Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Budesonide/Eformoterol

Proprietary Product Name: Symbicort Rapihaler

Sponsor: AstraZeneca Pty Ltd

December 2011

Updated February 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to product submission

Submission details

Type of Submission	New Strengths (50/3 & 100/3) including Extension of Indications New Dosing Range (200/6 only) Other simultaneous quality changes (100/6 and 200/6)
TGA Decision:	Budesonide 50/eformoterol 3: Approved in part (new strength); indication extension rejected. Budesonide 100/eformoterol 3 (new strength including indication extension): Rejected Budesonide 200/eformoterol 6 (new dosing range): Rejected
Date of TGA Decision:	Initial approval: 7 April 2011 (50/3) Initial rejections: 28 March 2011 (3 decisions – 100/3 maintenance, 200/6 dose range increase and indication extension [50/3, 100/3 and 100/6])[1] Final TGA decision for the 3 initial rejections: 24 August 2011[2]
AAT Decision[3]:*	Approval: 100/3 maintenance Approval: 200/6 dose range increase Approval: Indication extension [50/3, 100/3]
Date of AAT Decision:*	19 June 2012
Active ingredients:	Budesonide/Eformoterol[4]
Product Name:	Symbicort Rapihaler
Sponsor's Name and Address:	AstraZeneca Pty Ltd Alma Road North Ryde NSW 2113
Dose forms:	Pressurised metered dose inhaler
Strengths:	Budesonide 200 μg /eformoterol fumarate dihydrate 6 μg[5], Budesonide 100 μg /eformoterol fumarate dihydrate 6 μg,

[1] The proposed extension of registered indications for the 100/6 presentation was not formally applied for.

[2] Subject to appeal to the Administrative Appeals Tribunal (see Final Outcome)

[3] The sponsor appealed to the Administrative Appeals Tribunal for review of the 3 rejected decisions. By consent, the AAT set aside the decisions and substituted with 3 decisions of approval under subsection 25(1) of the *Therapeutic Goods Act 1989*. For further details see the Final Outcome section of this AusPAR.

[4] Eformoterol is the preferred name used in Australia. It is synonymous with the name formoterol used overseas.

	Budesonide 100 μg /eformoterol fumarate dihydrate 3 μg, Budesonide 50 μg /eformoterol fumarate dihydrate 3 μg
Containers:	Inhaler – pressurised metered dose
Pack sizes:	120 inhalations, packs of one or two inhaler canisters
Approved Therapeutic use:	50/3, 100/3 Symbicort Rapihaler is indicated for the treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β_2-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 β_2-agonist and inhaled corticosteroid therapy. There are two alternative treatment regimens: Symbicort maintenance and reliever therapy; Symbicort maintenance therapy. 100/6 Symbicort Rapihaler is indicated for the treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β_2-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 β_2-agonist and inhaled corticosteroid therapy. 200/6 ASTHMA: Symbicort Rapihaler is indicated for the treatment of asthma where use of a combination (inhaled corticosteroid and long acting β2-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 β2-agonist and inhaled corticosteroid therapy. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): Symbicort Rapihaler is indicated for the symptomatic treatment of moderate to severe COPD (FEV_1 < or = 50% predicted normal) in adults with frequent symptoms despite long acting bronchodilator use, and/or a history of recurrent exacerbations. Symbicort Rapihaler is not indicated for the initiation of bronchodilator therapy in COPD.
Route of administration:	Inhalation
Dosage:	ASTHMA: 2-4 inhalations twice daily, with additional inhalations as needed (50/3 and 100/3), 2 inhalations twice daily (100/6 and 200/6), 4 inhalations twice daily for adults 18 years and over who require a higher daily

[5] Symbicort inhalers are labelled in terms of their metered dose in Australia. Delivered dose is frequently used in this document. Refer to Table 2 for the corresponding metered and delivered doses.

	maintenance dose (200/6). COPD: 2 inhalations twice daily (200/6)
ARTG Number s	115552 (Budesonide 100/eformoterol 6), 115555 (Budesonide 200/eformoterol 6), 158898 (Budesonide 50/eformoterol 3) and 158899 (budesonide 100/eformoterol 3)

*AAT=Administrative Appeals Tribunal

Product background

This AusPAR describes a submission from AstraZeneca Pty Ltd (the sponsor) to register two new strengths of Symbicort Rapihaler (50/3 and 100/3) for "maintenance therapy" and "maintenance and reliever therapy" of asthma in adults and adolescents (12 years and older); and (b) amend the dosage regimen of Symbicort Rapihaler 200/6 for "maintenance therapy" of asthma in adults (18 years and older) to include a new maximum dose of four inhalations twice daily (bd). Simultaneous applications to make changes to the chemistry and quality control aspects, including adding an actuation counter to the registered Symbicort Rapihaler 100/6 and 200/6 pressurised metered dose inhalers have been considered separately and are not described in this AusPAR.

Symbicort Rapihaler is indicated for the regular treatment of asthma where use of a combination (inhaled corticosteroid and long acting β_2-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 β_2-agonist and inhaled corticosteroid therapy.

At the time of the original AusPAR (December 2011), the above were the approved indications for Symbicort Rapihaler in Australia. At this time, Symbicort (Rapihaler 200/6 and Turbuhaler) had also been registered for chronic obstructive pulmonary disease (COPD) in Australia.[6]

Regulatory status

Symbicort Rapihaler (100/6 and 200/6) received initial ARTG Registration in 2006 for asthma maintenance therapy.

At the time of submission (December 2008), Symbicort Rapihaler (or an alternative trade name product) in strengths of 100/6 and 200/6 was approved in Switzerland, USA and New Zealand. In New Zealand, the asthma indication was "the regular treatment of asthma where the use of a combination (inhaled corticosteroid and long-acting β_2-agonist) is appropriate". In the USA, the asthma indication was "the long-term maintenance treatment in patients 12 years of age and older". The Symbicort Rapihaler pressurised metered dose inhaler (pMDI) 50/3 and 100/3 strengths were not registered in any countries.[7]

Symbicort pMDI (any strength) was not registered in the European Union (EU).

[6] TGA. AusPAR for Budesonide/Eformoterol fumarate dehydrate. Available at: http://www.tga.gov.au/pmeds/auspar/auspar-symbicort.pdf

[7] The terms Symbicort Rapihaler and Symbicort pMDI are used interchangeably in this AusPAR.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Introduction

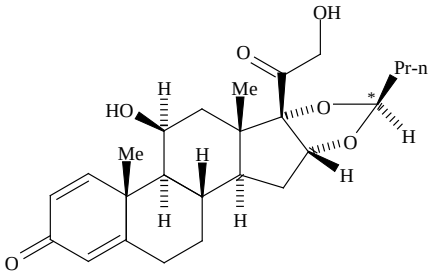
Symbicort Rapihaler pressurised metered dose inhalers deliver budesonide and eformoterol fumarate (referred to as eformoterol in the remainder of this AusPAR) and are used in the treatment of asthma and more recently, chronic obstructive pulmonary disease (COPD). Symbicort Rapihaler 100/6 and 200/6 budesonide/eformoterol pressurised metered dose inhalers are already registered. AstraZeneca now seeks to register two new strengths: Symbicort Rapihaler 50/3 and 100/3 pressurised metered dose inhalers.

Simultaneous changes proposed to:

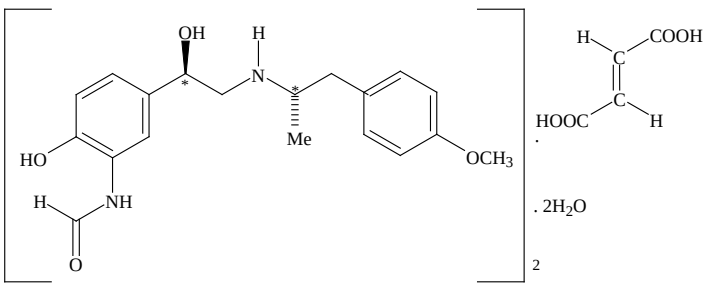
- expand dosage/treatment regimens [including asthma "maintenance and reliever therapy"] for Symbicort Rapihaler are addressed in the clinical evaluation
- chemistry and quality control aspects, including adding an actuation counter to the registered Symbicort Rapihaler 100/6 and 200/6 pressurised metered dose inhalers have been considered separately and are not described in this AusPAR.

Drug substance (active ingredient)

Budesonide is a synthetic steroid; the steroid nucleus is enantiomerically pure but the drug consists of a mixture of two epimers at the acetal substituent (*). Eformoterol is a long acting β_2 agonist. It has two chiral centres; the drug substance is the R*,R* racemic mixture (that is, containing the R,R + S,S enantiomeric pair); the dihydrate is used.



budesonide



eformoterol fumarate dihydrate

Drug product

Related combination products are already registered in Australia (Table 1). Symbicort Turbuhaler dry powder inhalers (budesonide/eformoterol 100/6, 200/6 and 400/12 μg) and Symbicort Rapihaler pressurised metered dose inhalers (100/6, 200/6 μg). Symbicort Rapihalers 100/6 and 200/6 were approved in 2006 on the basis of comparisons with the corresponding Turbuhaler products. Symbicort Rapihaler (100/6 and 200/6) is registered but not currently marketed in Australia.

Table 1: Range of Symbicort products registered in Australia

	Symbicort Rapihaler	Symbicort Turbuhaler
budesonide/eformoterol	*pressurised metered dose inhaler (pMDI)*	*dry powder inhaler (DPI)*
50/3	***proposed***	--
100/3	***proposed***	--
100/6	[registered]	registered
200/6	registered	registered
400/12	--	registered

Monotherapy products

Pulmicort Turbuhaler dry powder inhalers (100, 200 and 400 μg budesonide) and Oxis Turbuhaler dry powder inhalers (6 and 12 μg eformoterol) are currently registered by AstraZeneca. Foradile eformoterol inhalation capsules are registered by Novartis: 12 μg per capsule.

Pulmicort 50, 100 and 200 μg budesonide pressurised metered dose inhalers, formulated with chlorofluorocarbon propellants, were registered in Australia but the registrations were cancelled by AstraZeneca in 2003. An eformoterol pressurised metered dose inhaler has never been registered in Australia. Thus there are no corresponding single drug pressurised metered dose inhalers now available in Australia.

Labelling of doses: budesonide/eformoterol fumarate

Meaningful expression of dose for inhaled products is problematic. The labelled doses for the registered Pulmicort Turbuhaler (100, 200 or 400 μg budesonide) and Oxis Turbuhaler (6 or 12 μg eformoterol) dry powder inhalers are the masses of drugs mechanically metered within the device. Some of this drug is lost within the device, some is delivered to the patient during inhalation ('delivered dose') and about half of this then reaches the lung (the 'respirable dose'). The Symbicort Turbuhalers meter about 100/6, 200/6 or 400/12 μg doses, and deliver 80/4.5, 160/4.5 or 320/9 μg under controlled laboratory conditions. Although labelling of the delivered dose has recently become official practice for new products, Symbicort Turbuhalers were labelled in terms of the metered dose, for consistency with the older single drug Turbuhalers, even though the respirable doses were not identical.

All pressurised metered dose inhalers also have losses in the 'actuator' (mouthpiece) and suffer incomplete delivery to the lung. The delivered dose of budesonide is about 80% of the metered dose, while the delivered dose of eformoterol is about 75% of the metered dose. For consistency with Symbicort Turbuhaler, Symbicort Rapihaler (100/6 and 200/6) was approved with metered dose (that is, the doses of drugs metered by the valve, not all of which leaves the actuator and enters the patient's mouth) labelling. AstraZeneca proposes to label the two new strengths (50/3 and 100/3) in line with the already registered Symbicort Rapihaler strengths (that is, metered dose).

Thus in Australia, Symbicort products are labelled with metered doses for historical reasons. In Europe the same products are labelled with delivered doses. The metered and

delivered dose equivalents for each strength of Symbicort pMDI/Turbuhaler are outlined in Table 2.

Table 2: Symbicort (pMDI/Turbuhaler) metered dose and delivered dose.

Symbicort*	Metered dose (µg)		Delivered dose (µg)	
	Budesonide	*Eformoterol*	Budesonide	*Eformoterol*
50/3	**50**	**3**	40	2.25
100/3	**100**	**3**	80	2.25
100/6	**100**	**6**	80	4.5
200/6	**200**	**6**	160	4.5
400/12	**400**	**12**	320	9

*pMDI strengths: 50/3, 100/3, 100/6 and 200/6 µg/actuation (2 actuations per dose).
Turbuhaler strengths: 100/6, 200/6 and 400/12 µg/dose

The quality evaluator noted that this table is perhaps poorly worded and, in the absence of registered Pulmicort or Oxis pressurised metered dose inhalers, might be taken to imply equivalence between the Turbuhaler and Rapihaler dosage forms. Direct *in vitro* equivalence between the combination Turbuhaler and Rapihaler products has not been established in pharmaceutical chemistry data.

Formulations

Symbicort Rapihaler pressurised metered dose inhalers are formulated with macrogol 1000, povidone and the propellant apaflurane (1,1,1,2,3,3,3-heptafluoropropane or HFA-227). These are uncommon excipients for inhalation products but are also used in some other metered dose inhalers. These excipients are, in principle, undesirable because they coat onto evaporating aerosol droplets and increase their size, potentially reducing lung delivery. Macrogol (polyethylene glycol) is needed as a valve lubricant. Povidone is needed to stabilise the suspension.

The different Symbicort Rapihaler strengths are not direct scales (that is, they do not meter different volumes of the same suspension) but all use the same valve to deliver different amounts of drugs contained in the same propellant/excipient matrix.

Only 120 actuation packs are proposed for registration (that is, doses for 30 days); the inhalers are overfilled to ensure these can be delivered throughout the shelf life.

The four different Rapihaler inhalers (50/3, 100/3, 100/6 and 200/6) are all used as inhaler cans in red actuators (with the canister hidden under the dose counter). There is some differentiation of the strengths via different colours (and numerical dose) on a shield label on the front of the actuator.

Fine particle distribution

Characterisation of the delivered fine particle distribution uses *in vitro* testing, which mimics delivery to the lung. The test is carried out using a cascade impactor. Limits have been proposed for the fine particle dose.

No detailed *in vitro* comparison of Symbicort and Oxis or Pulmicort was provided.

