sildenafil, 20mg (as citrate) tablets (Revatio®) No. (596/10)
Pfizer Ltd

15 January 2010

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

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

This is an orphan indication for sildenafil with limited clinical evidence from post-hoc analysis of a short-term clinical trial.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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

Dosing information

20mg orally three times a day.

Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

Product availability date

29 May 2009

Sildenafil has been designated as an orphan medicinal product in this indication.

Summary of evidence on comparative efficacy

Pulmonary arterial hypertension (PAH) is a rare, progressive, and life-threatening disease. It is characterised by an increase in pulmonary vascular resistance leading to right ventricular failure and death.

Sildenafil is a phosphodiesterase type-5 (PDE5) inhibitor that blocks the degradation of cyclic guanosine monophosphate (cGMP) in the pulmonary vasculature and in patients with PAH this can lead to vasodilatation 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.

The licence in this indication was previously restricted to PAH classified as World Health Organisation functional class (FC) III. The subject of this submission is the extension of the licence to include patients with PAH classified as FC II.

The original submission for FC III patients was based on one pivotal randomised, double-blind, placebo-controlled study of 12 weeks' duration that was followed by a long-term open-label extension study. These studies recruited patients with PAH of any FC, and the submission for FC II patients is based on post-hoc sub-group analysis from the same two studies: New data are presented from a retrospective analysis of efficacy and safety outcomes from both studies by functional class in patients classified FC II and III that together represented 94% (261/278) of the randomised population of the 12-week study and 93% (64/69) of patients randomised to sildenafil at the licensed dose of 20mg three times daily. In addition the data from the long-term extension study are more mature than in the original submission.

The 12-week study enrolled 278 patients of whom 63% had primary (idiopathic) pulmonary hypertension, 30% PAH associated with connective tissue disease and 6% PAH following surgical repair of congenital heart lesions. Patients were randomised equally to receive sildenafil 20mg, 40mg or 80mg three times daily or placebo for 12 weeks, and 277 patients took at least one dose. Randomisation was stratified with respect to baseline walking distance, <325m or ≥325m, and cause of PAH. Study medication was added to the patients'

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 – baseline 6MWD was around 340metres.

At the licensed dose of 20mg three times a day in 69 evaluable patients, there was a statistically significant increase in the 6MWD compared with placebo for the pooled analysis (all classifications of FC) and for the FC II and FC III sub-groups (n=24 and n=40 respectively). Placebo-corrected increases were 45metres (95% CI: 20 to 70), 49metres (95% CI: 22 to 77) and 45metres (95% CI: 16 to 75) in the pooled FC group and the FC II and FC III sub-groups respectively. There was clinical improvement of at least one functional class in 28%, 17% and 30% of patients, respectively.

In the total study population, subgroup analysis indicated that results were generally consistent according to baseline walking distance, aetiology, functional class, gender, age and mean pulmonary artery pressure (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. Overall, sildenafil treated patients had statistically significant reductions in mean pulmonary artery pressure and pulmonary vascular resistance compared with placebo.

The open-label, uncontrolled extension phase was undertaken by 259 patients who completed the 12-week study. The dose was titrated between 20mg three times a day and 80mg three times daily according to clinical need. Three-year survival data were analysed according to baseline FC II or FC III in patients who had received sildenafil in the double-blind study. Of the 259 patients entering the extension study, 207 had been randomised to sildenafil in the first study. Survival was reported as 84% (95% CI 75% to 92%) in the FC II sub-group and 81% (95% CI 74% to 89%) for FC III. The percentage of patients with no change/improvement in functional class after three years of sildenafil treatment was 62% in patients classified as FC II at baseline and 59% in the FC III group.

Summary of evidence on comparative safety

In the 12-week pivotal study, the most commonly reported adverse events at the licensed dose of 20mg three times daily, with an incidence greater than placebo during the pivotal study, were headache, flushing, dyspepsia, back pain and dyspnoea. All were also more common than with placebo in patients with PAH classified as FC III and, with the exception of back pain, for FC II but there was no consistent pattern when comparing frequency between FC II and FC III.

No deaths and only two serious adverse events in the study were considered to be treatment-related. In the 20mg group one patient suffered a serious treatment-related adverse event (left ventricular dysfunction). Ocular testing at baseline and week 12 did not reveal any events considered as an issue for clinical concern.

There is a significant increase in flushing with sildenafil versus placebo, although this was only mild to moderate and transient.

Summary of clinical effectiveness issues

This is an orphan indication for sildenafil with limited clinical evidence from post-hoc analysis of a short-term clinical trial. This is common to treatments for rare conditions.

Compared with placebo, sildenafil does not show a statistically significant reduction in clinical worsening or Borg dyspnoea score at 12 weeks. Although three-year survival and safety data are available they come from an open-label extension study that exposed almost all patients to a higher than licensed dose of sildenafil.

At the licensed dose of 20mg three times daily, the placebo-adjusted increase in 6MWD in patients with PAH classified as FC II (49metres) is greater than seen for FC III or in a pooled analysis of all 20mg patients (both 45metres). However sub-group numbers in this post-hoc analysis are small. Pooled data for ambrisentan across the licensed doses 5mg to 10mg and across FC II and III show improvements in a similar range (45metres to 51metres). However, there are no direct comparative data assessing licensed doses of sildenafil with ambrisentan or other drugs licensed for PAH in terms of efficacy, safety or mortality.

