Submission to Post-Market Review of PBS Medicines Used to Treat Asthma in Children

April 2013

AstraZeneca appreciates the opportunity to provide a submission to the Post-Market Review of Pharmaceutical Benefits Scheme Medicines Used to Treat Asthma in Children.

All AstraZeneca communications and activities are guided by the approved marketing conditions and PBS listings of our medicines, and by the principles of quality use of medicines. We acknowledge the clinical issues which are the genesis of the current review and reiterate our comments to the initial review that it is important that this issue be considered in the context in which physicians make clinical decisions. That is, with an understanding of the individual patient circumstances, needs, condition and other patient-specific influences with which a prescribing physician is faced. The implication of this is that whether a medicine is used appropriately is not revealed solely by the prescribing pattern. This submission points out the limitations of the DUSC analysis, and illustrates that further detail is required to quantify any true inappropriate, or unjustified, use.

AstraZeneca notes and welcomes the Stakeholder meeting that will be scheduled for this review. This will be an important step in understanding prescribing practices related to the FDC agents in children with asthma, and in working together to optimize such practices.

Symbicort

AstraZeneca are the sponsor of Symbicort, a fixed-dose combination (FDC) product containing the inhaled corticosteroid (ICS) budesonide and the long-acting beta-agonist (LABA) eformoterol. Symbicort is currently approved for marketing as a dry-powder inhaler (DPI, Turbuhaler) and a pressurised metered-dose inhaler (MDI, Rapihaler).

The range of doses available for Turbuhaler and Rapihaler are presented in **Table 1.**

Table 1 Symbicort range of products

Symbicort presentation	Strengths	Dose delivered per inhalation
Turbuhaler (DPI)	100/6	100 mcg budesonide, 6 mcg eformoterol
	200/6	200 mcg budesonide, 6 mcg eformoterol
	400/12	400 mcg budesonide, 12 mcg eformoterol
Rapihaler (MDI)	50/3	50 mcg budesonide, 3 mcg eformoterol
	100/3	100 mcg budesonide, 3 mcg eformoterol
	200/6	100 mcg budesonide, 6 mcg eformoterol

DPI dry-powder inhaler mcg micrograms
MDI metered-dose inhaler

Like all MDIs, Symbicort Rapihaler is a 2 actuation product i.e. in order to ensure dose uniformity, each dosing occasion is always to consist of multiples of 2 actuations. The Symbicort Rapihaler MDI and Symbicort Turbuhaler DPI range are aligned to provide equivalent daily doses:

- two inhalations of the Rapihaler 50/3 will provide a therapeutically equivalent dose to one inhalation of the Turbuhaler 100/6 presentation and
- two inhalations of the Rapihaler 100/3 will provide a therapeutically equivalent dose to one inhalation of the Turbuhaler 200/6 presentation and
- two inhalations of the Rapihaler 200/6 will provide a therapeutically equivalent dose to one inhalation of the Turbuhaler 400/12 presentation

Symbicort is indicated for the treatment of asthma where use of a combination of ICS and LABA is appropriate in adults and adolescents, including in patients who are symptomatic on inhaled corticosteroid therapy and patients who are established on regular long acting β-agonist and inhaled corticosteroid therapy.

. There are two alternative treatment regimens within the asthma indication

- Symbicort maintenance and reliever therapy: whereby a patient uses Symbicort on a regular basis with additional doses as required for relief of symptoms. This is generally referred to as the asthma SMART regimen. The higher strength presentations (i.e. Turbuhaler 400/12 and Rapihaler 200/6) are not approved for use in the asthma SMART regimen.
- Symbicort maintenance therapy. A patient uses Symbicort on a regular basis and uses a short-acting beta agonist (SABA) as required for relief of symptoms.

Symbicort is also indicated for use in chronic obstructive pulmonary disease (COPD). This indication is not discussed further in this submission.

Symbicort is only indicated in people with asthma aged over 12 years of age. All communications for Symbicort state clearly that it is not approved for use in children under 12 years of age, consistent with the product information. It should be noted that less than 5% of scripts for Symbicort are for people under 18 years of age. The higher strength of Symbicort Turbuhaler 400/12 should only be used in patients aged 18 years and over.