In vitro fine particle distributions are consistent with proportional *in vitro* delivery from the four strengths ('*in vitro* linearity').

Stability

High humidity storage of the inhalers caused a significant change in the fine particle dose. Thus the inhalers are presented in foil pouches with a desiccant. The carton label warns that the inhaler should be discarded 3 months after opening of the pouch. The shelf life will be less than proposed by the sponsor because of changes seen in delivered doses and fine particle doses on storage.

Biopharmaceutics

The Symbicort products apparently act locally in the lungs. Systemic bioavailability data do not provide useful product comparisons for a locally acting product. Thus pharmacokinetic data have only been considered by the TGA's quality evaluators in the context of comparisons of the extent of systemic steroid exposure for safety purposes.

The PI states:

"The budesonide and eformoterol bioavailability of *Symbicort Rapihaler* and *Symbicort Turbuhaler* were similar after single doses containing 1280 µg budesonide and 36 µg eformoterol (8 inhalations) in healthy adult volunteers. The budesonide and eformoterol bioavailability from *Symbicort Rapihaler* was also comparable with that from similar doses of the component products, *Pulmicort Turbuhaler*, *Oxis Turbuhaler* and a specially prepared budesonide HFA pressurised inhalation suspension."

The PI separately claims therapeutic equivalence between Rapihaler and Turbuhaler presentations. The PI newly recommends that patients should "have their rescue inhaler available at all times, either Symbicort or a separate rapid-acting bronchodilator" (and a warning against rescue use is to be deleted). This does not distinguish between Turbuhaler and Rapihaler presentations.

No new bioavailability data were provided with this application to register the 50/3 and 100/3 strengths, although two previously evaluated biopharmaceutic studies (SD-039-0626 and SD-039-0730; evaluated as part of the original Symbicort Rapihaler submission) were cross-referenced within this current submission. AstraZeneca undertook a considerable number of pharmacokinetic studies with Symbicort Rapihaler in the original registration application, including the two referred studies. These involved dosing with more than the recommended number of inhalations to enable analysis of low blood levels.

Study SD-039-0730 was a three way, single dose, crossover pharmacokinetic comparison of Symbicort Rapihaler 200/6, Symbicort Turbuhaler 200/6 and Symbicort Turbuhaler 400/12. Twenty eight healthy volunteers took eight inhalations (200/6) or four inhalations (400/12), with a washout period of 7 days between treatments. The study showed slightly lower systemic budesonide bioavailability from the pressurised metered dose inhaler than from Symbicort Turbuhaler, almost within conventional bioequivalence limits.

Other pharmacokinetic studies included similar comparisons, but showed somewhat different results, outside bioequivalence limits. Thus Study 626 (single doses of 4 x 200/6 Rapihaler vs 4 x 200/6 Turbuhaler) showed significantly lower exposure to both drugs after metered dose inhaler treatments.

The original bioavailability data were consistent with the Symbicort Rapihaler pressurised metered dose inhalers giving no greater systemic steroid exposure than from registered Symbicort Turbuhaler dry powder inhalers.

Sponsor response to the initial quality and biopharmaceutic Summary for PSC

Based on the quality evaluator's *Quality and biopharmaceutic Summary for Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM)* for the first PSC meeting (131st meeting – refer below), the sponsor provided the following response:

The sponsor believed that the reason for referring the application to the PSC was unfounded and indicated a misinterpretation of the bridging approach/strategy outlined in the current application. It was important to note that:

- No claims had been made with regards to "*in vitro* equivalence" between the two delivery devices [Turbuhaler (dry powder inhaler, DPI) vs Rapihaler (pressurised metered dose inhaler, pMDI)] in the application.
- The development program for Symbicort Rapihaler was not designed nor intended to show "*in vitro* equivalence" between the 2 different devices. The program consisted of both clinical studies to demonstrate *in vivo* therapeutic equivalence (between Symbicort Turbuhaler and Rapihaler) and *in vitro* investigations to demonstrate linear dose relationships for all strengths of Symbicort Rapihaler. This was in accordance with the TGA-adopted EU guidance at the time.[8]
  A detailed discussion of the overall bridging strategy was provided in the sponsors response to the clinical evaluation report (refer *Clinical* section below) - the main points are summarised below.

Bridging strategy

There are four strengths of Symbicort Rapihaler: 50/3, 100/3, 100/6 and 200/6.

The two higher strength Symbicort Rapihalers (100/6 and 200/6) are currently registered in Australia. Their approval was based on *in vivo* therapeutic equivalence shown in two separate clinical studies (Studies 681 and 682; Table 3).

The application seeks to register two lower strength Symbicort Rapihalers (50/3 and 100/3) on the basis of a new *in vivo* therapeutic equivalence study (Study 003; as well as a supportive clinical safety study) and *in vitro* data demonstrating a linear dose relationship across all four strengths (Table 3).

[8] EMEA, Committee for Proprietary Medicinal Products (CPMP), 22 April 2004. CPMP Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) CPMP/EWP/4151/00.

Table 3: Sponsor's bridging strategy

Symbicort Rapihaler	Evidence supporting therapeutic equivalence with Symbicort Turbuhaler	
	Clinical studies / in vitro data	**TGA approval status**
50/3	Clinical study (D5897C00003) demonstrating in vivo therapeutic equivalence with Symbicort Turbuhaler 100/6	Clinical evaluator recommended approval based on demonstration of therapeutic equivalence [and subsequently registered]
100/3	Combination of • proven in vivo therapeutic equivalence in clinical studies for formulation strengths that bracket Symbicort Rapihaler 100/3 (50/3, 100/6, and 200/6) and • in vitro data showing linear dose relationships for both active ingredients from all formulation strengths	Approval sought via therapeutic equivalence demonstrated for 50/3, 100/6, and 200/6 **and** *in vitro* data across all 4 Rapihaler strengths
100/6	Clinical study (SD-039-0682) demonstrating in vivo therapeutic equivalence with Symbicort Turbuhaler 100/6	Approved by TGA; based on demonstration of therapeutic equivalence
200/6	Clinical study (SD-039-0681) demonstrating in vivo therapeutic equivalence with Symbicort Turbuhaler 200/6	Approved by TGA; based on demonstration of therapeutic equivalence

In terms of the formulation, the only difference between the new Symbicort Rapihaler 50/3 and 100/3 strengths and the approved higher strength Rapihaler products is the concentration of the drug substances. The composition of excipients is identical for all the strengths. All the Rapihaler products use the same valve metering chamber volume. The Symbicort Rapihaler 100/3 formulation strength has been developed to deliver, ex actuator, twice the dose of budesonide and an equivalent dose of formoterol as is

delivered by the Symbicort Rapihaler 50/3 (that is, the same relationship as for Symbicort Turbuhaler 200/6 and 100/6). *In vitro* data, which was presented in the submission demonstrates that all four Symbicort Rapihaler strengths give a linear response in terms of fine particle fraction and thus further confirms that Symbicort Rapihaler 100/3 performs in accordance with its nominal dose.

The rationale of the bridging strategy is based on the stepwise approach suggested in the TGA-adopted EU guidance[9] (which was essentially unchanged in updated Rev 1).[10] The guideline states that "In cases where different dose strengths of the same product contain a well-known active substance are sought, it can be sufficient to state the therapeutic equivalence clinically in vivo with one of those dose strengths. Thereafter it is necessary to give proof of a linear dose deposition relationship in vitro for each of the other dose strengths performed with a multistage impactor."

There are 3 clinical studies (Table 3) that showed in vivo therapeutic equivalence between Symbicort Turbuhaler and Rapihaler:

- Two previously evaluated studies (Studies 681 and 682) using the higher strength Symbicort Rapihalers (100/6 and 200/6; initial Symbicort Rapihaler submission cross-referenced in this submission) which resulted in the TGA approval of Symbicort Rapihaler 100/6 and 200/6 on the basis of in vivo therapeutic equivalence with Symbicort Turbuhaler (100/6 and 200/6).
- A third new study (Study 003) provided in this submission with the lowest Symbicort Rapihaler strength (50/3). The clinical evaluator recommended approval of Symbicort Rapihaler 50/3, based on therapeutic equivalence with Symbicort Turbuhaler (100/6) [see later].

Given the combination of proven *in vivo* therapeutic equivalence based on the clinical studies (mentioned above) for formulation strengths that bracket Symbicort Rapihaler 100/3 (that is, 50/3, 100/6, and 200/6) and the linear dose relationships (as shown in the *in vitro* data) for both active ingredients from all formulation strengths, there is sufficient evidence to justify the equivalence/bridging between Symbicort Rapihaler 100/3 and Symbicort Turbuhaler 200/6.

In conclusion, consistent with this guidance, the sponsor had performed both pharmaceutical *in vitro* analysis that confirmed all formulation strengths of Symbicort Rapihaler perform according to their nominal dose and clinical studies that have proven therapeutic equivalence across the range of formulation strengths.[8]

Advisory committee considerations

Initial meeting

Applications to register new strengths are not normally referred to the PSC, however the Clinical Delegate requested consideration of this application because of claims of "*in vitro* equivalence". The application was considered at the 131st meeting of the PSC.

[9] This guideline was revised during the evaluation of this submission - CPMP/EWP/4151/00 Rev 1 was adopted by CHMP in Jan 2009 (adopted by TGA on 23 Feb 2010).

[10] EMEA, Committee for Medicinal Products for Human Use (CHMP), 22 January 2009. Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents (CPMP/EWP/4151/00 Rev. 1).

The PSC was unable to recommend approval for registration on pharmaceutical grounds of Symbicort Rapihaler 50/3 and 100/3 in the absence of comparative data on the aerosol particle size distribution profiles.

The PSC agreed that the sponsor has not provided sufficient and adequate evidence to justify their claim in relation to equivalence/bridging between Symbicort Rapihaler and Symbicort Turbuhaler for all relevant/nominally equivalent doses. The Committee concluded that the combination Turbuhaler dry powder inhalers and Rapihaler pressurised metered dose inhalers should be considered as standalone products and are therefore not interchangeable.

The Committee did not accept that the limited data on *in vitro* comparisons of fine particle doses from Turbuhaler and Rapihaler formulations are compelling to conclude equivalence and agreed that comparison of particle size distribution of the formulations is very relevant for the products.

The PSC therefore concluded that comparisons of different strengths of a given inhaler should be based on the particle size distribution profiles of the aerosols.

Sponsor response

Based on the outcome of the initial PSC meeting where the committee was unable to recommend approval in the absence of comparative data on the aerosol particle size distribution profiles of the Symbicort Rapihaler presentations, the sponsor provided a formal response as it was considered that the Delegate and the PSC had erred in the evaluation. The main points are summarised below:

- The Symbicort Rapihaler development program was in accordance with the TGA-adopted EU guidelines.[8] The rationale for the bridging strategy for the current submission was based on a stepwise approach [as outlined above in the sponsor's response to the initial quality and biopharmaceutic summary for PSC].
- The comparative data on the aerosol particle size distribution profiles was provided in the current application.
- The sponsor recommended that the *in vitro* data, which was always in the submission, be evaluated and the matter be resubmitted back to PSC for further consideration.

The TGA subsequently reviewed the *in vitro* data and sent this issue back to a second PSC meeting (refer below).

Further meeting

The Delegate requested that the PSC consider the sponsor's response. Consequently, the application was reconsidered at the 133rd meeting of the PSC.

The PSC agreed that the issues of concern in relation to comparative data on the aerosol particle size distribution profiles raised at its 131st meeting had been adequately resolved. The *in vitro* data were consistent with dose linear delivery of drugs from the different strengths of the Rapihaler pressurised metered dose inhalers.

The Committee however noted the absence of *in vivo* data to support the *in vitro* characteristics of the product. The PSC considered that the sponsor should be asked to provide forced expiratory volume (FEV) data if available.

The PSC reiterated its recommendation that the sponsor had not provided sufficient *in vitro* evidence to justify any claim of equivalence between any doses of Symbicort Rapihaler (pressurised metered dose inhaler) and Symbicort Turbuhaler (dry powder inhaler).

The PSC therefore concluded that the issues in relation to switching between Symbicort Rapihaler and Symbicort Turbuhaler dose forms is a clinical issue and should be addressed by clinical data.

The PSC therefore concluded that approval of this application should be based on clinical data.

Quality summary and conclusions

Registration was recommended with respect to chemistry and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

According to the draft PI, the maximum recommended daily dose is 24 actuations of the proposed 50/3 or 100/3 formulations of Symbicort Rapihaler, which would result in maximum daily doses of 2400 µg budesonide and 72 µg eformoterol. These are the same doses of active ingredients that would result from (the maximum recommended) 12 inhalations/day from the currently registered Symbicort Turbuhaler 200/6 formulation.

It was noted in the nonclinical evaluation report for the original application for registration of Symbicort Rapihaler that if higher levels of the leachables are detected from longer term storage or higher clinical doses are taken by patients, the safety of the leachables should be re-assessed. On the basis that the new strengths proposed in this submission can lead to higher clinical doses of the excipients as well as higher doses of leachables, it was necessary to reassess their safety.

Pharmacology/Pharmacokinetics

No new pharmacological data were provided.

Toxicology

Budesonide and eformoterol

The maximum daily dose of the active ingredients (2400 µg budesonide /72 µg eformoterol; obtained from 24 actuations of the 100/3 formulation) is equivalent to that permitted for Symbicort Turbuhaler (following 12 actuations of the 200/6 formulation). No new nonclinical data relevant to this combination of active ingredients has been submitted. Multiples of the clinical exposure achieved in previously submitted toxicity studies in rats and dogs were previously noted to be low and are further reduced with the proposed increase in maximum dose. Nonetheless, in the previously evaluated study in rats at doses that induced substantial toxicity, there were no significant toxicological interactions between the two active ingredients. Furthermore, clinical experience with the Turbuhaler product should provide reassurance for the safety of the newly proposed maximum recommended dose.

