Scottish Medicines Consortium

sildenafil citrate 20mg tablets (Revatio®) No. (235/06)

Pfizer

New indication

6 January 2006

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

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.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Sildenafil citrate 20mg tablets (Revatio®)

Indication

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

Dosing information

20mg three times daily with tablets taken approximately 6 to 8 hours apart.

UK launch date

6 March 2006

Comparator medications

Licensed alternatives include oral bosentan, inhaled iloprost and continuous intravenous epoprostenol. Unlicensed and 'off-label' drugs are also in use.

Cost of relevant comparators

The table below includes only drug costs and not 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 nebulisers for iloprost is met by the manufacturer.

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. Therefore costs assume use of 1-2 vials per day. The cost for iloprost assumes the use of one vial per inhalation session.

Product	Regimen	Cost per year
Sildenafil 20mg tablets (Revatio®)	**20mg orally three times daily**	**£4,544**
Epoprostenol 1.5mg vials for infusion (Flolan®)	20-40ng/kg/min by continuous IV infusion	£47,000-£95,000
Iloprost 20 microgram vials for inhalation (Ventavis®)	2.5-5micrograms nebulised 6-9 times daily	£31,000-£46,000
Bosentan 125mg tablets (Tracleer®)	125mg orally twice daily	£21,000

Summary of evidence on comparative efficacy

Pulmonary arterial hypertension (PAH) is defined as an increased pulmonary artery pressure (PAP) (>25mm Hg at rest or > 30mm Hg during exercise). The factors considered responsible for the increased pressure include vasoconstriction, pulmonary vascular remodelling, inflammation and thrombosis. PAH is divided into three main subgroups: idiopathic PAH (formerly termed primary pulmonary hypertension), familial PAH and PAH related to risk factors or associated conditions. Treatment for PAH is mainly palliative; several relatively recent treatment advances, including intravenous epoprostenol, oral bosentan and inhaled iloprost, have improved outcomes and /or symptoms and exercise capacity.

Sildenafil is a phosphodiesterase type-5 (PDE5) inhibitor that blocks the degradation of cyclic guanosine monophosphate (cGMP) in the pulmonary vasculature as well as the corpus cavernosum of the penis. In the pulmonary vascular smooth muscle, the increased cGMP results in relaxation, which in patients with PAH can lead to vasodilation of the pulmonary vascular bed and the systemic circulation. Sildenafil has been granted orphan drug status in Europe for this indication and efficacy data are limited.

There is one pivotal randomised, double-blind, placebo-controlled study of 12 weeks duration which is followed by a long-term open-label extension study. This enrolled 278 patients of whom 63% had primary pulmonary hypertension, 30% PAH associated with connective tissue disease and 7% PAH following surgical repair of congenital heart lesions. Patients were randomised to receive sildenafil 20mg, 40mg or 80mg three times daily or placebo for 12 weeks and 277 patients took at least one dose. Study medication was added to the patient's stable background therapy, which could include anticoagulants, digoxin, calcium channel blockers, diuretics and/or oxygen. Patients who had previously failed on bosentan were excluded. The primary endpoint was the change from baseline in the 6 minute walking distance (6MWD) at week 12. In the 266 evaluable patients, there was a statistically significant increase in the 6MWD in all sildenafil groups compared to placebo with placebo-corrected increases of 45 metres (99% CI: 21, 70), 46 metres (99% CI: 20, 72) and 50 metres (99% CI: 23, 77) for 20mg, 40mg and 80mg respectively ($p<0.0001$ for each group). Sensitivity analysis using imputation methods for missing data calculated mean placebo-corrected treatment effects in 277 patients as 38 metres (99% CI: 12, 64; $p<0.001$) for 20mg, 45 metres (99% CI: 21, 70; $p<0.001$) for 40mg and 42 metres (99% CI: 9, 75; $p<0.001$) for 80mg sildenafil. There were no significant differences between the active groups. Subgroup analysis indicated that results were generally consistent according to baseline walking distance, aetiology, functional class, gender and mean PAP.

There was no significant difference in the change from baseline in the Borg dyspnoea scale between sildenafil and placebo-treated patients, nor was there any significant decrease in the time to, or incidence of, clinical worsening between the sildenafil and placebo groups. All sildenafil treated patients had statistically significant reductions in mean PAP and pulmonary vascular resistance compared to placebo. There was improvement of at least one functional class in 28%, 36% and 42% of sildenafil 20mg, 40mg and 80mg treated patients respectively. This compared to 7% in the placebo group, corresponding to a placebo-corrected difference of 21% (95% CI: 9, 33, $p=0.003$) for the sildenafil 20mg group.

An open-label, uncontrolled extension phase was undertaken by 259 patients during which the dose was increased to 80mg three times daily. An abstract reports that the one-year observed survival in the subgroup of patients with primary pulmonary hypertension was 96%. This is higher than that predicted from historical controls. Walking distance and functional

class status appeared to be stable. Of the 222 patients who completed 12 months of monotherapy with sildenafil, the change from baseline in the 6MWD was 51 metres.

