AWMSG Secretariat Assessment Report – Advice no. 1910
Sildenafil citrate (Revatio®▼) for the treatment of pulmonary arterial hypertension in patients currently prescribed oral sildenafil citrate but temporarily unable to take oral medicine

1.0 PRODUCT DETAILS

Licensed indication	Sildenafil citrate (Revatio®▼) solution for injection is for the treatment of patients with pulmonary arterial hypertension who are currently prescribed oral sildenafil citrate and who are temporarily unable to take oral medicine, but are otherwise clinically and haemodynamically stable[1].
Dosing	Sildenafil citrate solution for injection should be administered to patients already prescribed oral sildenafil citrate as a replacement for oral administration under conditions where they are temporarily unable to take oral sildenafil citrate therapy[1]. Sildenafil citrate solution for injection is for intravenous (IV) use as a bolus injection. The recommended dose is 10 mg (corresponding to 12.5 ml) three times a day. A 10 mg dose of sildenafil citrate solution for injection is predicted to provide exposure of sildenafil, and its N-desmethyl metabolite, and pharmacological effects comparable to those of a 20 mg oral dose[1].
Marketing authorisation date	10 December 2009[2].
UK Launch date	15 September 2010[2].

2.0 DECISION CONTEXT

2.1 Background

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary arteries, characterised by vascular proliferation and remodelling, leading to increasing pulmonary arterial resistance, and ultimately, right ventricular failure[3]. No curative therapy currently exists for PAH; treatment therefore focuses on prolonging survival and improving quality of life[3]. Standard treatment according to European Society of Cardiology guidelines[4] is summarised in section 2.3.

Sildenafil is a phosphodiesterase-5 inhibitor licensed in tablet formulation for treatment of patients with PAH classified as World Health Organisation functional class II (WHO FC-II) and class III (WHO FC-III)[5]. However, PAH patients may become temporarily unable to take oral medication or unable to absorb medications enterally: examples of such clinical scenarios include perioperative periods, acute gastrointestinal disturbance, malabsorption due to complications of connective tissue disease, or sudden illness involving diarrhoea and vomiting. In these circumstances it may be disadvantageous to the patient to interrupt PAH treatment or initiate an alternative therapy that may not be well tolerated[6]. In December 2009 the licence for sildenafil was extended to include a solution for injection[1].

2.2 Comparators

- Iloprost (Ventavis®▼) nebuliser solution.
- Epoprostenol (Flolan®▼) solution for IV infusion.

The company are of the opinion that apart from IV sildenafil there is no existing licensed treatment option for patients with PAH who are prescribed oral sildenafil but are temporarily unable to take their oral medication[2]. The company assert that only IV sildenafil offers continuity of treatment in patients prescribed oral sildenafil, and that neither epoprostenol nor iloprost is licensed for use in patients with PAH functional class II, meaning these treatments could not in any case be used in a number of patients within the licensed indication for IV sildenafil[7].

2.3 Guidance and related advice

- The All Wales Medicines Strategy Group (AWMSG) appraisal recommendation for oral sildenafil (June 2010)[8]. Oral sildenafil is recommended as an option for use within NHS Wales for the treatment of PAH (WHO FC-II or FC-III) to improve exercise capacity. AWMSG recommends that use of oral sildenafil be restricted to a physician experienced in the treatment of PAH, in association with a National Commissioning Group-designated expert centre[8].
- European Society of Cardiology and European Respiratory Society Task Force Guidelines (2009)[4]. These guidelines for the diagnosis and treatment of pulmonary hypertension contain an evidence-based treatment algorithm. This recommends ambrisentan, bosentan and sildenafil as initial therapy for the treatment of PAH WHO FC-II and the mentioned medicines plus sitaxentan, intravenous epoprostenol and inhaled iloprost for initial therapy in the treatment of PAH WHO FC-III. As no head-to-head comparisons among different products are available, no evidence-based first line treatment can be proposed[4].
- The consensus statement on the management of PAH in clinical practice in the UK and Ireland (2008)[9].
- A commissioning policy document for Wales (Health Commission Wales, 2007) lists sildenafil as first line therapy in newly diagnosed PAH patients unless contraindicated[10].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The limited submission provided by the company provides no new evidence on the efficacy of sildenafil[7]. This is considered acceptable by the European Medicines Agency (EMA) in the extension application for IV sildenafil[6], on the basis that the efficacy of oral sildenafil has already been established, and there is therefore no need to demonstrate efficacy separately for the IV formulation, provided equivalent doses are given. However, the company submission[7] cites two studies as being of particular relevance to the IV formulation; these are discussed below.