Excipients

In the Symbicort Rapihaler formulation, apaflurane (HFA-227) is used as a propellant, povidone (PVP K25) as a suspending agent and macrogol (PEG 1000) as a valve lubricant. These three excipients are also used in two other registered inhalation drug products

(non-Symbicort). The amounts released of each of these products per actuation are identical across all Symbicort Rapihaler strengths and the maximum number of actuations (per day) is increased from 4/day with the 100/6 and 200/6 formulations to 24/day with the proposed 50/3 and 100/3 formulations. Hence, the maximum patient exposures to these excipients are increased sixfold in comparison with the currently registered Symbicort formulations. The maximum patient exposures in the other registered (non-Symbicort) and currently proposed (Symbicort Rapihaler) products were compared. Since the exposures are primarily restricted to the respiratory tract, the dose ratios were calculated on an mg/kg basis only.

In a previous submission, the estimated inhaled doses of the excipients in the 3 month study in dogs were 0.42, 126 and 41835 µg/kg/day for povidone K25, PEG 1000 and apaflurane, respectively. Since the actual inhaled doses of budesonide/eformoterol were almost identical in the three month study in rats and because the doses of the excipients were estimated from the measured dose of budesonide based on the ratio of the excipients in the MDI formulation to budesonide (and assuming similar aerosol generation efficiency), very similar doses of the excipients can be assumed for the rat study. These doses are comparable to those anticipated in humans at the maximum recommended daily dose (24 actuations) of the proposed formulation of Symbicort Rapihaler on a mg/kg basis. There were no findings suggesting local or systemic toxicity from the excipients in these studies.

The sponsor submitted four new studies in animal species. Although these focussed on the inhalational toxicity of another active ingredient, the excipients used in the formulation were the same (apaflurane/HFA-227) or similar (PVP K30, PEG 600) to those in the proposed formulation. Therefore it was considered that the vehicle control data could provide some indications of toxicity of the excipients despite slight differences in chemical structure (with PVP K30, PEG 600) and the use of a single dose in these studies, and (in all but one of these studies) the absence of untreated controls. The estimated presented doses of the excipients in the animal studies relative to the exposures to these excipients expected in 12 year old adolescents following administration of the maximum dose (24 actuations) are detailed in Table 4.

Table 4: Dose and dose ratios in animal studies

Species; study duration; study no.	Dose			Animal/human dose ratio		
	PVP K30 (µg / kg / day)	PEG 600 (µg / kg / day)	Apaflurane (mg / kg / day)	PVP K30 / PVP K25	PEG 600 / PEG 1000	Apaflurane
Rats; 6 months; 96010	19	2200	764	42	16	17
Rats; 24 months; 98027	110	1300	4400	244	10	98
Dogs; 6 months; 96012	3	340	107	7	3	2
Dogs; 12 months; 98292	2	240	74	4	2	2

Apaflurane (HFA-227)

Apaflurane is used as a propellant to replace CFC propellants in MDI formulations. Its use in MDI products has been evaluated and approved by the TGA. The maximum daily exposure to apaflurane from Symbicort Rapihaler is 1.79 g (about 45 mg/kg/day for a 40 kg adolescent), which is lower than the daily exposure from an existing non-Symbicort registered product. Minimal toxicity was seen in animal models exposed to multiples of the maximum recommended dose in humans. Overall, the use of apaflurane at the proposed concentration in the Symbicort formulation is unlikely to present a safety risk to patients.

Povidone

Povidone (PVP) is widely used in oral and parenteral drug formulations and its use in inhalational products has only been introduced with the development of CFC-free MDI drug products. Povidone is available in a range of molecular weights (2.5–1200 kDa). The material used in Symbicort Rapihaler is PVP K25, which has an average molecular weight of approximately 30 kDa. The sponsor provided a safety assessment of povidone in a previous submission.

The disposition of povidone was not determined in inhalation studies with PVP K25. Available pharmacokinetics and toxicity studies in animals dosed with PVP K30 have been reviewed by the TGA previously for another non-Symbicort registered product.

Povidone is likely to be deposited in human lungs from the use of Symbicort but the maximum daily dose of povidone is low, 0.36 μg/kg/day for a 50 kg adult and 0.45 μg/kg/day for a 40 kg adolescent, which is comparable to the no effect dose of 0.42 μg/kg/day (on a body weight basis) observed in the 3 month rat and dog studies. Given the already approved clinical use of PVP K30 (resulting in more than tenfold the exposure to povidone that in the products proposed for registration) and the lack of toxicity findings in the animal studies with PVP K25 and PVP K30, the use of povidone K25 at the proposed concentration in the Symbicort formulation is considered unlikely to present a safety risk to patients.

Macrogol (polyethylene glycol, PEG)

There are a wide range of PEGs with average molecular weights from 190 to 9000 Da. PEGs are widely used in drug products, including CFC-free MDI formulations. The macrogol used in Symbicort is PEG 1000, which has an average molecular weight of approximately 1000 Da, compared to 600 Da for PEG 600 used in other non-AstraZeneca CFC-free products. Some inhalational toxicity studies with PEG have already been reviewed in a previous TGA evaluation. Briefly, no toxic effects were observed in inhalational toxicity studies with macrogol 200 in mice and rats, while decreased weight gain, neutrophilia and increased pulmonary weight associated with alveolar histiocytosis were seen with macrogol 3350. Inhalation studies showed no toxicity findings in rats or dogs treated with 126 μg/kg/day PEG 1000 plus apaflurane and povidone. The maximum human dose from the use of Symbicort is 107 μg/kg/day for a 50 kg adult and 134 μg/kg/day for a 40 kg adolescent, which are lower than the exposure to PEG 600 from a registered non-AstraZeneca CFC-free product. Minimal toxicity was seen in rat and dog studies in the current submission with inhalation of a formulation containing PEG 600, povidone K30 and apaflurane. The lack of toxicity in the Symbicort Rapihaler studies and the already approved use of PEG 600 in other MDI formulations suggest that the proposed use of macrogol 1000 in Symbicort Rapihaler is unlikely to pose a safety risk to patients.

The findings in the animal studies submitted here were minor and not consistent. Taking into account the length of these studies, the minimal findings attributable to treatment with the excipients at the administered doses (particularly the absence of findings in the respiratory tract), the magnitude of the dose ratios, the fact that these excipients were all

administered together, and considering the higher exposures to these excipients from a currently registered non-AstraZeneca product and despite the lack of specific focus of the newly submitted animal studies and the fact that non-identical (albeit similar) chemical entities were used, it was considered that these excipients are unlikely to present a significant risk of toxicity at the proposed doses.

Leachables

Twenty leachable chemical species were identified and 11 leachables were unidentified or partially identified in Symbicort Rapihaler after storage for up to 24 months. While most were qualitatively the same as those assessed in a previous submission, the exposures are increased due to the greater maximum number of daily actuations with the proposed formulations. Where data from Australian or overseas inhalational occupational standards were available, these were primarily relied upon in assessing the safety of these chemicals. The sponsor submitted a safety assessment of the leachables, which was based on available information on the specific compounds or structurally related chemicals; literature references were included in most cases. The risk assessments were based on the maximum clinical doses of 24 inhalations daily in adults with a body weight of 50 kg. Where toxicity data on the specific leachable was not available, information from structurally related products was used; this assumes that the leachable concerned is not significantly more toxic than the most toxic structurally related (or structurally relevant) chemical. There was no information regarding potential interactions between the leachables. Despite this, the estimated maximum daily exposures to all the leachables (including the unidentified or partially identified chemicals) are low and raise no toxicological concerns at the detected levels. Thus, they are considered unlikely to induce toxic effects from the proposed use of the product. If higher levels of the leachables are detected from longer term storage or higher clinical doses are taken by patients, or information comes to hand indicating that the toxicity of any of the leachables is greater than assumed for this risk assessment, the safety of the leachables should be re-assessed.

Nonclinical summary and conclusions

Symbicort Rapihaler contains povidone, macrogol 1000 and apaflurane as excipients. Doses of these excipients at the maximum recommended dose are increased up to sixfold relative to the currently registered Symbicort Rapihaler formulations, due to a sixfold increase in the maximum recommended number of actuations per day, from 4 with the current formulations to 24 with the proposed new strengths. However, greater doses of these excipients are provided by another currently registered non-AstraZeneca product. Moreover, the animal data from the previous submission and from the newly submitted studies in rats and dogs (6–24 months in duration) in the current submission did not show toxicities attributable to the excipients, at doses equivalent to or greater than at the maximum recommended clinical dose of the proposed formulations. Therefore, there is not likely to be any significant risk to patients due to the increased exposure to these excipients arising from the use of the newly proposed strengths.

The change in formulation and the increased number of actuations has also resulted in changes to the doses and profile of the leachables, necessitating a revision of their risk assessment. The estimated maximum daily exposures to all the leachables (including the unidentified or partially identified chemicals) were low, and based on the available information, their presence raises no toxicological concerns at the detected levels, that is, they are considered unlikely to induce toxic effects with clinical use of the Symbicort Rapihaler products.

There were no nonclinical objections to the approval of the new strengths and the extension of indications for Symbicort Rapihaler.

However, if higher levels of the leachables are detected from longer term storage or higher clinical doses are taken by patients, or information comes to hand indicating that the toxicity of any of the leachables is greater than assumed for this risk assessment, the safety of the leachables should be re-assessed.

IV. Clinical findings

Introduction

Symbicort Turbuhaler (100/6, 200/6, 400/12) and Symbicort Rapihaler (100/6, 200/6) are currently registered in Australia. Symbicort Turbuhalers 100/6 and 200/6 are both approved for the alternative asthma regimens of "maintenance and reliever therapy" and "maintenance therapy" in adults and adolescents (12 years and older), while Symbicort Turbuhaler 400/12 is approved for asthma "maintenance therapy" in adults (18 years and older). Symbicort Rapihalers 100/6 and 200/6 are currently both approved for asthma "maintenance therapy" in adults and adolescents (12 years and older) and the currently approved Symbicort Rapihaler PI states that the product "is not indicated for relief of acute symptoms, for which a short acting bronchodilator is required". The sponsor stated that Symbicort Rapihalers 100/6 and 200/6 were approved by the TGA in 2006 by demonstrating therapeutic equivalence to Symbicort Turbuhalers 100/6 and 200/6.

The approved doses of Symbicort Rapihaler (100/6, 200/6) for "maintenance therapy" of asthma in adults and adolescents (aged 12 and over) do not match the approved doses of Symbicort Turbuhaler (100/6, 200/6) (Table 5). The reason for these differences is that doses of Symbicort Rapihaler should always be given in multiples of two actuations to ensure adequate dose uniformity, while Symbicort Turbuhaler can be given as single inhalations. Consequently, the approved Symbicort Rapihaler 100/6 and 200/6 strengths cannot substitute for the approved Symbicort Turbuhaler 100/6 and 200/6 strengths where one inhalation of the Turbuhaler is approved (that is, certain doses of "maintenance therapy", or "maintenance and reliever therapy"). The two new Symbicort Rapihaler lower strengths of 50/3 and 100/3 were proposed to improve dosing flexibility and allow Symbicort Rapihaler to deliver the same dose range and treatment regimens for asthma as that approved for Symbicort Turbuhaler 100/6 and 200/6 in adults and adolescents (aged 12 and over).

Table 5: Dosages comparison between Symbicort Turbuhaler (100/6 and 200/6) and Symbicort pMDI (50/3, 100/3, 100/6 and 200/6).

Asthma Indication, Treatment Regimens:	**Symbicort Turbuhaler 100/6 and 200/6**	**Symbicort pMDI 100/6 and 200/6**	**Symbicort pMDI 50/3 and 100/3**
	Approved Dosages	***Approved Dosages***	***Proposed Dosages#***
Symbicort maintenance therapy	1-2 inhalations twice daily	2 actuations twice daily	**2** or 4 actuations twice daily
Symbicort maintenance and reliever therapy	*Maintenance dose:* 1-2 inhalations twice daily or 2 inhalations daily *As needed dose:* 1 inhalation	N/A	*Maintenance dose:* **2** or 4 actuations twice daily or 4 actuations daily *As needed dose:* **2** actuations
	Total daily dose of up to 12 inhalations can be used temporarily.		Total daily dose of up to 24 actuations can be used temporarily.

2 or 4 actuations of Symbicort Rapihaler 50/3 = 1-2 inhalations of Symbicort Turbuhaler 100/6;
2 or 4 actuations of Symbicort Rapihaler 100/3 = 1-2 inhalations of Symbicort Turbuhaler 200/6

The clinical documentation provided in the Australian submission is based on that submitted in 2008 in another major market, and as a consequence documents referred to patient populations (that is, paediatric use) which were not approved for Symbicort Turbuhaler in Australia.

The application submitted in the other major market included five studies (pivotal therapeutic equivalence studies – SD-039-0681 and SD-039-0682; pivotal long term safety Study SD-039-0715 and two supportive biopharmaceutic studies – SD-039-0626 and SD-039-0730) supporting approval of Symbicort Rapihaler 100/6 and 200/6 which were not physically provided in the current Australian submission. However, these studies were previously evaluated as part of the original Symbicort Rapihaler (100/6 and 200/6) application which was cross-referenced by the sponsor in this submission.

The three clinical studies which had not previously been evaluated by the TGA were physically provided in the current submission (D5897C00003 [hereinafter referred to as 003], D5897C00004 [004], and D5897C00005 [005]). Eformoterol was referred to as formoterol in the submitted studies.[4] The Australian approved term is eformoterol and this has been used throughout the clinical evaluation report, apart from where direct quotations are provided from documents using the term formoterol. Symbicort strengths were expressed as *delivered* doses, while in Australia Symbicort strengths Symbicort are expressed as *metered* doses. The metered and delivered dose equivalents for each strength of Symbicort pMDI/Turbuhaler are outlined in *Section II* (Table 2).

The sponsor applied for approval of two new strengths of Symbicort Rapihaler (50/3 and 100/3) and submitted three new clinical studies in support of its application [studies 003, 004, 005] in addition to cross-referencing to earlier clinical studies evaluated by the TGA as part of the initial Symbicort Rapihaler submission [for example, Studies 681, 682, 715, 626 and 730].

Study 003 (Phase III) was considered to be the pivotal efficacy and safety study supporting approval of the Symbicort Rapihaler 50/3. The secondary objectives of this study included a therapeutic equivalence analysis of Symbicort pMDI 40/2.25 [50/3] µg two actuations bd (n=253) and Symbicort Turbuhaler 80/4.5 [100/6] µg one inhalation bd (n=245) over a 6 week treatment period in adolescents and adults with asthma. However, the study did not compare Symbicort 40/2.25 [50/3] µg and Symbicort Turbuhaler 80/4.5 [100/6] µg

as reliever therapy on an "as needed" basis. Instead, patients used short acting β_2-agonists as reliever (that is, rescue) medication when experiencing asthma symptoms. Consequently, it was considered that this therapeutic equivalence study can only be used to support Symbicort Rapihaler 50/3 for "maintenance therapy" and not for "maintenance and reliever therapy".

