PUBLIC SUMMARY DOCUMENT

Product: Budesonide with Eformoterol Fumarate Dihydrate, powder for oral inhalation in breath actuated device, 100 micrograms-6 micrograms per dose, 200 micrograms-6 micrograms per dose Symbicort Turbuhaler®

Sponsor: AstraZeneca Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

To extend the current Restricted Benefit listing to include initiation of single maintenance and reliever therapy in patients who experience asthma symptoms while receiving treatment with inhaled or oral corticosteroids and in patients who experience asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid and a long acting beta-2 agonist.

2. Background

The PBAC has not previously considered an application to extend the listing to include single maintenance and reliever therapy.

3. Registration Status

Symbicort Turbuhalers 100/6 and 200/6 are registered by the TGA for the treatment of asthma where use of a combination (inhaled corticosteroid and long acting beta-agonist) is appropriate. This includes: patients who are symptomatic on inhaled corticosteroid therapy; patients who are established on regular long acting beta-agonist and inhaled corticosteroid therapy.

There are two alternative treatment regimens:

- Symbicort maintenance and reliever therapy, which was approved by the TGA in July 2006;
- Symbicort maintenance therapy.

Symbicort Turbuhaler 400/12 strength is not registered for the Symbicort maintenance and reliever therapy treatment regimen and should only be used in patients aged 18 years and older.

4. Listing Requested and PBAC's View

The requested listing comprised the addition of the following wording to the existing PBS listing :

Restricted benefit
For initiation of single maintenance and reliever therapy in patients who experience asthma symptoms while receiving treatment with inhaled corticosteroids;

For initiation of single maintenance and reliever therapy in patients who experience asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid and a long acting beta-2 agonist.

The sponsor requested the listing of additional two-inhaler presentations for both strengths for initiation of therapy.

The sponsor subsequently requested that patients who experience symptoms while receiving treatment oral corticosteroids also be included.

5. Clinical Place for the Proposed Therapy

The new restriction would allow use of a single maintenance and reliever therapy regimen for adults and adolescents (aged 12 years and older) who experience asthma symptoms while receiving treatment with oral or inhaled corticosteroids and in patients who experience asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid and a long acting beta-2 agonist.

6. Comparator

The submission nominated the fixed combination of fluticasone and salmeterol (Seretide®) plus as needed short acting beta agonist as the appropriate comparator.

7. Clinical Trials

The basis of the submission was 3 head-to-head randomised comparative trials comparing Symbicort as both maintenance and reliever asthma therapy with the main comparator, Seretide plus a short acting beta agonist for as-needed relief. The submission also included two additional head-to-head randomised comparative trials comparing Symbicort as both maintenance and reliever asthma therapy with Symbicort as maintenance therapy plus a short acting beta agonist for as-needed relief.

The trials published at the time of the submission were as follows:

Trial/First author	Protocol title/Publication title	Publication citation
COSMOS Vogelmeier, C (2005)	Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option?	*European Respiratory Journal* 2005; 26(5):819-28
STAY/O'Byrne (2005)	Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma.	*Am J Resp Crit Care Med* 2005; 171:129-37.
SMILE/Rabe, K.F (2006)	Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study.	Lancet 2006; 368: 744-53

8. Results of Trials

Symbicort maintenance and reliever therapy demonstrated superiority over Seretide plus a short acting beta agonist in the time to first severe asthma exacerbation in all the key trials except for one as yet unpublished randomised trial where there was no significant difference between the highest doses of Seretide and Symbicort maintenance and reliever therapy.

Symbicort maintenance and reliever regimen also demonstrated superiority in reducing the total number of asthma exacerbations, time to hospitalisation and oral steroid use compared to Seretide plus a short acting beta agonist.

The results of the analysis of the primary outcome measure in the key trials are summarised in the table below.

Analysis of the primary outcome-time to the first severe asthma exacerbation[a] in the key head-to-head trials.

Study (Treatment groups compared) (ITT)	Treatment doses compared	Hazard Ratio	95% Confidence interval	p-value
COMPASS 735 (N=3335) **SymMR *vs.* Ser+T**	Symbicort® 200/6 mcg/inhalation twice daily plus as-needed (SymMR) vs. two inhalations of Seretide® 25/125 mcg/ inhalation twice daily plus short acting ß$_2$ agonist (terbutaline 0.4 mg/ inhalation) as-needed, (Ser+T)	**0.67**	**(0.52,0.87)**	**0.003**
SymMR *vs.* Sym+T	Symbicort® 200/6 mcg/inhalation twice daily plus as-needed (SymMR) vs. Symbicort® 400/12 mcg/inhalation twice daily plus short acting ß$_2$ agonist (terbutaline 0.4 mg/ inhalation) as needed(Sym+T)	**0.74**	**(0.56,0.96)**	**0.023**
COSMOS 691 (N=2143) **SymMR *vs.* Ser+S**	Symbicort® 200/6 mcg/inhalation, twice daily plus as-needed vs. Seretide® Diskus® 50/100, 50/250 or 50/500 mcg) as maintenance plus short acting ß$_2$ agonist (salbutamol 0.4 mg/ inhalation) as-needed	**0.75[b]**	**(0.61,0.93)**	**0.0076**

