Public Summary Document

Product: Budesonide with eformoterol fumarate dihydrate, oral pressurised inhalation, 50 micrograms – 3 micrograms per dose, 100 micrograms – 3 micrograms per dose, 200 micrograms – 6 micrograms per dose, Symbicort Rapihaler®
Sponsor: AstraZeneca Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The re-submission requested Pharmaceutical Benefits Scheme (PBS) listing for the same asthma and chronic obstructive pulmonary disease (COPD) PBS indications as Symbicort Turbuhaler® dry powder inhaler (DPI).

2. Background

This was the fourth consideration by the PBAC and the first major submission for Symbicort® metered dose inhaler (MDI). Minor submissions were considered at the November 2010, November 2011 and November 2012 meetings.

3. Registration Status

Budesonide with eformoterol (50 microgram – 3 microgram) was first TGA registered on 20 April 2011. Budesonide with eformoterol (100 microgram – 3 microgram) was first TGA registered on 26 July 2012. Budesonide with Eformoterol (200 microgram – 6 microgram) was first TGA registered on 22 February 2006.

The TGA registered indications are::

- The treatment of asthma where use of a combination (inhaled corticosteroid and long-acting beta2-agonist) is appropriate in adults and adolescents. This includes:
    - patients who are symptomatic on inhaled corticosteroid therapy;
    - patients who are established on regular long-acting beta2-agonist and inhaled corticosteroid therapy.
- There are two alternative treatment regimens:
    - Symbicort maintenance therapy;
    - Symbicort maintenance and reliever therapy; (Symbicort Rapihaler 50/3 and Symbicort Rapihaler 100/3 only)

- The symptomatic treatment of moderate to severe COPD (FEV1 < or = 50% predicted normal) in adults with frequent symptoms despite long-acting bronchodilator use, and/or a history of recurrent exacerbations. Symbicort is not indicated for the initiation of bronchodilator therapy in COPD. (Symbicort Rapihaler 200/6 only)

4. Listing Requested and PBAC's View

A Restricted benefit listing was requested for the treatment of asthma (for both asthma maintenance and SMART regimen) and COPD, consistent with the current PBS listing for Symbicort Turbuhaler DPI.

The PBAC noted that the requested restriction was consistent with that for other currently PBS-listed asthma maintenance fixed dose combination corticosteroid (ICS) with long acting

beta agonist (LABA) products, in that those patients are required to be stabilised on concomitant inhaled budesonide and eformoterol before moving to the fixed dose combination.

The PBAC also noted that the National Asthma Council of Australia (NAC) had advised that its Guidelines Committee is currently revising the Asthma Management Handbook, the national treatment guidelines for asthma. It will be renamed the Australian Asthma Handbook when launched as the seventh edition due in November 2013. The NAC further advised PBAC that it believes it is no longer necessary for patients to be stabilised on separate LABA and ICS inhalers before commencing combination therapy. The NAC indicated that there are questions about the safety of the use of LABA without ICS and that there is increased risk of this happening when two separate inhalers are prescribed.

The PBAC also noted similar advice from The Thoracic Society of Australia and New Zealand (TSANZ) and Dr Helen Reddel (as Chair of the Science Committee for the Global Initiative for Asthma) with regard to the current restriction requirement for patients to be stabilised on separate LABA and ICS inhalers before commencing the combination.

The PBAC indicated its intention to review the PBS restrictions for all fixed dose combination ICS with LABA medicines with a view to aligning these restrictions with the new NAC treatment guidelines.

5. Clinical Place for the Proposed Therapy

The submission proposed that Symbicort® MDI would provide an alternative fixed dose combination device option for clinicians and patients for the treatment of asthma, including as SMART, and for the treatment of COPD. However, the PBAC noted that the proliferation of FDC options, indications, restrictions, doses, device types and colours had the potential to increase confusion in the use of these products, to the detriment of appropriate use of medicines.