3.1 Study A1481024[6]

This was a phase IIa study to assess the safety, efficacy and tolerability of IV sildenafil in patients with pulmonary hypertension. The primary study objective was to assess the effect of IV sildenafil on haemodynamic parameters in adults with pulmonary hypertension. Patients had either pulmonary venous hypertension due to congestive heart failure, hypoxic pulmonary hypertension or PAH. Only results from patients with PAH (n = 45) will be discussed here.

Following a baseline period, patients were dosed with a series of stepwise IV infusions of sildenafil, with the aim of maintaining predetermined plasma concentrations of sildenafil (10, 50, 100, 300 or 500 ng/ml); haemodynamic parameters were measured every ten minutes during dosing. The results suggest that a plasma sildenafil concentration of 100 ng/ml is sufficient for maximum reductions in pulmonary vascular resistance and pulmonary arterial pressure. Furthermore, pharmacokinetic studies with oral sildenafil indicate that mean maximum steady-state exposure following 20 mg oral sildenafil three times per day is 113 ng/ml. Targeting a plasma concentration of 100 ng/ml can therefore be considered clinically relevant.

3.2 Study A1481141[6]

Although this study was designed to compare clinical efficacy of oral sildenafil plus epoprostenol with placebo plus epoprostenol, a post-hoc analysis is presented to support the need for continued maintenance of oral therapy. This compared time to clinical worsening (defined as death, lung transplantation, hospitalisation related to the study disease, change in dose of epoprostenol or initiation of bosentan therapy) in the sildenafil and placebo groups over the first four weeks of treatment. This found a statistically significant increase in time to clinical worsening for the sildenafil group versus the placebo group.

4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

No new safety information was submitted as part of the limited company submission[7]. The EMA Variation Assessment Report for IV sildenafil highlights two studies as evidence on safety relating specifically to the IV formulation[6]. A1481262 was a single-centre, single-dose, open-label safety and pharmacokinetic study in which PAH patients (n = 10) received a 10 mg dose of sildenafil as IV bolus. Results for the PAH subgroup of study A1481024 (see section 3.1) were also included. In both studies the safety profile was comparable to that of oral sildenafil. However, the Committee for Medicinal Products for Human Use have highlighted that the number of patients studied is too limited to draw robust conclusions on safety[6]. The company will therefore undertake a targeted pharmacovigilance surveillance programme to continue gathering safety data[6].

5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- No new efficacy data on IV sildenafil was included in the limited submission by the company[7]. This is acceptable given that the efficacy of oral sildenafil has already been established, provided that equivalent doses are given[6]. In study A1481024, an IV infusion of sildenafil giving a plasma concentration of 100 ng/ml has been shown to be equivalent to oral sildenafil 20 mg in terms of plasma concentration. Additionally, in study A1481262 a small number (n =10) of patients previously on oral sildenafil 20 mg TID received 10 mg sildenafil as an IV bolus: concentration time curves for IV sildenafil fit well with those predicted based on population pharmacokinetic modelling[6].
- As outlined in section 2.2, expert opinion sought by the Welsh Medicines Partnership (WMP) during the preparation of this report suggests that iloprost nebuliser solution and IV epoprostenol solution for infusion are suitable comparators for IV sildenafil within its licensed indication. The company also highlight that both comparator treatments are licensed only for use in PAH WHO FC-III and not PAH WHO FC-II[7]. However, no attempt has been made to compare IV sildenafil with the comparators within the overlapping parts of their indications, that is, in PAH WHO FC-III patients. Nevertheless, only IV

sildenafil would allow for continuous treatment with a drug of the same class in patients prescribed, but temporarily unable to take, oral sildenafil[2,7].