Study 004 (Phase III) was considered not to be directly relevant to the submission as it included efficacy and safety data on Symbicort pMDI 40/2.25 [50/3] μg administered with (n=55) and without (n=52) spacer over a 4 week treatment period to children with asthma aged 6 to 11 years.

Study 005 (Phase I) was considered to be of marginal relevance to the submission. It compared the safety of the maximum recommended dose in adults (that is, delivered dose 1280/36 μg [metered dose 1600/48 μg]) in young healthy adults (n=30) treated with Symbicort pMDI 80/2.25 μg [100/3] eight actuations bd and Symbicort Turbuhaler 160/4.5 μg [200/6] four inhalations bd with each treatment being administered for 7.5 days in a cross-over design. It was considered that the submission did not include pivotal or adequate supportive studies to support approval of the Symbicort Rapihaler 100/3.

The sponsor also applied for approval of a new maximum dose maintenance treatment regimen in adults (age 18 and over) for the approved Symbicort Rapihaler 200/6. In support of this new maximum regimen the sponsor relied on a previously submitted "single dose" systemic bioavailability study in healthy subjects (n=28) [Study 730]. However, it was considered that this study cannot support approval of the proposed new maximum dose of Symbicort Rapihaler 200/6 in adults with asthma. It was considered that the submission does not include pivotal or adequate supportive studies to support approval of the new maximum dose of Symbicort Rapihaler 200/6 in adults with asthma.

There are three TGA-adopted EU guidelines of particular relevance to this application.[8,10,11] It is important to note that the guideline on clinical documentation requirements was updated during the evaluation.[9,10]

Pharmacokinetics/Pharmacodynamics

No new data were provided in the submission.

Efficacy

Introduction

The submission included two new efficacy studies [003, 004] not previously evaluated by the TGA.

Study 003 was considered by the evaluator to be the pivotal study physically provided in the submission. It was a Phase III, therapeutic equivalence study comparing Symbicort pMDI 40/2.25 [50/3] μg two actuations bd (n=253) and Symbicort Turbuhaler 80/4.5 [100/6] μg one inhalation bd (n=245) over a 6 week treatment period in adults and adolescents with asthma. In this study, demonstration of therapeutic equivalence of the two treatment regimens was a secondary objective, while the primary objective was to demonstrate that Symbicort pMDI 40/2.25 [50/3] μg two actuations bd was more efficacious than Pulmicort Turbuhaler 100 μg one inhalation bd. The other secondary objective was to compare the safety profiles of Symbicort pMDI 40/2.25 [50/3] μg two

[11] EMEA, Committee for Proprietary Medicinal Products (CPMP), 21 November 2002. Note for guidance on the clinical investigation of medicinal products in the treatment of asthma (CPMP/EWP/2922/01).

actuations bd, Symbicort Turbuhaler 80/4.5 [100/6] μg one inhalation bd and Pulmicort Turbuhaler 100 μg one inhalation bd.

Study 004 was a Phase III, randomized, open label study of 4 weeks duration in which the primary objective was to show that Symbicort pMDI 40/2.25 [50/3] μg four actuations bd with spacer (n=55) and without spacer (n=52) had similar systemic steroid potencies in children aged 6 to 11 years with asthma. The secondary objectives were to compare the clinical efficacy and safety of Symbicort pMDI 40/2.25 [50/3] μg four actuations bd, with or without spacer.

In addition to the efficacy evaluation of Study 003 and Study 004, this section also reviews the argument submitted by the sponsor to support approval on a new maximum dose of Symbicort Rapihaler 200/6 in adults aged 18 years and older.

Study 003 – Therapeutic Equivalence Study – Symbicort pMDI 40/2.25 [50/3] μg

The primary objective was to show that Symbicort pMDI 40/2.25 [50/3] μg two actuations bd was more efficacious than Pulmicort Turbuhaler 100 μg one inhalation bd over a 6 week treatment period in adults and adolescents with asthma. The secondary objectives were to compare the efficacy of Symbicort pMDI 40/2.25 [50/3] μg two actuations bd with that of Symbicort Turbuhaler 80/4.5 [100/6] μg one inhalation bd over a 6 week treatment period in adults and adolescents with asthma, and to investigate the safety profile of Symbicort pMDI 40/2.25 [50/3] μg two actuations bd, Symbicort Turbuhaler 80/4.5 [100/6] μg one inhalation bd and Pulmicort Turbuhaler 100 μg one inhalation bd.

The study was conducted in 4 European countries: Poland (22 centres), Hungary (17 centres), Czech Republic (13 centres), and Bulgaria (11 centres). The study was approved in each of the 4 countries by independent ethics committees, and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP). Informed consent was obtained from adult patients and from parents/legal guardians of adolescents.

The study was Phase III, multinational, multicentred, randomised, double dummy, active controlled and parallel group in design. It consisted of an initial, 2 week, run-in period in which patients continued their regular inhaled glucocorticoid steroid at the same dose (200 to 500 μg/day) until randomization. Following the run-in period, patients were randomized using a centralized computerized schedule to one of three treatments and started a 6 week, double blind, treatment period comparing the efficacy and safety of Symbicort pMDI 40/2.25 [50/3] μg (n=253) two actuations bd with Pulmicort Turbuhaler 100 μg (n=243) one inhalation bd and Symbicort Turbuhaler 80/4.5 [100/6] μg (n=246) one inhalation bd. A double dummy technique was used to achieve blinding. However, patients only received two (one of which was placebo) of three devices to reduce inconvenience. Bricanyl (terbutaline) Turbuhaler was provided as rescue medication. However, other short acting β_2-agonists were allowed as long as the same brand and strength was used throughout the study. Short acting β_2-agonists rescue medication was used as reliever medication for asthma symptoms and not for prophylaxis. The restricted and allowed medications are considered to be satisfactory for a study of this type.

The study included adults and adolescents (aged 12 years and above) with asthma defined according to the American Thoracic Society (ATS) criteria, clinically diagnosed at least 6 months prior to Visit 2. Subjects were also required to have a pre-bronchodilator forced expiratory volume in one second (FEV_1) ≥ 50% and ≤ 90% of predicted normal. Asthma treatment had to be stable before the study and during the run-in period. At randomization, total asthma symptom score (night-time plus daytime) was required to be >1 on at least 4 (any of the last 7) days of the run-in period, not including the morning recording at Visit 3. Asthma symptom scores were:

0 = no asthma,

1 = you are aware of your asthma symptoms but you can easily tolerate the symptoms,

2 = your asthma is causing you enough discomfort to cause problems with normal activities, or with sleep,

3 = you are unable to do your normal activities, or to sleep because of your asthma.

Overall, the inclusion criteria were designed to select a group of patients not adequately controlled on inhaled glucocorticosteroids alone and for whom treatment with an inhaled glucocorticosteroid in combination with a long acting β_2-agonist was considered to be appropriate.

Primary efficacy variable

The primary efficacy variable was the change in morning peak expiratory flow (mPEF) from baseline (mean of the 10 last days of the run-in period) to the treatment period (mean of the 6 week treatment period). The primary efficacy objective was the comparison of Symbicort pMDI 40/2.25 [50/3] μg two actuations bd and Pulmicort Turbuhaler 100 μg one inhalation bd and was assessed by the change in mPEF. The assessment was in the full analysis set using an analysis of variance (ANOVA) model with treatment and country as fixed factors, and the run-in mean as a covariate. The significance of the difference was assessed by p-values (two-sided), with values < 5% being considered significant, and 95% confidence intervals (CI).

PEF was recorded at home using a Mini-Wright PEF meter with patients instructed to record their PEF twice daily (morning and evening) with the highest value at each occasion being recorded in a diary. The mPEF measurement was done immediately on rising, after the patient had cleared mucus and before inhaling the morning dose of the investigational product. The evening measurement was done just before going to bed and before inhaling the evening dose of the investigational product. Patients were instructed to take their measurements while standing.

Secondary efficacy variables

The secondary efficacy objective was a comparison between Symbicort pMDI 40/2.25 μg [50/3] two actuations bd and Symbicort Turbuhaler 80/4.5 [100/6] μg one inhalation bd and was assessed by determining therapeutic equivalence. The 95% CI for the difference in mPEF was compared with the equivalence limits of ± 15 L/min. Non-inferiority (NI) was considered established if the lower limit of the 95%CI of the difference between Symbicort pMDI and Symbicort Turbuhaler was > -15 L/min. Therapeutic equivalence was considered established if the 95% CI of the difference in mPEF was contained entirely within the equivalence limits ± 15 L/min.

There were a number of secondary efficacy variables assessed as the change from baseline (mean of the 10 last days of the run-in period) to the treatment period (mean of the 6 week treatment period). These were:

- evening PEF (ePEF);
- asthma symptom score, day, night and total;
- percentage of nights with awakenings due to asthma symptoms;
- use of rescue medication, day, night and total;
- percentage of symptom free days (a night and day with no asthma symptoms, no awakenings due to asthma symptoms);
- percentage of asthma control days (a night and day with no asthma symptoms, no use of rescue medication, and no awakenings due to asthma symptoms);

- percentage of rescue free days; and
- FEV_1.

The FEV_1 was measured in the clinic and all other secondary efficacy variables were assessed by individual patients and recorded in their diary. Nominal p-values were reported for secondary variables and no adjustment for multiplicity was performed. The significance level for the p-value was < 5% (two-sided).

Statistical considerations

It was calculated that a sample size of 200 patients in each group would give a power of 90% to detect a true difference in mean change in mPEF of 13 L/min between Symbicort pMDI 40/2.25 [50/3] μg two actuations bd and Pulmicort Turbuhaler 100 μg one inhalation bd (the primary efficacy objective), assuming a standard deviation of 40 L/min. It was also calculated that a sample size of 200 patients in each group, assuming a standard deviation of 40 L/min, would give a power of 90% to find that the 95% CI for the difference in mPEF between Symbicort pMDI 40/2.25 [50/3] μg two actuations bd and Symbicort Turbuhaler 80/4.5 [100/6] μg one inhalation bd (the secondary efficacy objective) would be contained within the equivalence limits ± 15 L/min, given that the true mean difference is less than 1.5 L/min.

The "full analysis" set was used in all efficacy analyses. The full analysis set consisted of all randomized patients with data after randomization. No patients were excluded from the full analysis set due to protocol deviations. However, a stability analysis ("per protocol" analysis) was performed for the secondary objective of establishing therapeutic equivalence in mPEF between the two Symbicort treatments. This analysis used a "per protocol" set which included all randomized patients not violating any inclusion or exclusion criterion at study entry. The "safety analysis" set comprised all patients that took at least one dose of the investigational medicine.

The average value for the run-in period was calculated using all available data for the 10 last days before randomization and the average value for the treatment period was calculated using all available data after randomization. No imputation of missing data was performed for calculation of the averages. The period average for the sum of morning and evening measurements was calculated as the sum of the average of morning measurements and the average of evening measurements. For dichotomous variables (nights with awakenings due to asthma symptoms, symptom free days, asthma control days) the period averages were expressed as percentages (of the total number of days).

Where efficacy data were plotted, daily mean values of diary variables were calculated with imputation for missing data according to the following method applied to the run-in and the treatment periods separately. Missing data between the first and last entry was estimated using linear interpolation. Missing data after the last entry was estimated using the average of the last three days. Missing data before the first entry was estimated using the average for the first three days. These imputations were applied with the intention of reducing some of the day to day variability in mean values and to reduce possible bias introduced by withdrawals.

Subjects

The first patient was enrolled on 14 September 2007 and the last patient completed the study on 2 April 2008. A total of 898 patients were enrolled and of these 742 were randomized and 728 completed the study (Table 6). Of the randomized patients, 14 discontinued prematurely and discontinuations were similar in the three treatment groups. There were 53 patients randomized to one of the three treatment groups with a major protocol deviation. The most common major protocol deviation was inclusion of patients who failed to satisfy the inclusion and/or exclusion criteria (37 patients), with the other two major protocol deviations being failure to use the investigational product as

required (6 patients) and concomitant use of prohibited medications (10 patients). The pattern of major protocol deviation was similar for three treatment groups. No patients were excluded from the primary analysis because of these protocol deviations.

Table 6: Study 003 – Subject disposition

	Symbicort pMDI	Pulmicort Turbuhaler	Symbicort Turbuhaler	All
Enrolled patients				**898**
Not randomised				**156**
-Incorrect enrolment				**94**
-Adverse event				**9**
-Voluntary discontinuation by patient				**18**
-Patient lost to follow-up				**1**
-Severe non-compliance to protocol				**1**
-Intake of prohibited concomitant medication				**1**
-Other				**32**
Randomised	253	243	246	**742**
Discontinued	4	5	5	**14**
-Adverse event	3	3	2	**8**
-Voluntary discontinuation by patient	0	0	2	**2**
-Safety reasons	0	1	0	**1**
-Intake of prohibited concomitant medication	0	1	0	**1**
-Other	1	0	1	**2**
Completers	249	238	241	**728**

All 742 randomized patients were included in an "intention to treat" (ITT) analysis of efficacy. However, the "full analysis" set (all randomized patients with data after randomization) included 741 patients as 1 patient (Symbicort Turbuhaler) discontinued 6 days after randomization without efficacy data being recorded in the diary. The "stability" (per protocol) analysis included 712 randomized patients. The safety data set consisted of 742 patients (patients who took at least one dose of study medication and for whom safety data were collected after randomisation).