6. Comparator

The re-submission nominated budesonide/eformoterol fixed dose combination DPI as the main comparator. The re-submission also stated that it is anticipated that the majority of substitution for Symbicort® MDI will be from Seretide® MDI because of the very strong tendency for people to utilise asthma and COPD treatments by device (i.e. patients exclusively use MDI or DPI devices).

The PBAC considered the nominated comparators were appropriate. The Committee agreed that there is patient preference for using either the MDI or DPI device options.

7. Clinical Trials

The re-submission was based on:

- Two head-to-head randomised trials comparing Symbicort® MDI to Symbicort® DPI in patients with asthma where treatment was used as maintenance therapy (Trial 003, Trial 681).
- One randomised trial comparing Symbicort® MDI and Seretide® DPI in patients with asthma where treatment was used as maintenance therapy (Busse 2008).

- Two supportive head-to-head randomised trials comparing Symbicort® MDI to Symbicort® DPI in patients with asthma where treatment was used as maintenance therapy (Trial 715, Trial 682).

The re-submission presented in vivo therapeutic equivalence evidence for two of the budesonide/eformoterol MDI presentations and for one of the three indications requested (asthma maintenance). The PBAC noted that no evidence was presented in the re-submission to support the use of the Symbicort Rapihaler in COPD or asthma SMART indications. The PBAC recalled that data supporting the use of the device in COPD had previously been presented to the Committee in the November 2010 major submission. The PBAC noted the statement in the pre-PBAC response that the early bronchodilatory effects were consistent across the MDI and DPI devices.

The published trials and associated reports presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Trial 003	A 6-week, phase III, double-blind, randomized, multi-centre, parallel-group study evaluating the efficacy and safety of 2 actuations Symbicort® (budesonide/formoterol) pMDI 40/2.25 µg twice daily compared with 1 inhalation Symbicort® Turbuhaler® 80/4.5µg twice daily and 1 inhalation Pulmicort® (budesonide) Turbuhaler® 100 µg twice daily in adult and adolescent asthmatics.	Clinical study report D5897C00003. 21 July 2008 ClinicalTrials.gov Identifier: NCT00536731 Also available from: http://www.astrazenecaclinicaltrials.com/_mshost800325/content/clinical-trials/resources/pdf/8610807
Trial 681 Morice A et al.	Therapeutic comparison of a new budesonide/formoterol MDI with budesonide MDI and budesonide/formoterol DPI in asthma.	*International Journal of Clinical Practice* (2007); 61(11): 1874-1883.
Supplementary studies		
Trial 682 Morice A et al.	Efficacy and safety of a new pressurised metered-dose inhaler formulation of budesonide/formoterol in children with asthma: A superiority and therapeutic equivalence study.	*Pulmonary Pharmacology and Therapeutics* (2008); 21(1): 152-159.
Trial 715 Morice A et al.	Comparable long-term safety and efficacy of a novel budesonide/formoterol pressurized metered-dose inhaler versus budesonide/formoterol Turbuhaler® in adolescents and adults with asthma.	*Pulmonary Pharmacology and Therapeutics* (2008); 21(1): 32-39.
Trial 5 Busse W et al.	Comparison of adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients.	*Journal of Allergy and Clinical Immunology* 2008; 121 (6): 1407-1414.
Menendez R et al.	Peripheral airway effects of two ics/laba combinations as measured by impulse oscillometry (IOS) in young	*American Journal of Respiratory and Critical*

	adults with asthma.	*Care Medicine* 2011; 183: A2181.
Hampel F et al.	Early bronchodilatory effects of budesonide/formoterol MDI compared with fluticasone/salmeterol DPI and albuterol MDI : 2 randomized controlled trials in adults with persistent asthma previously treated with inhaled corticosteroids.	*Journal of Asthma* (2008); 45(4): 265-272.
Lindberg A et al.	Fast onset of effect of budesonide/formoterol versus salmeterol/fluticasone and salbutamol in patients with chronic obstructive pulmonary disease and reversible airway obstruction.	*Respirology* (2007); 12: 732-739.