[a] time to first severe exacerbation defined as at least one of the following: an oral glucocorticosteroid treatment due to asthma for ≥3 days and/or judged by the investigator and hospitalisation/emergency room treatment due to asthma. The COSMOS comparative trial is the only key trial that included an 'unscheduled visit' initiated by the patient in the definition of severe exacerbation; analysis conducted using Cox Proportional Hazards Model;
[b] hazard ratio excluding unscheduled visit criteria is 0.77 with a 95% CI (0.60, 0.93);
SymMR = Symbicort® maintenance and reliever therapy; Ser+T = Seretide® + terbutaline (short acting ß$_2$ agonist) as needed; Ser+S = Seretide ®+ salbutamol (short acting ß$_2$ agonist) as needed (Seretide® Diskus 50/100, 50/250 or 50/500mcg).

9. Clinical Claim

Symbicort, as maintenance and reliever, is more effective than and has a similar toxicity to
1) Seretide plus a short acting beta agonist and
2) Symbicort as a maintenance regimen plus a short acting beta agonist for as-needed relief.

10. Economic Analysis

Multiple preliminary economic evaluations, which were essentially cost-analysis in nature, were presented. The only resources included were drug costs.

Dominance (i.e. clinical advantages at a lower cost) was claimed in the trial-based cost analysis, but no information was presented about any confidence region on the incremental cost-effectiveness plane.

A modelled economic evaluation was not presented.

11. Estimated PBS Usage and Financial Implications

The sponsor estimated that the likely number of patients per year was between 50,000 to 100,000 in Year 5. The submission estimated that the net cost to the PBS to extend the listing to include single maintenance and reliever therapy would be $10 to 30 million per year.

However, the submission claimed that due to cost offsets associated with substitution of other fixed dose combinations and reduction in use of short-acting beta2 agonists there would be savings to the PBS. The PBAC noted advice that the overall market is expected to grow or to grow more rapidly as a result of listing Symbicort for maintenance and reliever therapy due to the promotional benefits of listing and the broader (more convenient) prescribing restrictions.

12. Recommendation and Reasons

The PBAC noted that the 'maintenance and reliever' approach using a combination of budesonide and eformoterol offers clinical advantages over the comparators, in regard to most of the outcome measures of the trials presented in the submission, at a potentially lower cost and at a reduced oral corticosteroid usage and lower inhaled corticosteroid burden.

The PBAC also noted that the National Asthma Campaign Handbook (2006) lists budesonide and eformoterol maintenance and reliever as an alternative in moderate to severe patients suitable for combination treatment. The sponsor requested that patients who experience symptoms while receiving treatment with oral corticosteroids also be included. The PBAC considered this to be reasonable.

The PBAC recommended amending the current listing as a restricted benefit to include single maintenance and reliever therapy in patients who had frequent asthma symptoms while taking oral or inhaled corticosteroids. The PBAC considered that it would be essential for the National Prescribing Service (NPS) to develop a RADAR document on this recommendation to ensure that the maintenance and reliever approach is not assumed to be suitable with any corticosteroid/long acting beta agonist combination or for the 400/12 budesonide-eformoterol strength.

The PBAC recommended that the Drug Utilisation Sub-Committee (DUSC) monitor usage based on concerns around the cost offsets associated with an anticipated decrease in the use of other reliever medications. The PBAC recommended a maximum quantity of one inhaler, as two inhalers as requested by the sponsor was not considered to be warranted for this more expensive reliever medication.

Recommendation

BUDESONIDE with EFORMOTEROL FUMARATE DIHYDRATE, powder for oral inhalation in breath actuated device, 100 micrograms-6 micrograms per dose, 200 micrograms-6 micrograms per dose.

Add to the current restriction for Symbicort 100/6 and 200/6 to read:

Restriction: Restricted benefit

For single maintenance and reliever therapy in a patient who experiences frequent asthma symptoms while receiving treatment with oral corticosteroids;

For single maintenance and reliever therapy in a patient who experiences frequent asthma symptoms while receiving treatment with inhaled corticosteroids;

For maintenance and reliever therapy in a patient who experiences frequent asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid and a long acting beta-2 –agonist.

Maximum Quantity: ‡1 (under all scenarios)
Repeats: 5 (under all scenarios)

BUDESONIDE with EFORMOTEROL FUMARATE DIHYDRATE, powder for oral inhalation in breath actuated device, 400 micrograms-12 micrograms per dose

Consequential to the recommendation to extend the current listings for Symbicort 100/6 and 200/6, the PBAC recommended that a NOTE precluding use of the 400/12 strength as 'maintenance and reliever' therapy be added to the current restriction.

Recommendation

Add to the current restriction for Symbicort 400/12 to read **:**

NOTE: Symbicort 400/12 is not recommended nor PBS-subsidised for use as 'maintenance and reliever' therapy.

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

AstraZeneca Australia welcomes the PBAC recommendation that Symbicort single maintenance and reliever therapy be listed on the PBS.