

PUBLIC SUMMARY DOCUMENT

Product: Sildenafil Citrate, tablet, 20 mg, Revatio®

Sponsor: Pfizer Australia Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) listing for the treatment of adult patients with primary pulmonary hypertension or pulmonary hypertension associated with connective tissue disease (CTD), including scleroderma in patients categorised as WHO (World Health Organisation) functional Class III.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This drug had not previously been considered by the PBAC for this indication.

3. Registration Status

Sildenafil (Revatio) is registered to treat patients with pulmonary arterial hypertension (PAH) classified as WHO functional classes II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. The efficacy of sildenafil has not been evaluated in patients currently on bosentan therapy.

Sildenafil (Viagra) is registered for the treatment of erectile dysfunction in adult males.

4. Listing Requested and PBAC's View

Section 100 (HIGHLY SPECIALISED DRUGS PROGRAM)

Public and private hospital authority required

The requested Section 100 restriction for sildenafil was for the treatment of Class III disease and was consistent with that of other PBS-subsidised PAH specific therapies ie bosentan, iloprost and epoprostenol.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Primary, or unexplained, pulmonary arterial hypertension (PAH) is a rare lung disorder which is characterized by sustained elevations of pulmonary artery pressure without a demonstrable cause.

Sildenafil will provide clinicians with an alternative treatment for all currently used agents in PAH class III patients.

6. Comparator

The submission nominated bosentan monohydrate as the comparator. The PBAC accepted this as appropriate.

7. Clinical Trials

The submission presented three pivotal randomised, double-blind, multi-centre, parallel group trials, one of sildenafil and two of bosentan, to provide an indirect comparison of sildenafil to bosentan using placebo as the common comparator. The comparison was made via an indirect meta-analysis of the primary outcome measure, the six minute walking test (6MWT). Only TGA approved dosage arms (sildenafil, 20 mg tds; bosentan, 62.5 mg for 4 weeks then 125 mg maintenance dose) were included in the primary indirect comparison.

These studies had been published at the time of submission, as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Sildenafil versus placebo		
SUPER-1: Trial A1481140 Galiè N et al (2005)	Sildenafil citrate therapy for pulmonary arterial hypertension.	New England Journal of Medicine, 353(20): 2148-2157
Bosentan versus placebo		
BREATHE-1: Bosentan Randomized trial of Endothelin Antagonist Therapy Rubin L et al (2002)	Bosentan therapy for pulmonary arterial hypertension.	New England Journal of Medicine, 346(12): 896-903
Study 351 Channick R et al (2001)	Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study.	Lancet, 358(9288): 1119-23
Supplementary trial: Sildenafil vs bosentan^a		
SERAPH: Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension Wilkins M et al (2005)	Sildenafil versus Endothelin Receptor antagonist for Pulmonary Hypertension (SERAPH) study.	American Journal of Respiratory and Critical Care Medicine, 171(11): 1292-1297

a: Not included as primary evidence because the sildenafil daily dose (50 mg tds) was higher than the TGA-approved daily dose.

8. Results of Trials

The results of the key comparative randomised trials showed that the distances walked in 6 minutes for placebo were similar across the sildenafil versus placebo and the bosentan versus placebo trials. Both sildenafil and bosentan resulted in a statistically significant increase in distance walked in six minutes compared to placebo. However, there was no statistically significant difference in the distance walked in 6 minutes between sildenafil and bosentan.

The incidence of adverse events in the sildenafil and bosentan trials was comparable.

9. Clinical Claim

The submission claimed that sildenafil was no worse than bosentan in terms of effectiveness and toxicity.

The PBAC agreed with the submission's claim on the basis of the data presented.

10. Economic Analysis

The submission presented a preliminary economic evaluation using a cost-minimisation approach. The resources included were drug costs, sildenafil and bosentan, and patient monitoring.

Equi-effective doses in the context of cost-minimisation were sildenafil 20 mg tds and bosentan 62.5 mg twice daily for 4 weeks then 125 mg twice daily as the maintenance dose. This was based on the doses used in short term trials and is consistent with TGA approved regimens.

The submission did not present an incremental cost effectiveness ratio but rather a series of cost effectiveness ratios for the two drugs. The incremental cost per metre gained in the 6 minute walk test was < \$15,000.

A modelled economic evaluation was not presented.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 5 of listing the likely number of patients treated would be < 10,000 and the financial savings to the PBS would be < \$10 million.

12. Recommendation and Reasons

The PBAC recommended listing on a cost minimisation basis with bosentan for the treatment of primary pulmonary hypertension or pulmonary hypertension associated with connective tissue disease in patients categorised as WHO functional class III, at the price proposed in the submission.

The PBAC agreed that on the basis of the data presented, sildenafil is no worse than bosentan in terms of effectiveness and has similar toxicity. The equi-effective doses are sildenafil 20 mg three times daily and bosentan 62.5 mg twice daily for 4 weeks followed by a maintenance dose of 125 mg twice daily.

The PBAC recommended that the PBS restriction be the same as that for bosentan, taking into account the differences in the TGA approved indications and dosage recommendations of the two agents. As sildenafil has a relatively rapid onset of action, the sponsor originally proposed that the duration of initial PBS-subsidised treatment with sildenafil be limited to 3 months as opposed to 6 months for bosentan, and that patients be assessed for response to treatment prior to the completion of this initial course of therapy. The PBAC had no objection to this proposal. However, following the PBAC meeting, in light of the additional burden of management that this restriction would require from clinicians, patients and Medicare Australia, the sponsor indicated that it had re-considered its position and agreed that the initial treatment period should be six months as for bosentan.

The PBAC further agreed that patients accessing sildenafil for pulmonary hypertension through the Special Access Scheme (SAS) at 1 November 2006 should be eligible to be grandfathered onto PBS-subsidised therapy.

The PBAC recommended that the restriction specify that no increased maximum quantities or repeats will be authorised consistent with the TGA approved maximum dosage and recommended the 20 day safety net rule should not apply.

Recommendation

The PBS listing restriction can be found in the Schedule of Pharmaceutical Benefits at www.pbs.gov.au.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The Sponsor welcomes the PBAC's recommendation for the listing of sildenafil (Revatio) on the PBS as it provides the specialist clinicians treating this comparatively rare and debilitating condition with an alternative therapy that acts on one of the three pathophysiological pathways associated with PAH that is not targeted by the other currently listed PAH therapies.