PUBLIC SUMMARY DOCUMENT

Product: Fluticasone propionate with salmeterol xinafoate, oral pressurised inhalation 250 micrograms-25 micrograms (base) per dose (120) doses, CFC-free formulation, powder for oral inhalation in breath actuated device 500 micrograms- 50 micrograms (base) per dose(60), Seretide MDI 250/25®, Seretide Accuhaler 500/50®

Sponsor: GlaxoSmithKline Australia Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

To extend the restricted benefit listing of the highest strengths of Seretide MDI and Accuhaler to include the long-term maintenance treatment of chronic obstructive pulmonary disease (COPD) in patients with a history of repeated exacerbations.

2. Background

Seretide was first considered by the PBAC in March 2000. The PBAC recommended the listing of Seretide at its March 2000 meeting as a Restricted Benefit for patients who previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids and who are stabilised on concomitant inhaled salmeterol xinafoate and fluticasone propionate.

3. Registration Status

Seretide (for COPD) is registered by the TGA for the symptomatic treatment of patients with severe COPD (FEV1<50% predicted normal) and a history of repeated exacerbations who have significant symptoms despite regular beta-2 agonist bronchodilator therapy. Seretide is not indicated for the initiation of bronchodilator therapy in COPD.

4. Listing Requested and PBAC's View

Restricted benefit
For the long-term maintenance treatment of chronic obstructive pulmonary disease in patients who have a history of repeated exacerbations.

See Recommendation and Reasons for the PBAC's view

5. Clinical Place for the Proposed Therapy

Seretide will provide an alternative therapy to tiotropium for patients with chronic obstructive pulmonary disease with a history of repeated exacerbations.

6. Comparator

The submission nominated tiotropium bromide monohydrate as the main comparator, which was considered appropriate by the PBAC.

7. Clinical Trials

The submission provided one key randomised trial comparing Seretide (fluticasone 500 mcg with salmeterol 50 mcg twice daily) with tiotropium 18 mcg once daily in patients with COPD over 104 weeks. Two supportive trials comparing the same drugs in a similar population over 12 weeks and 3 weeks respectively were also provided.

None of the trials were published at the time of the submission.

8. Results of Trials

There was no statistically significant difference in the rate of health care utilisation exacerbations, the primary outcome of the trial, between treatments. All-cause mortality, one of the safety outcomes in the trial, had been relied on in the economic evaluations.

There were more death events in the tiotropium group than in the Seretide group. The majority of the fatalities were associated with cardiac disorders, with a greater percentage occurring in the tiotropium group compared with the Seretide group.

The PBAC noted there was a small possibility that over this short time period, potentially improved management of COPD with Seretide may have impacted on the general health of these patients (both Seretide and tiotropium provide symptom control, although do not affect the COPD disease process), resulting in a lower all-cause mortality rate.

The PBAC considered that there was no plausible biological mechanism to support such a difference. Further, the all cause mortality data could be considered an unexpected finding because the trial had not predefined the hypothesis that Seretide has a role in the prevention of mortality in patients with COPD.

9. Clinical Claim

The submission claimed that Seretide is more effective than tiotropium bromide monohydrate with similar toxicity.

See Recommendations and Reasons for PBAC's view.

10. Economic Analysis

A preliminary economic evaluation was presented. The choice of the cost-effectiveness approach was not considered valid as the PBAC did not accept the clinical claim of superior effectiveness. The resources included in the evaluation were the costs of study drugs, concomitant medications, and COPD-related health care resources other than medications.

The trial-based incremental discounted cost per extra discounted life-year gained was less than $15,000.

The trial-based incremental discounted cost per extra discounted responder gained was also less than $15,000.

A modelled economic evaluation was presented adopting a cost-utility approach. As in the preliminary economic evaluation, the total resources consumed and the outcomes observed within the trial period of two years are used in the economic evaluation. The only difference from the preliminary economic evaluation was that utility weights have been generated by mapping scores from the St George's Respiratory Questionnaire to EQ5D values, using Ordinary Least Squares Regression. The PBAC noted that as COPD is a chronic condition that needs long-term treatment, the costs and effectiveness observed within two years may not be adequate to predict the long-term cost-effectiveness.

The base case modelled incremental discounted cost per extra discounted quality-adjusted life-year was less than $15,000.

11. Estimated PBS Usage and Financial Implications

The net financial cost per year to the PBS (after off-sets in the use of substituted drugs) was estimated to be less than $10 million.

12. Recommendation and Reasons

The PBAC recommended a restricted benefit listing on a cost-minimisation basis with the equi-effective doses being fluticasone 500 mcg/salmeterol 50 mcg inhaled twice daily being equivalent to tiotropium bromide monohydrate 18 mcg inhaled once daily in the treatment of COPD. The recommended restriction reflects the wording of the TGA registered indication.

The PBAC did not accept the claim that fluticasone propionate with salmeterol xinafoate had significant advantages in terms of clinical effectiveness and toxicity over tiotropium. The PBAC considered that the all-cause mortality data could be considered an unexpected finding because this was a positive secondary outcome when the primary outcome analysis showed no statistically significant difference between treatment groups and the trial had not predefined the hypothesis that Seretide has a role in the prevention of deaths in patients with COPD. Therefore, its use as the foundation of an economic claim was not appropriate.

In the Pre-PBAC response, the sponsor advised it would be willing to accept a therapeutic relativity of no difference in effectiveness and safety between Seretide and tiotropium, based on the results of the trial 40036.

Recommendation
FLUTICASONE PROPIONATE with SALMETEROL XINAFOATE, oral pressurised inhalation 250 micrograms-25 micrograms (base) per dose (120) doses, CFC-free formulation, powder for oral inhalation in breath actuated device 500 micrograms- 50 micrograms (base) per dose(60)

Add the following to the current listings:

> Restricted benefit
> Symptomatic treatment of chronic obstructive pulmonary disease (COPD) where, the FEV1 is <50% predicted normal, and there is a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy.

NOTE:
Seretide is not indicated for the initiation of bronchodilator therapy in COPD.

Maximum Quantity: 1
Repeats: 5

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 chose not to make a comment.