8. Results of Trials

The re-submission nominated equivalence limits of -15L/min and 15L/min in morning peak expiratory flow (mPEF) for establishing non-inferiority and therapeutic equivalence.

Results of the primary outcome of change from baseline in mPEF across the randomised trials comparing Symbicort® MDI and DPI

In both Trials 003 and 681, the 95% confidence interval (CI) for the difference was well within the pre-specified equivalence limits of ±15 L/min, thus therapeutic equivalence between Symbicort® MDI and DPI was considered to be established. Similarly, the results reported in Trial 682 also supported a claim of non-inferiority. The results for other outcomes generally demonstrated no statistically significant differences between the two Symbicort® presentations (but potentially clinically significant differences were not known). A potentially important exception to this was "percentage asthma symptom-free days" (-6.2; 95% CI: -12.0, -0.4) and "control days" (-6.5; 95% CI: -12.3, -0.8) in Trial 681, in which patients treated with Symbicort® MDI reported statistically significantly fewer such days compared with those treated with the DPI (using a daily metered dose of 800/24 for both presentations). These estimates suggested an average of five fewer days of being symptom-free or well controlled over a 12 week (84 day) period, which may be clinically significant. Thus the potential for Symbicort® MDI being inferior to Symbicort® DPI in terms of effectiveness could not be excluded.

The PBAC agreed that the data presented in the Pre-Sub-Committee Response were sufficient to show that Symbicort® MDI was non-inferior to the DPI for other patient relevant outcomes, including total use of rescue medicines, rescue free days and awakening.

Results of the secondary outcome of change from baseline in mPEF – Trial 5 (Busse 2008) a randomised, open-label study

A comparison of fixed-dose Symbicort® MDI and Seretide® DPI demonstrated no statistically significant difference between the two treatments with respect to change in mPEF and the differences were within the pre-specified equivalence limits of +15 L/min. A claim of non-inferiority would thus be justified. Similarly, no significant differences were reported for any of the other outcomes reported in the trial, notably (RD; 95% CI):

- Symptom-free days (%): -0.18 (-5.05, 4.68);
- Asthma control days (%): 1.38 (-3.41, 6.18); and

- Rescue medication use (puffs/day): -0.07 (-0.24, 0.10).

With regard to comparative harms, there were no major differences between groups in terms of the number of patients experiencing an adverse effect or serious adverse effect in the Symbicort MDI vs. Symbicort DPI studies.

In Trial 5 (Busse 2008), a randomised, open-label study, discontinuations due to drug-related adverse effects were considerably higher in the Symbicort® MDI group compared to the Seretide® DPI group (0,5% in adjustable-dose Symbicort arm, 2.8% in fixed-dose Symbicort arm vs 0.7% in Seretide fixed-dose arm). Thus, the potential for Symbicort® MDI to be inferior to Seretide® DPI in terms of safety cannot be excluded based on the available data.

Based on the data presented, the PBAC considered that Symbicort MDI was non-inferior to both Symbicort DPI and Seretide DPI.

9. Clinical Claim

The re-submission described Symbicort® MDI as equivalent in terms of comparative effectiveness and equivalent in terms of comparative safety over Symbicort® DPI.

The PBAC considered that the clinical claim was adequately supported by the data provided.

10. Economic Analysis

The submission presented a cost-minimisation analysis versus the main comparator (Turbuhaler DPI) based on a non-inferiority claim for mPEF outcome, but not including additional costs/offsets for administration/adverse events.