Of the 742 randomized patients, 317 (43%) were male and 425 (57%) were female. All patients were White and the average age was 40.7 (range: 12-78) years. Median time since asthma diagnosis was 7 (range: 1-56) years. Of the 742 patients, 104 (14%) were aged 12-17 years, 591 (80.0%) were aged 18-64 years, and 47 (6%) were aged ≥ 65 years. All 742 patients had used inhaled glucocorticosteroid prior to study entry with the average daily dose being 388 (range: 160-500) µg and the most common dose being 400 µg in 339 (46%) patients. Long acting β_2-stimulants had been used by 452 (61%) patients prior to study entry. Overall, the disease and demographic characteristics were similar among the three treatment groups. The mean FEV_1 at the start of the run-in period (Visit 2) in the 742 randomized patients was 2.3 (range: 0.99, 4.32) L and the mean percentage of the predicted normal FEV_1 value was 73.5 % (range: 50, 90). During the last 10 days of run-in, all patients had asthma symptoms, 83 (11%) patients did not use any rescue medication and 182 (25%) patients did not experience any night-time awakenings due to asthma.

At study entry the most common (≥ 5% of all patients) diagnoses other than asthma in the 742 randomized patients were allergic rhinitis (32%), hypertension (17%), perennial rhinitis (8%), gastroesophageal reflux disease (5%) and allergic conjunctivitis (5%). Overall, the distribution of disease type at study entry was similar among the three

treatment groups. At study entry, 81% of the 742 randomized patients were taking inhaled short acting β_2-agonists, 70% were taking glucocorticosteroids, 32% were taking inhaled combinations of long acting β_2-agonists and glucocorticosteroids, and 30% were taking long acting β_2-agonists. All other asthma medications were being taken by ≤ 5% to ≥ 2% of patients (that is, xanthines, combination β_2-agonist and anticholinergic, leukotriene receptor agonist, antihistamines, piperazines, allergen extracts, anticholinergics). After randomization and before the last dose, 97% of the 742 randomized patients used inhaled short acting β_2-agonists, 16% used piperazine derivatives, 10% used nasal corticosteroids, 9% used ACE inhibitors, and 6% used combination progestogens and oestrogens. Self reported compliance with study medication was high with, on average, 97% of patients reporting taking their medication.

Efficacy results

The primary efficacy objective was to show that Symbicort pMDI 40/2.25 [50/3] µg two actuations bd was more efficacious than Pulmicort Turbuhaler 100 µg one inhalation bd over a 6 week treatment period in adolescents and adults with asthma as assessed by change in mPEF. The adjusted mean mPEF increased by 12.2 L/min with Symbicort pMDI, 4.15 L/min with Pulmicort Turbuhaler and 13.1 L/min with Symbicort Turbuhaler. The results showed that the mean change from baseline in mPEF was greater with Symbicort pMDI than with Pulmicort Turbuhaler, and that the mean difference was statistically significant (Table 7).

Table 7: Study 003 – Primary efficacy objective (superiority of Symbicort pMDI compared with Pulmicort Turbuhaler), results for change in morning peak expiratory flow (mPEF) L/min (ITT analysis)

		Run-in (baseline)		Treatment			
Treatment	n	Mean	Range	Mean	Range	Adjusted Mean Change *	p-value
Symbicort pMDI	253	347	149, 736	360	145, 797	8.07 [95% CI: 3.26, 12.9]	0.001
Pulmicort Turbuhaler	243	351	156, 644	356	147, 623		

* ANOVA adjusted mean change from baseline.

The secondary efficacy objective was to compare the efficacy of Symbicort pMDI 40/2.25 [50/3] µg two actuations bd with that of Symbicort Turbuhaler 80/4.5 [100/6] µg one inhalation bd over a 6 week treatment period in adolescents and adults with asthma. The results for the change in mPEF showed that the two treatments were therapeutically equivalent as the 95% CI of -5.73 to 3.88 L/min for the mean difference between treatments of -0.921 L/min was within the pre-specified equivalence interval of ±15 L/min (Table 8). The results for the per protocol analysis showed that the adjusted mean difference between Symbicort pMDI (12.3 L/min) and Symbicort Turbuhaler (13.92 L/min) was -1.5 L/min [95%CI: -6.4, 3.4] with the 95% CI being within the pre-specified equivalence interval of ±15 L/min.

Table 8: Study 003 – Secondary objective (equivalence of Symbicort pMDI and Symbicort Turbuhaler), results for change in morning peak expiratory flow (mPEF) L/min (ITT analysis)

		Run-in (baseline)		Treatment			
Treatment	n	Mean	Range	Mean	Range	Adjusted Mean Change *	p-value
Symbicort pMDI	253	347	149, 736	360	145, 797	-0.921 [95%CI: -5.73, 3.88]	0.707
Symbicort Turbuhaler	245	347	177, 630	372	190, 672		

* ANOVA adjusted mean change from baseline.

The time profiles for the daily mean mPEF for the three treatments (Symbicort pMDI, Symbicort Turbuhaler, Pulmicort Turbuhaler) showed a greater increase for both Symbicort pMDI and Symbicort Turbuhaler compared with Pulmicort Turbuhaler. The mPEF curves showed that the increase was immediate with each of the three treatments and was stable over time.

The results for the change from baseline in the FEV_1 showed no statistically significant differences for the pairwise comparisons between the three treatment groups with mean values increasing slightly in all three groups. The results for the change from baseline in evening PEF showed that both Symbicort treatments were statistically significantly superior to Pulmicort Turbuhaler, while the difference between Symbicort treatments was not statistically significant. The results for the asthma symptom scores showed no statistically significant difference between the two Symbicort treatments, while the difference between Symbicort Turbuhaler and Pulmicort Turbuhaler were statistically significant for all four variables (Symbicort Turbuhaler superior) and the difference between Symbicort pMDI and Pulmicort Turbuhaler were statistically significant for three of the four variables (Symbicort pMDI superior). The results for use of rescue medication showed no statistically significant difference between the two Symbicort treatments, while the differences between Symbicort Turbuhaler and Pulmicort Turbuhaler were statistically significant for two of the three variables (Symbicort Turbuhaler superior) and the difference between Symbicort pMDI and Pulmicort Turbuhaler were statistically significant for all three of the variables (Symbicort pMDI superior). The results for the derived variables showed no statistically significant difference between the two Symbicort treatments, while the differences between Symbicort Turbuhaler and Pulmicort Turbuhaler were statistically significant for all three variables (Symbicort Turbuhaler superior) and the differences between Symbicort pMDI and Pulmicort Turbuhaler were statistically significant for one of the three variables (Symbicort pMDI superior).

Evaluator comment

This was a good quality study. However, the evaluator considered that it supported Symbicort pMDI 40/2.25 [100/3] for "maintenance therapy" only. Neither Symbicort pMDI nor Symbicort Turbuhaler were used "as needed" for relief of asthma symptoms. Instead, short acting β_2-agonists were used to relieve asthma symptoms in all three treatment groups. Consequently, it was considered that the study has not demonstrated therapeutic equivalence of Symbicort pMDI 40/2.25 [50/3] μg and Symbicort Turbuhaler 80/4.5 [100/6] μg for "maintenance and reliever" therapy.

The study showed that Symbicort pMDI 40/2.25 [50/3] μg two actuations bd was more efficacious than Pulmicort Turbuhaler 100 μg one inhalation bd over a 6 week treatment period in adolescents and adults with asthma as assessed by mPEF (primary efficacy

objective). The 6 week double blind treatment duration is considered to be acceptable for demonstration of therapeutic equivalence. The TGA-adopted regulatory guideline recommends that equivalence studies for inhaled glucocorticosteroids should be a minimum of 6-8 weeks.[118] However, the same guideline suggests that therapeutic equivalence studies should collect safety data for a minimum observation period of 3 months. It is noted that the previously submitted therapeutic equivalence Study 681 [Symbicort Rapihaler 200/6 (2 inhalations bd) compared to Pulmicort pMDI (200μg; 2 inhalations bd) and Symbicort Turbuhaler 200/6 (2 inhalations bd)] was of 12 weeks duration.

The difference in mPEF between Symbicort pMDI 40/2.25 [50/3] μg two actuations bd and Pulmicort Turbuhaler 100 μg one inhalation bd was about 8 L/min. This figure was lower than the 13 L/min difference specified in the sample size calculations. This raises doubts about the clinical significance of a mPEF difference of 8 L/min as, presumably, the sponsor selected a figure of 13 L/min for the sample size calculations because it was considered to be clinically meaningful. Furthermore, in the previously submitted Study 681 in a similar patient population the difference in the mPEF between Symbicort pMDI 160/4.5 [200/6] μg two actuations bd and Pulmicort Turbuhaler 200 μg two actuations bd was 28.6 L/min [95%CI: 20.9, 36.4], with the difference favouring Symbicort pMDI. In addition, the difference in FEV_1 in Study 681 also statistically significantly favoured Symbicort pMDI 160/4.5 [200/6] μg over Pulmicort Turbuhaler 200 μg (difference 0.21 [95%CI: 0.135, 0.279]). The difference between Study 681 and Study 003 in lung function outcomes might be due to the higher delivered dose of both eformoterol and budesonide in Study 681 compared with Study 003 (eformoterol 18 versus 9 μg, and budesonide 640 vs 160 μg) and the longer duration of treatment in Study 681 compared with Study 003 (12 weeks vs 6 weeks).

Most secondary efficacy variables supported the superiority of Symbicort pMDI 40/2.25 [50/3] μg two actuations bd over Pulmicort Turbuhaler 100 μg one inhalation bd. Symbicort pMDI increased evening PEF, reduced total daily asthma symptoms, night-time asthma symptoms, and awakenings due to asthma symptoms, and increased the number of rescue free days and decreased the total use of rescue medication compared to Pulmicort Turbuhaler (all differences statistically significant). No statistically significant differences were observed in symptom free days (main symptom variable), daytime symptoms, asthma control days or FEV_1. There is inconsistency between the results for lung function as assessed by mPEF (Symbicort pMDI statistically significantly superior to Pulmicort Turbuhaler) and FEV_1 (no statistically significant difference between the two treatments). The sponsor argued that this discrepancy might be explained by the longer duration between the previous (evening) dose and FEV_1 measurement (which took place in a clinic rather than at home after rising) and by the lower dose of eformoterol (4.5 μg per dosing occasion compared with 9 μg).

The study showed that Symbicort pMDI 40/2.25 [50/3] μg two actuations bd and Symbicort Turbuhaler 80/4.5 [100/6] μg one inhalation bd over a 6 week treatment period in adolescents and adults were therapeutically equivalent as assessed by mPEF (secondary efficacy objective). The results showed equivalence of the two Symbicort treatments in both the ITT and per protocol analyses. The sponsor indicated that the pre-specified equivalence limits of ±15 L/min were also applied in the previously submitted therapeutic equivalence Study 681 to support the original approval of Symbicort Rapihaler. The equivalence interval of ±15 L/min for mPEF has also been used in a published paper to support the equivalence of salmeterol/fluticasone (50/100 μg bd) administered by CFC-free inhaler or dry powder inhaler to patients with mild to moderate

asthma [Bateman *et al*, 2001].[12] The equivalence interval of ±15 L/min for mPEF has also been used in a published paper comparing salmeterol (Diskus salmeterol inhaler) and fluticasone (Diskus fluticasone inhaler) given concurrently with a combination product (Diskus Seretide Inhaler) in children with asthma [Van den Berg *et al*., 2000].[13] Overall, the available data indicate that the selected equivalence limit of ±15 L/min for the mPEF is clinically acceptable. Support for the therapeutic equivalence of the two Symbicort products comes from analyses of the other secondary efficacy variables which consistently showed no statistically significant difference between the two products. The study did not compare the therapeutic equivalence of Symbicort pMDI and Symbicort Turbuhaler for "maintenance and reliever" therapy as reliever medications were short acting β2-agonists rather than the Symbicort products.

Study 004 – Symbicort pMDI 40/2.25 [50/3] μg – With and Without Spacer in Children

The primary objective of Study 004 was to show that Symbicort pMDI 40/2.25 [50/3] μg four actuations bd with spacer had similar systemic steroid potency as Symbicort pMDI 40/2.25 [50/3] μg four actuations bd in children with asthma. The secondary objectives were to compare the clinical efficacy and safety of Symbicort pMDI 40/2.25 [50/3] μg four actuations bd, with or without spacer in children with asthma.

The study was conducted in Poland (7 centres), Hungary (3 centres) and Russia (2 centres). It was approved in each of the 3 countries by independent ethics committees and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines. Informed consent was obtained from adult patients and from parents/legal guardians of adolescents.

The study was Phase III, multinational, multicentred, randomised, open label and parallel group in design in children aged 6 to 11 years with symptomatic asthma despite regular use of inhaled glucocorticosteroids. It consisted of a 2 week run-in period in which patients were treated with Pulmicort pMDI 100 μg two actuations bd. On completion of the 2 week run-in period, patients were randomized (1:1) to 4 weeks treatment with either Symbicort pMDI 40/2.25 [50/3] μg four actuations bd with or without a spacer (AeroChamber Plus, valved holding centre [VHC]). Patients used their own short acting β_2-agonist as reliever medication. The pre-study treatment restrictions were similar to those in Study 003 as were the medications not allowed and allowed during the study.

The study included children aged 6 to 11 years with asthma diagnosed according to the American Thoracic Society definition [ATS, 1987] at least 6 months prior to the start of the run-in period.[14] The inclusion criteria were designed to select a group of children in whom treatment with inhaled CGS and long acting β_2-agonist was considered appropriate according to asthma guidelines [GINA, 2007].[15] The inclusion criteria prior to the run-in period included a PEF ≥ 50% of predicted normal (pre-bronchodilator) and daily use of inhaled glucocorticosteroid (any brand) for ≥ 3 months. The inclusion criteria at

[12] Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 μg bd) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. Respir Med 2001; 95: 136-46.

[13] Van den Berg NJ et al. Salmeterol/fluticasone propionate (50/100 μg) in combination in a Diskus inhaler (Seretide) is effective and safe in children with asthma. Pediatr Pulmonol 2000; 30: 97-105.

[14] ATS: Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, November 1986. Am Rev Respir Dis 1987; 136: 225-44.

[15] GINA: Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Revised edition 2007. The GINA reports are available on www.ginasthma.org.

randomisation included a mean mPEF of 50% to 80% of post-bronchodilator PEF at Visit 2 or 3, total asthma symptom score (night plus day-time) of ≥ 1 and stable asthma treatment during the run-in period.