There is no requirement for liver function monitoring before and during treatment with sildenafil as is required for endothelin receptor antagonists. However because of lack of data sildenafil is contra-indicated in severe hepatic failure and should not be used in pregnancy unless strictly necessary.

Co-administration of sildenafil with nitric oxide donors or nitrates in any form is contra-indicated. Sildenafil is principally metabolised by the cytochrome P450 isoforms 3A4 and 2C9 and has the potential for interaction with drugs metabolised by these routes. Combination with potent cytochrome P450 3A4 inhibitors is contra-indicated (refer to Summary of Product Characteristics (SPC)).

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis comparing sildenafil with ambrisentan for the treatment of adult FC II patients with pulmonary arterial hypertension (PAH) treated within a designated Scottish Pulmonary Vascular Unit (SPVU) setting over a year period. Ambrisentan was considered an appropriate comparator based on views of Scottish clinicians. In the absence of direct comparative clinical trial data, an indirect comparison was used with data on ambrisentan taken from pooled analysis of relevant clinical studies. Compared with evidence from the sildenafil trial, the submission stated that there was no difference in 6 minute walking distance, the primary outcome measure, for both treatments and therefore concluded that these agents appear to be as effective as each other in this patient group. The ambrisentan data included patients with FC III but the manufacturer assumed that ambrisentan would demonstrate the same clinical benefit in the FC II patient subgroup. Adverse events were assumed similar between treatments and thus were not included in the analysis. Costs included medicines used, general practitioner visits, hospital care (including two specialist visits per year, blood tests and monitoring costs), and costs of subsequent treatment prescribed when the disease progressed.

The submission stated that NHS costs per patient per year for sildenafil 20mg three times daily were £6,056 compared to £21,840 for ambrisentan 5mg, resulting in a cost saving of £15,784. Sensitivity analysis in the submission showed that varying the probability of deterioration in the sildenafil 20mg three times daily group from 9% (base case) to 36% and

switching patients to endothelin receptor antagonists reduced the cost saving by £6,220 to £9,564.

The main issue with the submission was the use of pooled data for ambrisentan for functional class II and III as a proxy for benefit in FC II patients only.

However, the data supplied on clinical benefits were judged adequate and hence the economic case for sildenafil use was accepted.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Consensus statement on the management of pulmonary hypertension in clinical practice in the UK (2008) provides an algorithm for treatment of idiopathic PAH (IPAH), familial PAH or anorexogen-associated PAH. Treatment options included either sildenafil or sitaxentan for the management of FC II PAH, and sildenafil is also listed as an option for patients with FC III PAH, though not as the preferred choice. A separate algorithm is given for PAH associated with connective tissue disease in which sildenafil is listed as one of three alternative options after bosentan (the preferred option) in patients with scleroderma.

The National Institute for Health and Clinical Excellence (NICE) has published a review of the clinical and cost effectiveness of five drug technologies for PAH (including sildenafil) that was completed in August 2007 and last updated in February 2008. It concluded that addition of all five technologies to supportive treatment had been shown to be more effective than supportive treatment alone, however current evidence does not allow adequate comparisons between the technologies nor for the use of combinations of the technologies.

Additional information: comparators

The endothelin receptor antagonists bosentan and ambrisentan are licensed for use in patients with PAH classified as FC II, though bosentan is not recommended by SMC in this indication. Other products licensed for treatment of PAH are included in the table below.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
sildenafil (Revatio)	**20mg orally three times daily**	**4,532**
epoprostenol (Flolan)	20 to 40 nanograms/kg/minute by continuous intravenous infusion*	91,000 to 136,500
iloprost (Ventavis)	2.5 to 5micrograms nebulised 6-9 times daily**	29,698 to 44,548
ambrisentan (Volibris)	5 to 10mg once daily	20,033
sitaxentan (Thelin)	100mg orally once daily	20,020
bosentan (Tracleer)	125mg orally twice daily (maintenance dose) ***	19,410

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 03 November 2009 or from Monthly Index of Medical Specialities November 2009

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

** One 10microgram ampoule is used per administration

*** Initial bosentan dose is 62.5mg for four weeks but 62.5mg and 125mg tablets are costed equally.

Additional information: budget impact

The manufacturer estimated that 35% of FC II patients receive sildenafil already with the remainder receiving ambrisentan. If it were assumed that all ambrisentan patients were switched to sildenafil 20mg three times per day the saving would be £331k in year one, rising to £474k by year 5. If half the sildenafil patients were on 20mg three times daily and half on 80mg three times daily (unlicensed dose) the savings would be smaller at £186k and £266k respectively.

The manufacturer estimated that 33 patients would be treated with sildenafil in year one rising to 47 by year five. However, expert opinion suggests patient numbers will be lower, especially in year 5, and hence the savings may be an overestimate.

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 ***04 December 2009.***

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.

Galie, N., Ghofrani, H., Torbicki, A. et al. Sildenafil Citrate Therapy for Pulmonary Arterial Hypertention. N Engl J Med, 2005. 353:20; 2148-57

European Medicines Agency. Assessment Report for Revatio 18 June 2009. EMEA/381319/2009

European Medicines Agency. Assessment Report for sildenafil (Revatio) EMEA/H/C/638/II/0021