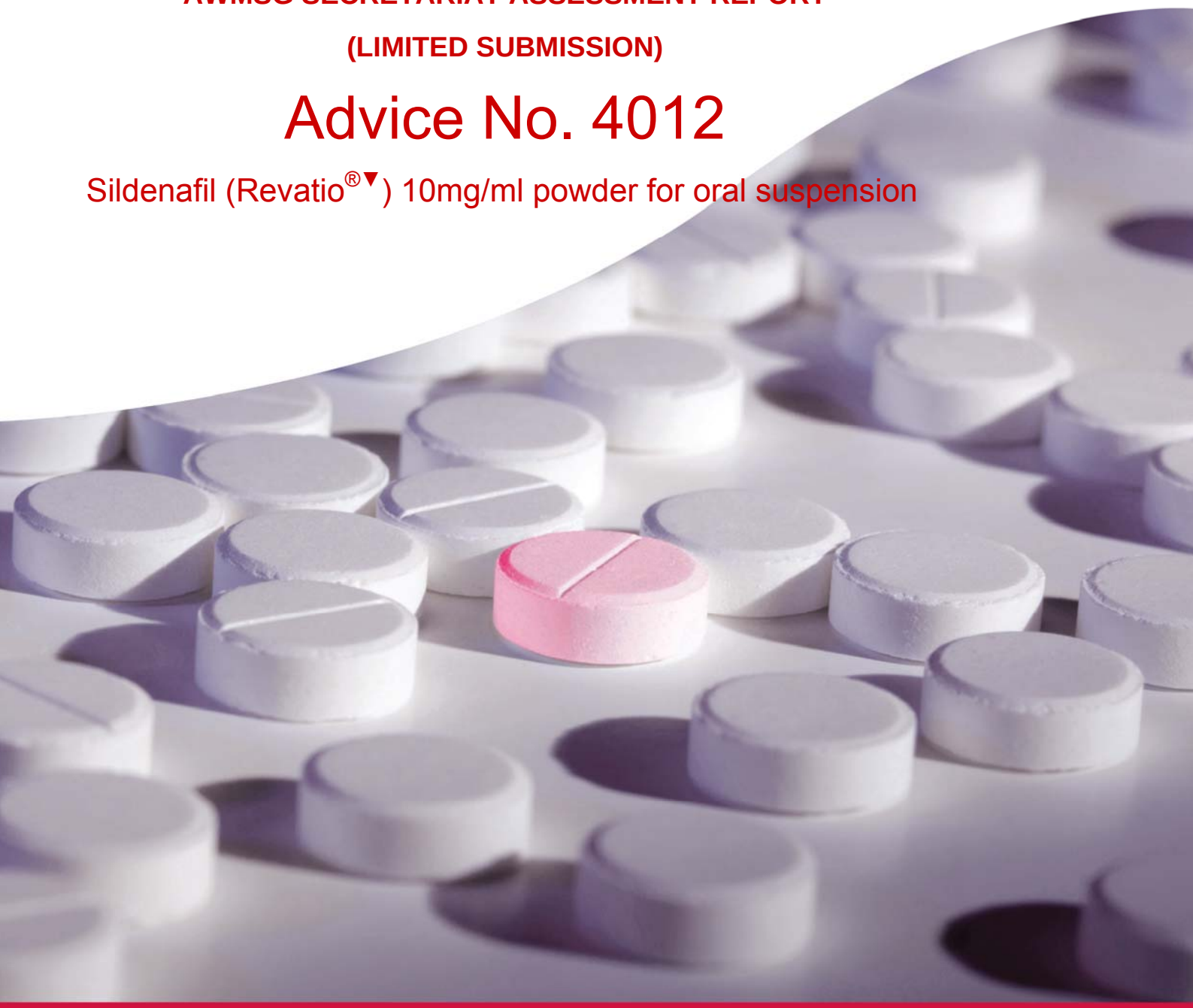
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 4012

Sildenafil (Revatio®▼) 10mg/ml powder for oral suspension



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 4012
Sildenafil (Revatio®▼) 10 mg/ml powder for oral suspension

This assessment report is based on evidence from a limited submission by Pfizer Ltd on 10 July 2012[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Sildenafil (Revatio®▼) powder for oral suspension for the treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease[2].
Marketing authorisation date	21 March 2012 (sildenafil 20 mg film-coated tablet originally licensed for treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity on 28 October 2005)[3,4].
Comparators	The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was sildenafil (Revatio®▼) tablets.
Limited submission details	Sildenafil (Revatio®▼) for the above indication met the following criteria for eligibility for a limited submission: • New formulation with a pro-rata or lower cost per treatment. • A minor licence extension. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Summary of evidence provided in submission

The company has provided a randomised, open label, three way crossover study A1481293 which compares the bioavailability of 2 ml of sildenafil 10 mg/ ml powder for oral solution (POS) with sildenafil administered as one 20 mg tablet and two 10 mg tablets in healthy adult subjects[5]. Sildenafil POS produced data for the pharmacokinetic endpoints area under the plasma concentration curve from time zero extrapolated to infinity (AUC_{inf}), area under the curve from time zero to last quantifiable concentration (AUC_{last}) and peak concentration (C_{max}), which was comparable to both the 20 mg tablet and the two 10 mg tablets, and was within accepted bioequivalence criteria. Based on evidence from this study, a marketing authorisation extension was granted for the use of sildenafil POS in the treatment of adult and paediatric patients with PAH[5].

