivity analysis were undertaken.

The modelled estimates of mean costs of treatment and QALYs for a hypothetical cohort of 100 patients are shown below.

Table i: Expected costs, QALYs and incremental cost effectiveness of a hypothetical cohort of 100 patients with PPH.

	Costs (£m)	**QALYs**	**ICER**
Option A; iloprost then epoprostenol	29.8	308	
Option B; epoprostenol	64.6	305	
Incremental	**Costs**	**QALYs**	
Iloprost then epoprostenol vs. epoprostenol	-34.8	4	Dominant

Using inhaled iloprost before epoprostenol offers significant savings compared to treating immediately with epoprostenol, with no detrimental impact on health outcome. Sensitivity analysis found that cost savings were reported in almost all analyses save those looking at the impact of time horizon. Most analyses found only small differences in per patient QALYs between the two arms.

A probabilistic sensitivity analysis was performed, including variation in the proportion of patients improving and deteriorating, drug dose and utility. A cost effectiveness acceptability curve (CEAC) was calculated, showing the estimated likelihood that a strategy of initiating treatment with iloprost will be preferred to epoprostenol at differing levels of willingness to pay for a QALY gained. The CEAC indicates that the model found a high degree of confidence that iloprost remains a cost effective treatment strategy relative to epoprostenol.

An estimated 24 patients with PPH NYHA class III disease receive prostacyclin treatment in England and Wales. Using inhaled iloprost in these patients results in an estimated incremental reduction in mean lifetime direct costs of £348,000 per patient, compared to infused epoprostenol alone, without a meaningful incremental gain or loss in QALYs. Assuming the number of patients on treatment remains constant, using inhaled iloprost as an alternative to epoprostenol will save the NHS £10.4 million over the next 5 years.