Primary and secondary outcome variables

The primary outcome variable was a pharmacodynamic (safety) variable, namely 24 hour urinary free cortisol (UFC). The UFC was measured at baseline (Visit 3) and at Visit 5. The amount of creatinine in the 24 hour urine sample was also measured to "check the quality" of the collection. The urine was analysed by a central laboratory. During the collection period the children stayed in the clinic.

The secondary outcome variables were efficacy variables and included FEV_1, mPEF, ePEF, night-time awakenings due to asthma symptoms, use of reliever medication and asthma symptom score day and night. These secondary variables assessed the efficacy of both treatments as regards both pulmonary function (FEV_1 and PEF) and asthma symptoms.

Statistical considerations

As regards the primary efficacy variable, the UFC level at end of treatment was expressed as a percentage of the level at baseline and levels were compared by analysis of covariance (ANCOVA) following a log transformation. The ANCOVA model included fixed factors for treatment and country, and the logarithm of the baseline UFC level was used as a covariate. The ratio of treatment effects was obtained from the result of the ANCOVA and expressed as a percentage. A 95% CI for the ratio was also calculated along with a p-value for the difference between treatments. An analysis of the primary variable excluding erroneously included patients was made as a check of the stability of the results.

It was estimated that 50 patients per treatment group would give a power of 80% to detect a true difference of about 50% in UFC levels. This was based on a residual standard deviation of 0.7 on the logarithmic scale, two sided test and a significance level of 5%. Alternatively, the precision of the study would be such that the 95% CI for the ratio of treatment effects would extend from 76% to 132%. The study was not an equivalence trial. The sample size was not calculated to establish formal equivalence and the 76% to 132% confidence interval limits did not represent equivalence limits.

As regards the secondary efficacy variables, changes in FEV_1 (expressed in L and as percent of predicted normal) from baseline (Visit 3) to the mean value of Visit 4 and Visit 5 were analysed. For PEF and other electronic diary (eDiary) variables, changes from baseline, the average during the last 10 days before Visit 3 to the average of the whole treatment period, were analysed. Treatment differences were compared using ANCOVA with treatment and country as fixed factors and with the baseline value as a covariate, and 95% CIs were also calculated for the differences. All tests were two sided and p-values ≤ 0.05 were considered statistically significant. No statistical adjustment of the p-value was made for multiple testing.

The efficacy analyses were based on the “full analysis” set (FAS) which included all randomized patients with post randomization efficacy data. The analysis of the primary efficacy variable was based on 105 patients as all 107 randomized patients had on-treatment data but 2 lacked baseline data. A secondary analysis excluded 3 erroneously included patients and was thus based on 102 patients. All 107 patients were included in the safety analysis set.

Subjects

Of the 137 subjects enrolled, 107 were randomised (55 to Symbicort pMDI with spacer of whom all completed and 52 to Symbicort pMDI without spacer of whom all completed). The reasons for 30 of the enrolled patients not being randomised were failed inclusion criteria (n=26), patient's request (n=2), adverse event (n=1) and incorrect enrollment

(n=1). The first patient entered the study on 19 September 2007 and the last patient finished the study on 22 February 2008. Of the 107 patients randomised, none discontinued the study. All 107 patients were analysed for efficacy and safety in an "intention to treat" analysis.

Of the 107 randomized patients, 64 (59.8%) were males and 43 (40.2%) were females, average age was 8.8 (range: 6 to 11) years and all were White (Caucasians). The median time since diagnosis of asthma was 3.2 (range: 0.4 to 9.0) years. During the last 10 days of run-in, 33 (31%) patients used no rescue medication, all (100%) had asthma symptoms at least once and 33 (31%) had no nights with awakenings due to asthma. The two treatment groups were generally comparable, apart from baseline lung function as assessed by FEV_1 and mPEF which was better in the Symbicort pMDI without spacer group.

The most common (≥ 5%) current diagnoses (apart from asthma) were allergic rhinitis (44%), atopic dermatitis (9%), seasonal allergy (7%), conjunctivitis allergic (6%), perennial rhinitis (6%), and gastroesophageal reflux disease (5%). The most commonly (≥ 5%) prescribed medications at study entry were glucocorticosteroids (88%), inhaled short acting β_2-agonists (85%), inhaled long acting β_2-agonists (22%), leukotriene receptor antagonists (17%) and inhaled combinations of long acting β_2-agonists and glucocorticosteroids (16%). All patients had been treated with inhaled glucocorticosteroids prior to study entry with the mean dose being 441 (range: 375-800) μg. The most commonly (≥ 5%) used medications in the study after randomization were inhaled short acting β_2-agonists (97%), piperazine derivatives (24%), glucocorticosteroids (12%), other systemic antihistamines (11%) and corticosteroids (7%). There were no significant differences between the two groups as regards current diagnoses, prescribed medication at study entry and medications used after randomization. In general, compliance was good in both treatment groups (92.5% for Symbicort pMDI with spacer and 93.1% with Symbicort pMDI without spacer).

Results

Primary outcome variable (Pharmacodynamics/Safety)

The results for the 24 hour UFC for the two treatments are summarised in Table 9. The results showed that there was no statistically significant difference between the two treatment groups in change in 24 hour UFC levels. In the Symbicort pMDI with spacer group, the 24 hour UFC decreased by 6.4% and in the Symbicort pMDI without space group it increased by 7.6%. The ratio of the two treatments indicates that the 24 hour UFC level in the Symbicort pMDI with spacer group was 13% lower than in the Symbicort pMDI without spacer group.

Table 9: Study 004 – Results for the primary efficacy variable, 24-hour UFC levels

Treatment	Geometric mean ratio (adjusted)	95% confidence interval	p-value
Symbicort pMDI with spacer	0.936	(0.797, 1.099)	
Symbicort pMDI	1.076	(0.916, 1.264)	
Ratio	0.870	(0.713, 1.061)	0.1666

ANCOVA adjusted for baseline and country.

Safety

Overview of safety

The safety data have been evaluated for each of the three new studies [studies 003, 004, and 005]. The efficacy of *studies 003* and *004* have been considered above as both studies included efficacy and safety data. Study 005 has been considered exclusively under safety as it included no efficacy data but only safety data in healthy adult volunteers (n=30) exposed to the highest approved dose in adults (that is, metered dose budesonide/eformoterol of 1600/48 μg [delivered dose 1280/36 μg]).

Study 003

Exposure

This study has been outlined in *Efficacy.* The study included 742 randomized patients all of whom were evaluated for safety, and of whom only 14 (1.9%) discontinued. The exposure details of the three treatment groups are summarized in Table 10 and show that exposure parameters were similar for the three treatment group.

Table 10: Study 003 - Summary of exposure time in the safety population

		Symbicort pMDI n=253	Pulmicort Turbuhaler n=243	Symbicort Turbuhaler n=246
Exposure time (days)	Mean	42.1	41.8	41.8
	Median	42	42	42
	Range	12-62	8-71	6-60
	Total	10641	10169	10286

Adverse events

The overall summary of adverse events (AEs) is provided in Table 11. There was a higher percentage of patients in the Symbicort pMDI with at least one AE than in the Pulmicort Turbuhaler and Symbicort Turbuhaler groups (15%, 13%, 12%, respectively). Most of the AEs in the three treatment groups were considered to be mild and serious adverse events (SAEs) (fatal and non-fatal) were uncommon (only 2 reports, 1 each in the Pulmicort Turbuhaler and Symbicort Turbuhaler groups and none in the Symbicort pMDI group). Discontinuations due to AEs were also uncommon (9 [1%]) and occurred most frequently in the Pulmicort Turbuhaler group. AEs occurring in the study after administration of the first dose and classified by the MedDRA System Organ Class (SOC) are provided in Table 12.[16] The results were generally similar for each of the treatment groups with the most commonly affected organ system being *Infections and Infestations*.

[16] MedDRA = Medical Dictionary for Regulatory Activities

Table 11: Study 003 - Number (%) of patients who had an adverse event in any category and number of adverse events by category

	Symbicort pMDI n=253	Pulmicort Turbuhaler n=243	Symbicort Turbuhaler n=246	All n=742
Number (%) of patients who had an adverse event in each category[a]				
Any adverse events (AEs)	38 (15%)	31 (13%)	30 (12%)	**99 (13%)**
Serious adverse events (SAEs)				
SAEs leading to death	0	0	0	**0**
SAEs other than death	0	1 (<0.5%)	1 (<0.5%)	**2 (<0.5%)**
DAEs[b]	3 (1%)	4 (2%)	2 (1%)	**9 (1%)**
Other significant adverse events	0	0	0	**0**
Total number of AEs[c]				
Any AEs	43	39	36	118
Maximum intensity				
mild	34	27	26	**87**
moderate	9	10	8	**27**
severe	0	2	2	**4**
Max No. of AEs/patient	4	3	2	**4**
Causally related AEs[d]	1	5	2	**8**
SAEs (fatal and non-fatal)	0	1	1	**2**
Causally related SAEs (fatal and non-fatal)[d]	0	0	0	**0**
DAEs	3	5	2	**10**
Other significant adverse events	0	0	0	**0**

[a] Patients with multiple events in the same category are counted once in each category.
[b] Discontinuation of investigational product due to AEs.
[c] Multiple events with the same preferred term are counted once for each patient and category.
[d] As assessed by the investigator.
Note: Subject E0303011/276 had an AE that started during run-in (before randomisation) which became a DAE during treatment and is therefore not included in this table.

Table 12: Study 003 - Adverse events by System Organ Class (SOC)

System Organ Class	Symbicort pMDI n=253	Pulmicort Turbuhaler n=243	Symbicort Turbuhaler n=246	All n=742
Infections and infestations	30 (12%)	18 (7%)	20 (8%)	**68 (9%)**
Respiratory, thoracic and mediastinal disorders	3 (1%)	6 (2%)	6 (2%)	**15 (2%)**
Nervous system disorders	0	3 (1%)	2 (1%)	**5 (1%)**
Gastrointestinal disorders	3 (1%)	1 (<0.5%)	1 (<0.5%)	**5 (1%)**
Musculoskeletal and connective tissue disorders	3 (1%)	1 (<0.5%)	0	**4 (1%)**
Skin and subcutaneous tissue disorders	1 (<0.5%)	2 (1%)	1 (<0.5%)	**4 (1%)**
Cardiac disorders	0	2 (1%)	1 (<0.5%)	**3 (<0.5%)**
Eye disorders	0	2 (1%)	0	**2 (<0.5%)**
Vascular disorders	1 (<0.5%)	1 (<0.5%)	0	**2 (<0.5%)**
General disorders and administration site conditions	1 (<0.5%)	0	0	**1 (<0.5%)**
Surgical and medical procedures	0	0	1 (<0.5%)	**1 (<0.5%)**
Injury, poisoning and procedural complications	0	1 (<0.5%)	0	**1 (<0.5%)**
Metabolism and nutrition disorders	1 (<0.5%)	0	0	**1 (<0.5%)**

Number (%) of patients with AEs, sorted by decreasing order of frequency as summarised over all treatment groups.

The most frequently reported AEs occurring in at least 1% of patients by Preferred Term (PT) in the total population (n=742) were bronchitis (2%), pharyngitis (2%), nasopharyngitis (2%), viral infection (2%), asthma (2%) and viral upper respiratory tract infections (URTIs) (2%). Overall, the distribution of these AEs was similar in the three treatment groups. Examination of the AEs occurring with a frequency of less than 1% (n<1) in the treatment groups did not reveal any unusual AEs. The majority of AEs were rated as being mild in intensity (73.7%, 87/118) with only 4 AEs patients being rated as severe in intensity (3 asthma, 1 influenza). The only AEs considered to be causally related to treatment (as judged by the investigator) were dysphonia (2 events) and 1 event each of tremor, sinus tachycardia, pharyngolaryngeal pain, palpitations, headache and diabetes mellitus. Of the 8 patients with a causally related AE, 5 were in the Pulmicort Turbuhaler group, 2 in the Symbicort Turbuhaler group, and 1 in the Symbicort pMDI group. Overall, 3 patients reported a cardiac AE: 2/243 (0.8%) patients in the Pulmicort Turbuhaler group (1 palpitations and 1 sinus tachycardia); and 1/246 (0.4%) patient in the Symbicort Turbuhaler group (1 tachycardia).

No deaths were reported in the study. Serious AEs were reported in 2 patients (asthma in both patients with 1 in the Pulmicort Turbuhaler group and 1 in the Symbicort Turbuhaler group). There were 10 patients who discontinued due to AEs, 5 in the Pulmicort Turbuhaler group (3 asthma, 1 each headache and palpitations), 3 in the Symbicort pMDI group (1 bronchitis, 2 dyspnoea), and 2 in the Symbicort Turbuhaler group (2 asthma). Laboratory screening (clinical chemistry and haematology) and vital signs (pulse, blood pressure) were undertaken at Visit 2 (beginning of the run-in period) but not after start of treatment.

The incidence of AEs was similar in male and female subjects: 15% (n=15 m; n=23 f) in both sexes with Symbicort pMDI; 8% (n=9) and 17% (n=22) with Pulmicort Turbuhaler, respectively; and 13% (n=13) and 12% (n=17) with Symbicort Turbuhaler, respectively. Examination of the AEs by PT did not identify any clinically meaningful differences between the sexes in the AE profiles. The incidence of AEs in both Symbicort groups was higher in subjects aged 12 to 17 than in subjects aged 18-64 years. Examination of the AEs

by PT did not identify any clinically meaningful differences between the ages 12-17 years and 18-64 years. However, pharyngitis and viral URTIs occurred more frequently in the younger age group with Symbicort. The study included 104 (14.0%) subjects aged 12 to 17 years. The number of subjects in the study aged ≥ 65 years was relatively small (6.3%; 47/742). The total number of patients reporting AEs in the ≥ 65 year age group was small (n=6, 12.8%). Consequently, although examination of the AEs by PT did not give rise to concern in these elderly patients these findings should be interpreted cautiously.

Evaluator comment

All three treatments were well tolerated and no clinically meaningful differences were observed among the three treatment groups. No new safety concerns were observed with Symbicort pMDI 40/2.25 [50/3] µg two actuations bd. However, it was noted that the duration of this therapeutic equivalence study was only 6 weeks which was shorter than the recommended duration of 12 weeks for collection of appropriate safety data recommended in the relevant regulatory guidance document.[8]

Study 004

Exposure

This study has been outlined in *Efficacy*. In this study, 107 patients with a mean age of 8.8 (range: 6-11) years were randomized and evaluated for safety. The duration of exposure to Symbicort pMDI was similar in the two treatment groups (Table 13).