Symbicort is included on the Pharmaceutical Benefits Scheme (PBS) for

- patients who previously had frequent episodes of asthma while receiving treatment with:

    - oral corticosteroids and who have been stabilised on concomitant inhaled eformoterol fumarate dihydrate and budesonide;
    - inhaled corticosteroids and who have been stabilised on concomitant inhaled eformoterol fumarate dihydrate and budesonide;
- for single maintenance and reliever therapy (Turbuhaler 100/6 and 200/6 only) in a patient who experiences frequent asthma symptoms while receiving treatment with
    - oral corticosteroids
    - inhaled corticosteroids
    - a combination of an inhaled corticosteroid and a long-acting beta-2 agonist

It is important to note that, in addition to patients being stabilised on the monocomponents (i.e budesonide and eformoterol), this listing also allows for patients that have frequent asthma symptoms while being treated with any oral or inhaled corticosteroids to access PBS-subsidised Symbicort. Additionally, a patient that has frequent asthma symptoms on Seretide (fluticasone/ salmeterol) may be appropriately prescribed Symbicort. This is unlike Seretide FDC which is only reimbursed for patients who have been stabilised on the salmeterol and fluticasone monocomponents.

Symbicort clinical evidence in children

Given the limited time to prepare a submission, a comprehensive literature search to identify all evidence of Symbicort in children was not feasible (this work is ongoing – see below). However, a review of the clinical trial evidence in children previously considered by the PBAC has been conducted and is summarised in **Table 2.** As Symbicort is not approved for use in children under 12 years of age, specific data in this age cohort has not previously been provided to the PBAC.

Symbicort Turbuhaler 200/6 received a positive recommendation from the PBAC in March 2002. The comparator was the monocomponents given concomitantly and the submission included two trials, both of which enrolled asthmatic patients over the age of 18 years of age.

The asthma SMART regimen was recommended by the PBAC in March 2007. The submission included 5 trials, 4 of which included asthmatic patients over 12 years of age and 1 of which included patients over 4 years of age.

A submission for Symbicort Rapihaler will be considered by PBAC in due course and included 4 studies, 3 of which include patients over 12 years of age and 1 supportive study which enrolled patients between 6 and 11 years of age.

.

Table 2 PBS History of Symbicort presentations

Indication	Presentation	PBS history	Summary	Clinical evidence considered	Children included?
Asthma maintenance	Turbuhaler 100/6, 200/6, 400/12	200/6 recommended March 2002, 100/6 recommended November 2004, 400/12 recommended March 2004,	Cost-minimisation compared with individual components	Studies included in the 200/6 submission: COMBAT (Zetterstrom, 2001) COMSAFE (Rosenhall, 2002)	Comparator was budesonide and eformoterol given as monocomponents. Included asthmatic patients over the age of 18 years only.
Asthma SMART	Turbuhaler 100/6, 200/6	Recommended March 2007	The PBAC recommended for listing, noting the "clinical advantages over the comparators in regard to most of the outcomes 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".	Studies: AHEAD (Bousquet, 2007) COMPASS (Kuna, 2007) COSMOS (Vogelmeier, 2005) SMILE study (Rabe, 2006) STAY study [(Bisgaard, 2006) and (O'Byrne, 2005)]	Comparator was Seretide plus SABA (AHEAD, COMPASS and COSMOS studies). Secondary comparator was Symbicort plus SABA (SMILE and STAY studies). 4 trials included patients over 12 years of age, 1 included patients between 4 and 80 years of age.
Asthma maintenance, asthma SMART[1]	Rapihaler 50/3, 100/3 and 200/6 (maintenance only)	To be considered	Major submisison requesting PBS listing for Symbicort Rapihaler on the basis of clinical equivalence to Symbicort Turbuhaler at equivalent daily doses.	Study 003 Study 681 (Morice, 2007) Study 682 (Morice, 2008b) Study 715 (Morice, 2008a)	Comparator was Symbicort Turbuhaler. Two trials were pivotal (Study 003 and Study 681) and two trials were supportive (Study 682 and Study 715) 3 trials included patients over 12 years of age,1 supportive trial included patients aged 6 to 11 years

1. Also COPD

Utilisation patterns of FDCs

The DUSC analysis reveals patterns of use which may provide some information on the usage of fixed dose combinations.

Firstly, the pattern of use by age (Figure 7.4.8 and Figure 7.4.9 of DUSC report) suggests an adherence to the TGA approved indications for the two FDCs. Specifically, the majority of Symbicort usage occurs in patients over 12 years, whereas for Seretide, the majority of use is after 4 years.

Secondly, the report suggests that a proportion of patients utilise these FDCs without use of a prior preventer medication.

It is important to acknowledge that a utilisation pattern on its own reveals limited information about the clinical appropriateness of medicine usage. A physician takes into consideration many aspects of an individual patient's situation, condition, co-morbidities, personality etc when determining the course of treatment.

In the case of the DUSC analysis, there are design elements which will further limit the conclusions which can be drawn:

1) The analysis fails to account for the fact that the two FDC products which are the primary focus of the analysis have different clinical and PBS uses. Symbicort is used in people symptomatic on any oral or inhaled corticosteroid, in people stabilised on eformoterol and budesonide or an alternative FDC. Seretide is only reimbursed for people stabilised on salmeterol and fluticasone as monocomponents

2) The analysis examines only a two year usage history. This approach fails to account for the fact that asthma is a long-term condition which may not be adequately captured in a 2 year medication history, especially for the older children which are relevant for Symbicort which is only indicated in children over 12 years of age.