- In addition to the post-hoc analysis of study A1481141 (see section 3.2), there is some additional clinical evidence suggesting that patient condition deteriorates as a result of interruption of sildenafil treatment. This includes one open-label[11] and one double-blind[12] study, both of which demonstrate clinical worsening in some patients following cessation of sildenafil treatment. However, patient numbers in these studies are low (total for both studies = 18) and include patients with classifications of pulmonary hypertension not limited to PAH. Therefore, whilst the available evidence suggests there is a clinical need for IV sildenafil treatment in patients unable to take their oral medication, it is unclear what proportion of patients would benefit and over what timescale.
- The available evidence on safety suggests that the safety profiles of IV and oral sildenafil are comparable[1,6]. However, safety data specific to the licensed dose of IV sildenafil (10 mg IV bolus) are very limited. This issue will be addressed by the planned pharmacovigilance[6].
- Sildenafil is not recommended for use in patients below 18 years of age, due to insufficient data on safety and efficacy[1].
- European Society of Cardiology guidelines highlight that in clinical practice, up-titration beyond 20 mg three times daily (often 40 mg to 80 mg three times daily) for oral sildenafil is needed quite frequently[4]. No data is available on IV sildenafil beyond the licensed 10 mg dose (equivalent to 20 mg oral sildenafil).

6.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

6.1 Cost effectiveness evidence

The abbreviated company submission[7] does not include any evidence on the cost-effectiveness of the use of IV sildenafil in patients with PAH who are currently prescribed oral sildenafil and who are temporarily unable to take oral medicine, but are otherwise clinically and haemodynamically stable.

6.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of IV sildenafil in this population.

7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

7.1 Budget impact evidence

7.1.1 Context and Methods

The company assumes that 100 patients are currently receiving treatment for PAH in Wales, based on a Health Commission Wales report published in 2007. The report estimates prevalence to be between 90 and 300 patients in Wales, and that less than 100 patients receive funded treatment via NHS Wales[10]. The same report highlighted that there is a lack of reliable epidemiological data for PAH.

Data on hospitalised patients who are temporarily unable to take oral PAH therapy is lacking. Therefore, estimates obtained from the Scottish Pulmonary Vascular Unit have been extrapolated to Wales, from which the company anticipates there will be fewer than 20 patients per year eligible for treatment with IV sildenafil. Given the uncertainty surrounding the number of patients eligible for treatment, a range of 20–50 patients per year has been considered; the company considers that this covers a worst-case scenario of up to 50% of all patients in Wales being admitted to hospital and all receiving IV sildenafil treatment.

The company has based its analysis on the assumption that all patients would receive 10 mg IV sildenafil three times daily. Treatment duration is assumed to be three days, reportedly based on company-sought expert opinion and market research (no further details provided). Other non-oral licensed PAH treatments are implicitly assumed not to be used in any patients. Eligible patient numbers are assumed to be constant throughout the next five years.

7.1.2 Results

Based on a cost of £407.52 per patient for a three day treatment period (£45.28 × 3 vials per day = £135.84 per day) the estimated annual budget impact is £8,150.40 to £20,376 per year for 20 to 50 patients.

7.1.3 WMP critique of the company's budget impact estimates

The budget impact estimates appear subject to uncertainty due to a lack of reliable epidemiological data in the target population. The basis of the assumed duration of IV sildenafil treatment is also uncertain and variation from this would impact on the estimated budget impact.

7.2 Comparative unit costs

IV sildenafil is licensed for use in WHO FC-II and FC-III PAH in patients who are currently prescribed oral sildenafil and who are temporarily unable to take oral medicine, but are otherwise clinically and haemodynamically stable[1]. Oral sildenafil is dosed at 20 mg three times daily (at a cost equivalent to £12.45 per day)[13], and IV sildenafil is dosed at 10 mg bolus injection three times daily, with each injection considered to be comparable to 20 mg of oral sildenafil[1]. Unit costs of IV sildenafil are discussed in section 7.1.2. Other non-oral PAH treatments have different licensed indications: inhaled iloprost is licensed for use only in class III PAH[14], and IV infused epoprostenol is licensed for use in patients with class III and IV PAH who do not respond adequately to conventional treatment[15]. Dosing of these drugs is tailored to the patient, which makes comparative costing difficult.

8.0 ADDITIONAL INFORMATION

8.1 Shared care arrangements

WMP is of the opinion that sildenafil is not suitable for shared care between primary and secondary care within NHS Wales. Sildenafil should only be initiated and monitored by a physician experienced in the treatment of PAH[1].

8.2 Product information

One 50 ml vial contains 40 mg of sildenafil (as citrate). The recommended dose of 10 mg requires a volume of 12.5 ml, to be administered as an intravenous bolus injection; for single use only. Each dose therefore requires a new vial.

Any unused product or waste material should be disposed of in accordance with local requirements.

This assessment report is based on evidence from a limited submission by Pfizer Worldwide Biopharmaceutical Businesses on 10 August 2010.

This report should be cited as:
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