Table 13: Study 004 - Exposure duration

		Symbicort pMDI with spacer n=55	Symbicort pMDI n=52
Exposure time (days)	Mean	28.9	28.8
	Median	28	29
	Range	26-34	25-34
	Total	1588	1495

Adverse events

The number of patients reporting AEs was low in both treatment groups. The overall summary of AEs is provided in Table 14.

Table 14: Study 004 - Number (%) of patients who had an adverse event in any category, and number of adverse events by category, during treatment

	Symbicort pMDI with spacer n=55	Symbicort pMDI n=52	All n=107
Number (%) of patients who had an adverse event in each category[a]			
Any adverse events	5 (9%)	8 (15%)	13 (12%)
Serious adverse events (SAEs)			
SAEs leading to death	0	0	0
SAEs other than death	0	0	0
DAEs[b]	0	0	0
Other significant adverse events	0	0	0
Total number of adverse events[c]			
Any adverse events	6	10	16
Maximum intensity			
mild	6	9	15
moderate	0	1	1
severe	0	0	0
not assessed	0	0	0
Max No. of AEs/patient	2	3	3
Causally related AEs[d]	2	0	2
SAEs (fatal and non-fatal)	0	0	0
Causally related SAEs (fatal and non-fatal)[d]	0	0	0
DAEs	0	0	0
Other significant adverse events	0	0	0

Data derived from Appendix 12.2.7, Table 2.
[a] Patients with multiple events in the same category are counted once in each category.
[b] Premature discontinuation of treatment with investigational product due to an adverse event(s)
[c] Multiple events with the same preferred term are counted once for each patient and category.
[d] As assessed by the investigator.

AEs occurring in the study after administration of the first dose and classified by SOC are provided below in Table 15. The most commonly affected SOC was *Infections and Infestations* and AEs in this system were more common with Symbicort pMDI without spacer (12%) than with spacer (4%). Reported AEs in all other organ systems were similar for both treatment groups.

Table 15: Study 004 – All adverse events by system organ class (SOC)

System Organ Class	Symbicort pMDI with spacer n=55	Symbicort pMDI n=52	All n=107
Infections and infestations	2 (4%)	6 (12%)	8 (7%)
Nervous system disorders	1 (2%)	1 (2%)	2 (2%)
Respiratory, thoracic and mediastinal disorders	1 (2%)	1 (2%)	2 (2%)
Gastrointestinal disorders	0	1 (2%)	1 (1%)
Renal and urinary disorders	1 (2%)	0	1 (1%)
Ear and labyrinth disorders	1 (2%)	0	1 (1%)

The only AEs occurring in more than one patient in the total population were nasopharyngitis, headache, and viral upper respiratory tract infection (Table 16). Each of these AEs occurred in 2 (2%) patients. Both nasopharyngitis and viral URTI occurred in 2 (4%) patients in the Symbicort pMDI without spacer group compared with 0 patients in the with spacer group.

Table 16: Study 004 – All adverse events by preferred term (PT)

Preferred term	Symbicort pMDI with spacer n=55	Symbicort pMDI n=52	All n=107
Nasopharyngitis	0	2 (4%)	2 (2%)
Headache	1 (2%)	1 (2%)	2 (2%)
Viral upper respiratory tract infection	0	2 (4%)	2 (2%)
Urinary tract infection	1 (2%)	0	1 (1%)
Rhinitis	1 (2%)	0	1 (1%)
Nocturia	1 (2%)	0	1 (1%)
Diarrhoea	0	1 (2%)	1 (1%)
Influenza	0	1 (2%)	1 (1%)
Cough	1 (2%)	0	1 (1%)
Dysphonia	0	1 (2%)	1 (1%)
Bronchitis	0	1 (2%)	1 (1%)
Vertigo	1 (2%)	0	1 (1%)
Abdominal pain upper	0	1 (2%)	1 (1%)

Data derived from Appendix 12.2.7, Table 2.
Number (%) of patients with AEs, sorted by decreasing order of frequency as summarised over all treatment groups.

No AEs were rated as being of severe intensity. In the Symbicort pMDI with spacer group, 5 patients experienced 6 mild AEs. In the Symbicort pMDI without spacer group, 8 patients experienced 9 mild AEs and 1 patient experienced a moderate AE (nasopharyngitis). In only 2 patients were AEs considered to be causally related to treatments, as judged by the investigator, and both occurred in the Symbicort pMDI with spacer group (1 cough, 1 nocturia). No deaths or serious AEs were reported in the study. There were no reported cardiac AEs.

The only clinical laboratory test undertaken was urinalysis (glucose, haemoglobin and albumin) at baseline and after treatment. All urinalyses were negative for the three variables at baseline and at end of treatment for both treatment groups. There were no significant changes in pulse rate or blood pressure (systolic and diastolic) from baseline to treatment end for both treatment groups.

Evaluator comment

The safety data from this study raise no concerns. The number of AEs was low in both treatment groups and there were no reported SAEs, deaths or discontinuations due to AEs. There were no significant differences between the safety profiles of Symbicort pMDI 40/2.25 [50/3] μg four actuations bd, with and without spacer, in children (6-11 years) with asthma. The duration of the study was only 4 weeks which was too short to adequately assess the adverse event data. The relevant regulatory guideline suggests that therapeutic equivalence studies should collect safety data for three months.[8]

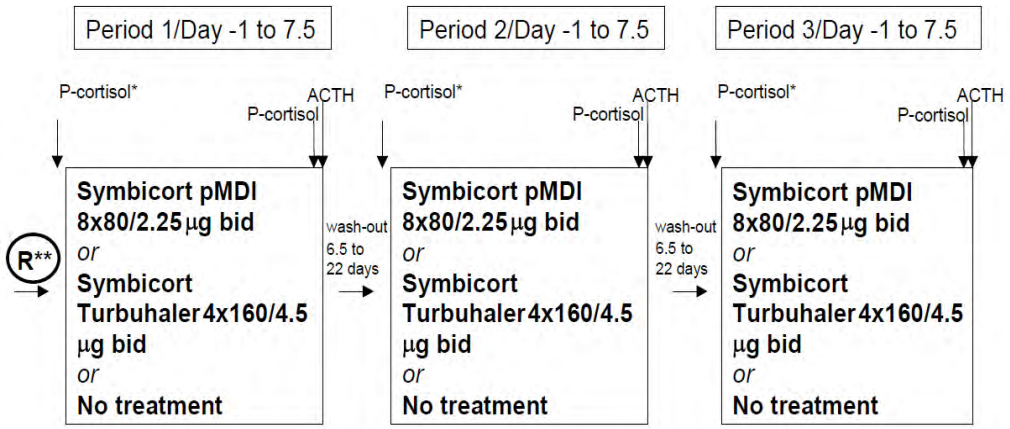
Study 005 – Symbicort pMDI 80/2.25 [100/3] μg vs Symbicort pMDI 160/4.5 [200/6] μg

Study 005 was a Phase I safety study in healthy volunteers aimed at evaluating the safety of high dose Symbicort pMDI actuations and Symbicort Turbuhaler inhalations. The primary objective was to demonstrate that the systemic effects of 8 actuations of Symbicort pMDI 80/2.25 [100/3] μg bd were not greater than those of 4 inhalations of Symbicort Turbuhaler 160/4.5 [200/6] μg bd by measurement of the average plasma cortisol concentration during 24 hours in healthy subjects on Day 7 of each treatment period. The secondary objective of the study was to evaluate the safety and tolerability of Symbicort pMDI 80/2.25 [100/3] μg by assessment of adverse events (AEs).

The study was undertaken at one centre in Sweden. It was approved by an independent ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki and the ICH/GCP. Informed consent was obtained from all subjects.

The study was randomized, open label, three period and crossover in design and was undertaken in healthy male and female subjects aged 18 to 45 years (inclusive). The study design is outlined in Figure 1.

Figure 1: Study 005 – Study design.



ACTH adrenocorticotropic hormone; bid twice daily; pMDI pressurized metered dose inhaler.
*) Baseline
**) Randomisation

The three treatment periods (no treatment, Symbicort pMDI 8 x 80/2.25 [100/3] μg bd, Symbicort Turbuhaler 4 x 160/4.5 [200/6] μg bd) were identical, with the exception that the subjects were not required to come to the study site for inhalation of study drug for the "no treatment" period. The two Symbicort treatment periods involved bd dosing for 7.5 days. The nominal daily budesonide/eformoterol dose of 1280/36 μg [1600/48] for both treatments was chosen as this is the highest approved maintenance dose in adults aged 18 years and over (that is, 2 inhalations bd of Symbicort Turbuhaler 320/9 [400/12] – Note, this is also the highest dose proposed for Symbicort Rapihaler 200/6 [4 inhalations bd] as part of this submission). The sponsor considered the maximum approved dose in adults to be the appropriate dose for studies of the systemic effects of budesonide/eformoterol.

At the start of each treatment period subjects stayed overnight in the study site to measure baseline 24 hour plasma cortisol. For the two treatment periods in which Symbicort (pMDI or Turbuhaler) were administered subjects began treatment on the morning of Day 1 (after 24 hour plasma cortisol samples were taken). Subjects received their Symbicort treatment bd from Day 1 until the morning dose on Day 8 under supervision at the study site. During the no-treatment period, the subjects did not have to return to the study site on Day 2 to Day 6. For all treatment periods, the subjects stayed

overnight at the study site from Day 7 to Day 8 in order to collect end of treatment 24 hour plasma cortisol. Plasma cortisol concentration was also measured after an adrenocorticotropic hormone (ACTH) test on Day 8. The treatment periods were separated by wash-out periods of 6.5 to 22 days. The third treatment period was followed by a follow up visit 7 to 13 days after Day 8. The inclusion and exclusion criteria were designed to recruit healthy subjects of both sexes aged 18-45 years inclusive.

Primary safety (Pharmacodynamic) and secondary safety (Adverse Event) outcomes

The primary safety (pharmacodynamic) outcome aimed to demonstrate that the systemic effects (plasma cortisol concentration) of 8 actuations of Symbicort pMDI 80/2.25 [100/3] μg bd were not greater than those of 4 inhalations of Symbicort Turbuhaler 160/4.5 [200/6] μg bd. The primary safety (pharmacodynamic) variable was the 24 hour plasma cortisol concentration measured before and after treatment. The average plasma cortisol concentration over 24 hours ($AUC_{0\text{-}24h/24}$) was calculated as $AUC_{0\text{-}24h/24}$, where the area under the plasma cortisol curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) was calculated by the trapezoidal method. The secondary safety (pharmacodynamic) variable was plasma cortisol concentration after an ACTH stimulations test undertaken to detect impairment of adrenal activity.

Statistical considerations

The 24 hour average plasma cortisol concentration ($AUC_{0\text{-}24h/24}$) was compared between treatments and analysed in a multiplicative analysis of variance (ANOVA) model with treatment, visit and subjects as fixed factors, and the baseline measurement as a covariate (log transformed). The variable analysed was the logarithm of the ratio between the average after and before treatment. The corresponding two-sided 95% CI for the difference between Symbicort pMDI and Symbicort Turbuhaler was calculated. It was then back transformed to a 95%CI for the ratio, which was used in the formal assessment of equivalence between Symbicort pMDI and Symbicort Turbuhaler. Non-inferiority (NI) was considered established if the lower limit of the 95%CI for the ratio was > 0.8 and equivalence was considered established if the whole 95%CI was within the interval 0.8 to 1.25. The sponsor indicated that the equivalence limits 0.8 to 1.25 have been used previously in Study SD-039-0675. The plasma cortisol evaluation was undertaken in the "full analysis" set (FAS) comprising of all subjects who completed both active treatments. A sample size of 25 subjects (completed) was calculated to have a power of 90% to show equivalence between Symbicort pMDI and Symbicort Turbuhaler as evaluated by the outlined procedure. This was based on a true difference between treatments of at most 10.5%. The sponsor estimated that based on Study SD-039-0675, a residual standard deviation of 0.13 (logarithmic scale) for the plasma cortisol concentrations could be expected. The plasma cortisol concentration after ACTH stimulation (calculated as the maximum of the 30 and 60 minute values) was analysed in a similar manner to that for the 24 hour average plasma cortisol concentration. The variable analysed was the logarithm of the plasma cortisol concentration after stimulation. All hypothesis testing was done using two sided alternative hypotheses, and p-values < 5% were considered statistically significant. AEs were evaluated by descriptive statistics and qualitative analysis. The safety population included all subjects who took at least 1 dose of the randomised investigational products and for whom data had been collected after randomisation.

Subjects

A total of 45 subjects were enrolled and 30 of these were randomised with all randomized subjects receiving treatment. One subject voluntarily discontinued prior to her period of no-treatment. Consequently, 29 subjects completed the study. Of the 30 randomised subjects, all were analysed for safety and all were analysed for pharmacodynamics in an ITT analysis. The first subject entered the study on 19 December 2007 and the last subject finished on 11 March 2008. Of the 30 randomized subjects: 14 (46.7%) were male and 16

(53.3%) were female; the average age was 26.9 (range: 20 to 43) years; the mean body mass index (BMI) was 22.6 kg/m^2 [range: 19 to 28]; all were White; and only 1 subject had been a previous smoker.

Results – Primary safety outcome (Plasma Cortisol)

The results for the average 24 hour plasma cortisol concentration before and after treatment (primary safety/pharmacodynamic variable) are summarised in Tables 17 and 18. Plasma cortisol suppression after treatment was 38.9% with Symbicort pMDI, 59.7% with Symbicort Turbuhaler and 3.2% with no-treatment. Suppression after Symbicort pMDI was about one third less than after Symbicort Turbuhaler. The ratio after/before treatment with Symbicort pMDI was significantly larger than that for Symbicort Turbuhaler by a factor of 1.516 [95% CI: 1.249, 1.775]; p<0.001. The 95% CI did not fall within the pre-specified equivalence limits of 0.8 to 1.25. Both active treatments significantly depressed the average plasma cortisol concentration more than no-treatment; p<0.001.