A small published study has reported results of a comparison with bosentan but using sildenafil doses higher than licensed. Patients with PAH functional class III were randomised to receive sildenafil (50mg three times daily, n=14) or bosentan (125mg twice daily, n=12) for 16 weeks. The primary endpoint was the change from baseline in right ventricular mass as measured by cardiovascular magnetic resonance imaging. This is not a recognised endpoint in such trials. Other secondary endpoints included the 6MWD, cardiac index, Borg dyspnoea index and quality of life. No significant differences were found between the treatments in any of the endpoints.

Summary of evidence on comparative safety

The most commonly reported adverse events, with an incidence ≥ 10%, during the pivotal study were headache, flushing, dyspepsia, back pain, diarrhoea and limb pain. Other less commonly reported events (≥3%-10%) and more frequent with sildenafil than placebo, included myalgia, cough, epistaxis, insomnia, pyrexia, influenza and visual disturbances.

Co-administration of sildenafil with nitric oxide donors or nitrates in any form is contra-indicated. Sildenafil is metabolised by the cytochrome P450 isoforms 3A4 and 2C9 and has the potential for interaction with drugs metabolised by these routes. Concurrent use with potent cytochrome P450 3A4 inhibitors is contra-indicated.

Oral sildenafil avoids the need for central venous access and the associated increased risk of infection, as is necessary with intravenous epoprostenol. It also appears to be free from the hepatotoxicity associated with bosentan.

Summary of clinical effectiveness issues

Common to treatments of rare conditions, the clinical trial data on sildenafil are limited. Epoprostenol is the only treatment to offer survival benefit. There are as yet no data on survival with sildenafil.

The treatment effect on 6MWD is similar in magnitude to that seen with bosentan (46 metres) and inhaled iloprost (36 metres) and exceeds that considered to be clinically relevant (40 metres). However, there are no comparative data assessing appropriate doses of these drugs with meaningful endpoints. The product licence restricts use to patients with functional class III disease. Only 58% of the study population were of functional class III, albeit that treatment effects were generally consistent across subgroups.

Since the study excluded patients who previously failed bosentan therapy, there are no data on sildenafil as a second-line agent.

The oral formulation of sildenafil offers an advantage in administration over iloprost and epoprostenol. Unlike the oral alternative, bosentan, it has not been associated with hepatotoxicity or potential teratogenicity.

Summary of comparative health economic evidence

The manufacturer populates a one year Markov model with transition probabilities derived from the sildenafil open-label extension trial, augmented with some expert opinion as to the likelihood of switching to second-line therapy among patients who deteriorate.This model is used to estimate the cost and impact of treatment with the first line therapies sildenafil and bosentan. Other than the addition of liver function tests for bosentan and an increase in dose for patients who deteriorate but remain on bosentan, the costs and clinical effectiveness of bosentan in terms of PAH and its progression are assumed to be identical to those of sildenafil.

The model results in the same estimate of the average annual quality of life for sildenafil and bosentan over the year modelling: 0.64 QALYs, with 94% of patients surviving to the end of the year.The only difference in clinical effectiveness within the modelling is a slight difference in adverse event rates for sildenafil and bosentan. These adverse events only affect costs, resulting in a minor cost increase of £16 for bosentan relative to sildenafil. There is no patient impact from this.

The only source of cost differences are the first line therapy drug costs coupled with the additional liver function testing costs for bosentan.

The modelling results in an annual cost for those initiating on sildenafil of £13,000 as against £26,000 for those initiating on bosentan: a net saving of £13,000. However, the clinical equivalence is assumed rather than demonstrated. It is not clear that patient benefits would be the same under both treatments and this may affect variables such as switching rates to second-line therapies. This in turn would affect relative costs.

The acquisition cost of sildenafil is less than bosentan. While it has not been demonstrated that downstream costs and patient impact are the same under both treatments this is an orphan indication with limited long term data.

Patient and public involvement

A Patient Interest Group submission was not provided.

Budget impact

With 21 of an estimated 107 eligible patients being initiated on sildenafil rather than bosentan, the manufacturer estimated that the gross annual cost of treatment is £2,190,000 for the 107 patients on either treatment. This compares with £2,460,000 were all 107 to be initiated on bosentan. A net annual saving of £270,000 is anticipated over the first five years following introduction of sildenafil.

Guidelines and protocols

European Guidelines on the diagnosis and treatment of pulmonary arterial hypertension recommend oral sildenafil as one of the treatment options for patients with NYHA class III disease. In patients with class III disease, the options include oral bosentan, inhaled iloprost, oral sildenafil and intravenous epoprostenol. Although epoprostenol tends to be used in patients refractory to bosentan, iloprost or sildenafil, some physicians still use it 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."

SMC has more recently also issued advice on inhaled iloprost (Ventavis®), November 2005. This stated that "it is accepted for restricted use within NHS Scotland for the treatment of patients with NYHA 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."

Sildenafil is also available in 25mg, 50mg and 100mg tablets as Viagra® for the treatment of erectile dysfunction.

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 December 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.

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