The PBAC accepted the following equi-effective doses for the purposes of cost minimisation:

- Two inhalations twice daily of Symbicort® 50/3 MDI will provide equivalent daily doses to one inhalation twice daily of Symbicort® 100/6 DPI.
- Two inhalations twice daily of Symbicort® 100/3 MDI will provide equivalent daily doses to one inhalation twice daily of Symbicort® 200/6 DPI.
- Two inhalations twice daily of Symbicort® 200/6 MDI will provide equivalent daily doses to one inhalation twice daily of Symbicort® 400/12 DPI.

The requested prices for the low-, medium- and high-dose of Symbicort® MDI were equivalent to the low-, medium- and high-dose of Symbicort® DPI and the corresponding cost-minimisation analysis demonstrated cost neutrality.

The total costs per inhalation and costs per day for Symbicort® MDI and Seretide® MDI were also calculated, based on a comparison between the corresponding low-, mid- and high-strength presentations. The re-submission stated that this demonstrates that Symbicort® MDI is cost-saving when substitution for Seretide® MDI occurs directly between the low-, medium- and high strength presentations on a cost per inhalation basis. However, the PBAC noted that the dosing regimens are different for Symbicort® and Seretide® MDIs (2-4 inhalations twice daily vs 2 inhalations twice daily respectively). .

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be more than 200,000 in Year 5, at an estimated net saving per year to the PBS of between $10 million - $30 million in Year 5.

Overall, the PBAC considered the submission's estimates of PBS usage and financial implications to be uncertain.

The financial implications are yet to be verified.

12. Recommendation and Reasons

The PBAC recommended the listing of budesonide with eformoterol (MDI) for treatment of asthma and COPD on a cost-minimisation basis with budesonide with eformoterol DPI.

The PBAC noted that data were not presented in the current re-submission for the use of the Symbicort Rapihaler in COPD, but that such data had previously been presented to the Committee in the November 2010 major submission and the PBAC had recommended listing in COPD on this basis.

The PBAC considered the submission's utilisation estimates to be highly uncertain.

The PBAC noted that the restriction wording proposed by the sponsor is consistent with that for other currently PBS-listed asthma maintenance fixed dose combination corticosteroid (ICS) with long acting beta agonist (LABA) products, in that the proposed new listing requires patients to be stabilised on concomitant inhaled budesonide and eformoterol before moving to the fixed dose combination.

Consistent with NAC concerns about the safety of the use of LABA without ICS and increased risk of this happening when two separate inhalers are prescribed, the PBAC indicated its intention to review the PBS restrictions for all fixed dose combination ICS with LABA medicines with a view to aligning these restrictions with the new NAC treatment guidelines. Other issues to consider in this review include whether to specify a class of medicine or the component medicine in these restrictions and whether any age restrictions should apply. The Committee requested its Secretariat request the input of sponsors of PBS subsidised ICS with LABA combinations and other relevant stakeholders prior to PBAC considering this issue further.

The PBAC recommended that budesonide with eformoterol pressurised metered dose inhaler is suitable for inclusion in the medicines for prescribing by nurse practitioners within collaborative arrangements.

Outcome:
Recommended

Recommended listing

Add the following new items:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
BUDESONIDE with EFORMOTEROL FUMARATE DIHYDRATE			
Oral pressurised inhalation 50-micrograms-3 micrograms per dose (120 doses)	2	5	Symbicort Rapihaler 50/3 AP
Oral pressurised inhalation 100-micrograms-3 micrograms per dose (120 doses)	2	5	Symbicort Rapihaler 100/3 AP

Condition/Indication:	Asthma
Restriction:	Restricted Benefit *Restriction to be finalised*

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
BUDESONIDE with EFORMOTEROL FUMARATE DIHYDRATE			
Oral pressurised inhalation 200-micrograms-6 micrograms per dose (120 doses)	2	5	Symbicort Rapihaler 200/6 AP

Condition/Indication:	Asthma
Restriction:	Restricted Benefit *Restriction to be finalised*

Condition/Indication:	Chronic obstructive pulmonary disease (COPD)
Restriction:	Restricted Benefit *Restriction to be finalised*

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 had no comments.