In addition, the company provided evidence from a randomised, double-blind paediatric trial A1481131 of sildenafil tablets compared to placebo for children aged between 1 and 17 years (n = 234) with pulmonary arterial hypertension (PAH), together with evidence from an extension trial A1481156[1,6,7]. Patients were randomised to receive placebo or one of three sildenafil treatment groups

administered three times daily; low sildenafil dose (10 mg), medium dose (≥ 8 kg to 20 kg weight group: 10 mg dose; > 20 kg to 45 kg group: 20 mg dose; > 45 kg group: 40 mg), and high dose (≥ 8 kg to 20 kg group: 20 mg dose; > 20 kg to 45 kg group: 40 mg dose; > 45 kg group: 80 mg)[6,7]. It should be noted that the licensed dose for treatment of PAH in paediatric patients ≤ 20 kg is 10 mg and > 20 kg is 20 mg, both administered three times a day[2,8].

The primary endpoint was the percentage change in peak oxygen consumption (VO_2), normalised to body weight, as assessed by cardiopulmonary exercise testing (CPET) from baseline to week 16. . A borderline, non-significant increase in peak VO_2 of 7.7% (confidence interval: -0.19%, 15.6%; p = 0.056) was found for the sildenafil group compared to the placebo group[6]. Haemodynamic parameters demonstrated similar improvements in patients, including those aged less than seven years and patients analysed as part of the primary endpoint[7].
Clinical trials in paediatric patients with PAH treated with sildenafil tablets did not identify any new safety signals that had not been already identified in the adult PAH population[7]. However, the Committee for Medicinal Products for Human Use (CHMP) noted a trend in the clinical study A1481131 and the ongoing extension trial, A1481156 for higher mortality and increased rate of serious adverse events (SAEs) in patients who received the higher sildenafil dose compared with lower doses[7]. Barst et al concluded that deaths in the A1481156 trial were related to aetiology and baseline disease severity; most deaths were investigator-assessed as being associated with disease progression and none were considered to be causally related to study treatment[6].

2.2 Points to note

- For paediatric patients aged 1–17 years old, the recommended dose of sildenafil in patients ≤ 20 kg is 10 mg three times a day (1 ml of compounded suspension) and for patients > 20 kg is 20 mg (2 ml of compounded suspension or 1 tablet) three times a day. Higher than recommended doses should not be used in paediatric patients with PAH[2,8].
- At the time of licensing, CHMP concluded that sildenafil is associated with improvements in clinical endpoints that are relevant to the treatment of PAH, including exercise capacity, pulmonary haemodynamics and World Health Organisation (WHO) functional class[7].
- On reviewing the results from the clinical study A1481131 and the ongoing extension trial, A1481156, CHMP reported a trend for higher mortality and increased rate of SAEs and more patients with first events of clinical worsening with the higher sildenafil dose compared with lower doses; however, a direct causal relationship was not made in any of the cases. CHMP reported in the European Public Assessment Report (EPAR) that the data should be interpreted cautiously considering the uncontrolled nature of the long-term extension study, and the possible confounding by disease severity. After clinical review of the causes of death they found no biologically plausible explanation for the observed imbalance of deaths related to sildenafil dose[7]. CHMP also stated that the overall long-term data do not suggest that the higher sildenafil doses provide a significant benefit over lower doses and as a precautionary measure the high sildenafil dose was not recommended[7,8]. CHMP considered that most of the SAEs were not treatment-related and a review of the published literature and post marketing information for sildenafil did not identify any additional safety risks for paediatric patients[7].

- Subsequent to the company submission, the Food and Drugs Administration (FDA) issued a drug safety communication recommending that sildenafil should not be prescribed to children (aged between 1 and 17 years) for the treatment of PAH[9]. The recommendation was based on results from the A1481131 and A1481156 trials, from which the FDA concluded that children taking a high dose of sildenafil had a higher risk of death than children taking a low dose and that the low doses of sildenafil were not effective in improving exercise ability. Most deaths were caused by pulmonary hypertension and heart failure, which are the most common causes of death in children with PAH[9].
- AWTTC contacted the Medicines and Healthcare products Regulatory Agency (MHRA) to determine their views on the FDA safety alert. In response, MHRA drew attention to the analysis undertaken by CHMP[7] and a letter circulated by Pfizer Ltd in September 2011[10]. This communication to healthcare professionals drew attention to the higher mortality rate associated with the high sildenafil dose in the paediatric clinical trials and the potential dose response relationship and stressed that doses of sildenafil higher than those recommended in the SPC should not be used[10]. Further, MHRA stressed that product information for prescribers and patients had been updated accordingly.
- In June 2010, All Wales Medicines Strategy Group (AWMSG) recommended the use of sildenafil tablets for the treatment of PAH (WHO functional class II or III) to improve exercise capacity in adults[11].
- An extemporaneously prepared suspension from sildenafil tablets, was licensed under exceptional circumstances for use in the interim period until the POS formulation was available[7,8]. However, sildenafil 10 mg/ml POS offers a more convenient formulation for paediatric patients than the extemporaneous suspension which has to be prepared by a pharmacist, has a 28-day shelf life and has to be stored in the fridge[8].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

Based on the National Audit of Pulmonary Hypertension, 2011, the company notes that 376 children attended the designated pulmonary hypertension centre at Great Ormond Street Hospital for Children in 2011[12]. Four percent of these are assumed to be Welsh patients, equivalent to 15 children aged 1–17 years with PAH in Wales[1]. Commercial in confidence information removed.

3.2 AWTTC critique of the budget impact analysis

Commercial in confidence information removed.

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

AWTTC is of the opinion that if approved, sildenafil (Revatio®▼) powder for oral suspension is appropriate for specialist only prescribing within NHS Wales for the above indication.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 26 July 2012

Date range of evidence search: No date limits were applied to database searches.

REFERENCES

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http://www.ic.nhs.uk/webfiles/Services/NCASP/audits%20and%20reports/NHS_IC_Pulmonary_Hypertension_Audit_V1.0.pdf. Accessed Jul 2012.