3) The tables presented in the report (i.e Table 7.4.8 – 7.4.10, page 23) include patients between 4 and 14 years of age. Given Symbicort is only indicated in patients over 12 years of age and usage in children under 12 years of age is very limited, it is unclear how relevant these analyses are to Symbicort specifically. Additionally, the listings of Symbicort and Seretide are different, with the Symbicort listing allowing access for

patients with frequent asthma symptoms on any oral or inhaled corticosteroid, in people stabilised on eformoterol and budesonide or an alternative FDC

4) The analysis does not include oral steroids as a relevant medicine in a patient's history, though this is an appropriate PBS condition for Symbicort. Additionally, patients may receive a supply of oral corticosteroids through a hospital (i.e following an emergency department visit) which may not be identified in the Medicare Australia database.

Without additional analyses and consultation with a range of relevant stakeholders, it is unclear how the current DUSC analysis may contribute to understanding to what extent the FDCs are used in a manner which is consistent with the principles of QUM.

Ongoing work

Due to the limited time to prepare a comprehensive submission to the review, a number of projects are ongoing:

1. Systematic search of the literature and sponsor databases to identify all trials of (a) Symbicort and (b) budesonide and eformoterol in children versus the relevant comparators

2. Review the utilisation data taking into consideration a longer usage history

3. Review the usage of oral steroids in the prescription history of Concession patients

4. Review utilisation of Symbicort in General patients, including the use of oral steroids

5. Explore the possibility of linking FDC usage to asthma hospitalisation rates recently reported by AIHW

AstraZeneca would be happy to provide these analyses once completed.

Finally, AstraZeneca are interested in working with the PBAC to generate a robust assessment of the magnitude of this issue and to determine activities or programs which would work to optimise the usage of these medicines.

References – available on request

Bisgaard, H., Le Roux, P., Bjamer, D., Dymek, A., Vermeulen, J. H. & Hultquist, C. 2006. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest,* 130**,** 1733-43.

Bousquet, J., Boulet, L. P., Peters, M. J., Magnussen, H., Quiralte, J., Martinez-Aguilar, N. E. & Carlsheimer, A. 2007. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med,* 101**,** 2437-46.

Cates, C. J. & Lasserson, T. J. 2009. Combination formoterol and budesonide as maintenance and reliever therapy versus inhaled steroid maintenance for chronic asthma in adults and children. *Cochrane Database Syst Rev***,** CD007313.

Kuna, P., Peters, M. J., Manjra, A. I., Jorup, C., Naya, I. P., Martinez-Jimenez, N. E. & Buhl, R. 2007. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract,* 61**,** 725-36.

Morice, A. H., Hochmuth, L., Ekelund, J., Thoren, A. & Puterman, A. S. 2008a. 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. *Pulm Pharmacol Ther,* 21**,** 32-9.

Morice, A. H., Peterson, S., Beckman, O. & Kukova, Z. 2008b. Efficacy and safety of a new pressurised metered-dose inhaler formulation of budesonide/formoterol in children with asthma: a superiority and therapeutic equivalence study. *Pulm Pharmacol Ther,* 21**,** 152-9.

Morice, A. H., Peterson, S., Beckman, O. & Osmanliev, D. 2007. Therapeutic comparison of a new budesonide/formoterol pMDI with budesonide pMDI and budesonide/formoterol DPI in asthma. *Int J Clin Pract,* 61**,** 1874-83.

Ni Chroinin, M., Lasserson, T. J., Greenstone, I. & Ducharme, F. M. 2009. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. *Cochrane Database Syst Rev***,** CD007949.

O'byrne, P. M., Bisgaard, H., Godard, P. P., Pistolesi, M., Palmqvist, M., Zhu, Y., Ekstrom, T. & Bateman, E. D. 2005. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med,* 171**,** 129-36.

Rabe, K. F., Atienza, T., Magyar, P., Larsson, P., Jorup, C. & Lalloo, U. G. 2006. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet,* 368**,** 744-53.

Rosenhall, L., Heinig, J. H., Lindqvist, A., Leegaard, J., Stahl, E. & Bergqvist, P. B. 2002. Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. *Int J Clin Pract,* 56**,** 427-33.

Vogelmeier, C., D'urzo, A., Pauwels, R., Merino, J. M., Jaspal, M., Boutet, S., Naya, I. & Price, D. 2005. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J,* 26**,** 819-28.

Zetterstrom, O., Buhl, R., Mellem, H., Perpina, M., Hedman, J., O'neill, S. & Ekstrom, T. 2001. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. *Eur Respir J,* 18**,** 262-8.