Table 17: Study 005 - Geometric mean values and ranges for the average 24 hour plasma cortisol concentration (nmol/L)

		Before treatment		Ratio after/before		Adjusted[a]	
Treatment	n	Gmean	Range	Gmean	Range	ratio	Suppression
Symbicort pMDI	30	207.7	145-370	0.604	0.25-1.31	0.611	38.9%
Symbicort TBH	30	204.1	144-299	0.407	0.15-0.87	0.403	59.7%
No treatment	28	205.2	122-273	0.976	0.65-1.68	0.968	3.2%

Gmean geometric mean; pMDI pressurized metered dose inhaler; TBH Turbuhaler.
[a] Adjusted for baseline and period by ANCOVA.

Table 18: Study 005 - Treatment comparisons of the change from baseline in average 24 hour plasma cortisol concentration (nmol/L)

Contrast	Estimated ratio	95% confidence interval	p-value
pMDI vs. TBH	1.516	(1.294, 1.775)	<0.001
pMDI vs. No treatment	0.631	(0.537, 0.742)	<0.001
TBH vs. No treatment	0.417	(0.354, 0.490)	<0.001

pMDI pressurized metered dose inhaler; TBH Turbuhaler.

The results for plasma cortisol concentration after ACTH stimulation (secondary safety/pharmacodynamic variable) are summarised in Table 19. The estimated geometric mean [range] values (nmol/L) for Symbicort pMDI, Symbicort Turbuhaler, and no-treatment were 574.2 [235, 784], 510.5 [220-740] and 654.5 [448, 852], respectively. The estimated mean geometric ratio between Symbicort pMDI and Symbicort Turbuhaler was 1.125 (that is, the plasma cortisol concentration after ACTH stimulation was 12.5% higher after Symbicort pMDI than after Symbicort Turbuhaler). Compared to no-treatment there was suppression by 12.6% after Symbicort pMDI and by 22.3% after Symbicort Turbuhaler.

Table 19: Study 005 – Plasma cortisol after ACTH stimulation

Contrast	Estimated ratio	Suppression (compared to no treatment)	95% confidence interval for the ratio	p-value
pMDI vs. TBH	1.125		(1.050, 1.206)	0.0013
pMDI vs. No treatment	0.874	12.6%	(0.815, 0.938)	<0.001
TBH vs. No treatment	0.777	22.3%	(0.724, 0.833)	<0.001

Data derived from Appendix 12.2.6, Table 1.
ACTH adrenocorticotropic hormone; pMDI pressurized metered dose inhaler; TBH Turbuhaler.

Evaluator comment – primary outcome

The primary objective of the study was satisfied as the systemic effects (plasma cortisol concentration) of 8 actuations of Symbicort pMDI 80/2.25 [100/3] μg bd were not greater than those of 4 inhalations of Symbicort Turbuhaler 160/4.5 [200/6] μg bd. Plasma cortisol suppression was statistically significantly lower after Symbicort pMDI than after Symbicort Turbuhaler measured both as average 24 hour plasma cortisol concentration and as plasma cortisol after ACTH stimulation. The results for 24 hour plasma concentration showed that Symbicort pMDI was NI to Symbicort Turbuhaler (lower 95% CI of the estimated ratio > 0.8) but that the two treatments were not equivalent (95%CI for the estimated ratio outside the pre-specified equivalence interval of 0.8 to 1.25). The wash-out period of 6.5 to 22 days between treatments was adequate as budesonide has an average plasma elimination half-life of 4 hours (Symbicort Rapihaler PI). Consequently, steady state budesonide plasma concentrations will be achieved in about 20 hours (5 half-lives) and elimination will be complete at about 20 hours (5 half-lives) after stopping treatment. The study showed that in healthy young adults Symbicort pMDI at the maximum recommended dose plasma cortisol suppression was not greater than Symbicort Turbuhaler at the same dose. However, the study was in healthy subjects rather than patients with asthma whose plasma cortisol concentrations might be suppressed by prior glucocorticosteroid therapy before starting treatment with Symbicort. There were no data in the current submission on plasma cortisol suppression in patients with asthma.

The sponsor stated that the actual size of the difference in plasma cortisol suppression between Symbicort pMDI and Symbicort Turbuhaler was not unexpected "given the difference in the *in vitro* performance of the two batches of product used". The sponsor stated that the mean delivered dose of budesonide for the Symbicort pMDI and Symbicort Turbuhaler batches used in the study were 161 μg and 151 μg, respectively, and the corresponding fine particle doses were 72 μg and 90 μg. Both batches were within the specification acceptance ranges for mean delivered dose (±15% of nominal, 136-184 μg/actuation for Symbicort pMDI [clinical trial specification] and ±20% of label claim, 128 to 192 μg/inhalation for Symbicort Turbuhaler [commercial specification]) and fine particle dose (not less than 62 μg for Symbicort pMDI [clinical trial specification] and 64-101 μg for Symbicort Turbuhaler [commercial specification]).

Results – Secondary outcomes (Adverse Events)

The secondary objective was to compare the safety and tolerability profile of 8 actuations of Symbicort pMDI 80/2.25 [100/3] μg with 4 inhalations of Symbicort Turbuhaler 160/4.5 [200/6] μg bd. All 30 randomized healthy young adult subjects were evaluated for safety. All 30 subjects received both products for 7.5 days in a crossover design with adequate wash-out between treatment periods. AEs were experienced by 57% (n=17) of Symbicort pMDI treated subjects, 60% (n=18) of Symbicort Turbuhaler treated subjects, and 28% (n=8) of no-treatment subjects. The AEs reported by PT are summarised in Table 20. Tremor was the most common AE in both Symbicort groups (22%) followed by headache (13%), nasopharyngitis (10%), pharyngeal pain (8%), dysmenorrhoea (7%),

and pyrexia (5%). Overall, the adverse event profiles of both Symbicort treatments were similar.

Table 20: Study 005 – Adverse events by PT (number (%) of subjects with AEs)

Preferred term	Symbicort pMDI n=30	Symbicort TBH n=30	No treatm n=29
Tremor	7 (23%)	6 (20%)	0
Nasopharyngitis	4 (13%)	2 (7%)	4 (14%)
Headache	3 (10%)	5 (17%)	1 (3%)
Pharyngolaryngeal pain	2 (7%)	3 (10%)	1 (3%)
Dysmenorrhoea	2 (7%)	2 (7%)	1 (3%)
Pyrexia	2 (7%)	1 (3%)	1 (3%)
Mouth ulceration	1 (3%)	0	1 (3%)
Muscle tightness	1 (3%)	1 (3%)	0
Palpitations	1 (3%)	1 (3%)	0
Throat irritation	0	2 (7%)	0
Abdominal pain upper	0	1 (3%)	0
Abnormal sensation in eye	0	1 (3%)	0
Back pain	0	0	1 (3%)
Cough	0	0	1 (3%)
Dizziness	1 (3%)	0	0
Dry mouth	1 (3%)	0	0
Dyspepsia	0	1 (3%)	0
Emotional distress	0	1 (3%)	0
Epistaxis	0	1 (3%)	0
Fatigue	1 (3%)	0	0
Influenza	0	0	1 (3%)
Muscular weakness	0	1 (3%)	0
Myalgia	1 (3%)	0	0
Nasal congestion	0	0	1 (3%)
Nausea	1 (3%)	0	0
Phlebitis	0	0	1 (3%)
Rhinitis	0	1 (3%)	0

The majority of AEs reported after treatment with Symbicort were of mild or moderate intensity. There were two AEs of severe intensity reported for each Symbicort treatment: pyrexia and dysmenorrhoea after Symbicort pMDI; and pyrexia and abdominal pain upper after Symbicort Turbuhaler. All AE reports of tremor, palpitations, muscle tightness, abnormal sensations in the eye and emotional distress with Symbicort treatments were considered by the investigators to be causally related to treatment. There were no reports of death, serious adverse events or discontinuations due to adverse events. There were two reports of cardiac AEs (1 report of palpitations in each of the Symbicort treatment groups). Clinical laboratory data, vital signs, and electrocardiograms were assessed at enrolment and at follow up visit (Visit 6) but were not discussed in the report.

Evaluator comments – secondary outcomes

The study showed that that the AE profiles in 30 healthy young adults aged 20 to 43 years were similar for 8 actuations of Symbicort pMDI 80/2.25 [100/3] μg bd and 4 inhalations of Symbicort Turbuhaler 160/4.5 [200/6] μg bd. There were no unexpected AEs seen with two treatments. However, there were no data on these high doses in patients with asthma, subject numbers were small (n=30), and treatment duration was short (7.5 days). These limitations raise doubts about the generalisability of the findings to the patient population

in whom high dose Symbicort pMDI is likely to be used (that is, adults aged 18 years or older with asthma unresponsive to lower doses).

Other safety matters

There are two safety matters which require specific consideration: (a) the association between long acting β_2-agonists and asthma related deaths; and (b) the safety of increased exposure to Symbicort Rapihaler propellants with the new proposed maximum dose in adults.

If the two new Symbicort Rapihaler strengths (50/3, 100/3) for the asthma "maintenance and reliever therapy" regimen are approved then up to 24 daily inhalations of the new strengths can be used temporarily with the normal maximum number of daily inhalations being 16. The current maximum approved number of daily Symbicort Rapihaler inhalations is 4 daily (Symbicort Rapihaler 100/6 and 200/6). In the current submission the maximum number of daily inhalations of Symbicort Rapihaler 100/3 was 16 for 7.5 days in healthy adults in Study 005. The reported adverse events in this short term study did not give rise to particular safety concerns. However, there are concerns about the generalisability of these short term results in healthy subjects to patients with asthma requiring longer term treatment.

Postmarketing

The submission did not include a postmarketing report, as these had been supplied separately to the TGA as part of the conditions of registration for currently registered Symbicort presentations.

In the sponsor's *Clinical Overview* the clinical expert included a brief summary of postmarketing data. In this summary it was indicated that as of 30 April 2008 there had been an estimated postmarketing experience of 4.2 billion treatment days for Symbicort Turbuhaler, more than 1.4 billion for Oxis (formoterol) Turbuhaler and 16.4 billion for Pulmicort (budesonide) all formulations. The most commonly reported adverse reactions with Symbicort from postmarketing surveillance data are commonly reported local class effects of inhaled glucocorticosteroids, such as oral candidiasis, hoarseness and dysphonia, and the pharmacologically predictable side effects of β_2-agonists such as tremor, headache and palpitations. The most serious potential adverse reactions of inhaled glucocorticosteroids are the long term systemic effects of high cumulative doses such as osteoporosis, diabetes mellitus and adrenal insufficiency, and the most serious potential adverse reactions associated with β_2-agonists are cardiac effects. Symbicort pMDI was approved for use in asthma patients 12 years and above in the US in 2006 and postmarketing experience with Symbicort pMDI now comprises more than 37 million treatment days. The sponsor considered that there were no signals from either the US clinical studies or the postmarketing experience of any new safety concerns with Symbicort pMDI.

Clinical summary and conclusions

Symbicort Rapihaler 50/3

It was considered that the submission has satisfactorily established the efficacy and safety of Symbicort Rapihaler 50/3 for asthma maintenance therapy in adults and adolescents (12 years and older). The submission showed that Symbicort pMDI 40/2.25 [50/3] μg two actuations bd was therapeutically equivalent to Symbicort Turbuhaler 80/4.5 [100/6] μg one inhalation bd as regards reduction in mPEF over a 6 week treatment period in adolescents and adults with asthma [Study 003]. Demonstration of therapeutic

equivalence was a secondary objective of Study 003 and was based on equivalence limits of ± 15 L/min for the difference in mPEF with equivalence being established if the 95%CI for the difference in mPEF was included completely within the equivalence limits. The equivalence limits are based on similar published and unpublished therapeutic equivalence studies and are considered to be satisfactory. The 6 week study duration is considered to be satisfactory as regards demonstration of therapeutic equivalence but is shorter that the relevant regulatory guidelines of 3 months for safety observations considered to be acceptable for demonstration of therapeutic equivalence.[8] However, the 6 week safety data for both Symbicort pMDI and Symbicort Turbuhaler were similar and there are long term safety from other studies (for example, Studies 715, 681 and 682) and postmarket surveillance data which allow the safety of the proposed Symbicort pMDI maintenance dose to be inferred. Overall, it was considered that the efficacy and safety of Symbicort Rapihaler 50/3 is similar to that of Symbicort Turbuhaler 100/6 at corresponding doses. Study 003 also demonstrated that Symbicort pMDI 40/2.25 [50/3] μg two actuations bd was statistically significantly superior to Pulmicort Turbuhaler 100 μg bd as assessed by change in mPEF with treatment (primary efficacy objective). However, the difference between treatments was only 8.07 L/min [95%CI: 3.26, 12.9] which raises doubts about the clinical significance of the difference. Despite these doubts, most of the secondary variables (asthma symptoms, rescue) showed that Symbicort pMDI was superior to Pulmicort Turbuhaler. Overall, it was considered that the submission has satisfactorily established the efficacy and safety of Symbicort Rapihaler 50/3 for asthma maintenance therapy at doses corresponding to those approved for Symbicort Turbuhaler 100/6.

It was considered that Study 003 does not support approval of Symbicort Rapihaler 50/3 for asthma "maintenance and reliever" therapy. The study compared fixed doses of Symbicort pMDI 40/2.25 [50/3] μg and Symbicort Turbuhaler 80/4.5 [100/6] μg with patients in both treatment groups using short acting β_2-agonists for relief of asthma symptoms ("as needed") rather than the relevant Symbicort products. Consequently, in the absence of a specific "stand alone" clinical efficacy and safety study or a therapeutic equivalence study of Symbicort Rapihaler 50/3 for "maintenance and reliever therapy" in adults and adolescents it was recommended that the application be rejected for this indication.

Symbicort Rapihaler 100/3

The submission did not include a "stand alone" efficacy and safety study with Symbicort Rapihaler 100/3 or a therapeutic equivalence study comparing corresponding doses of this product with Symbicort Turbuhaler 200/6. The submission included a short term safety study in a small number of healthy volunteers [Study 005]. In this crossover study (n=30), the effects on plasma cortisol concentration (primary safety outcome) of 8 actuations of Symbicort pMDI 80/2.25 [100/3] μg bd for 7.5 days were not greater than those of 4 inhalations of Symbicort Turbuhaler 160/4.5 [200/6] μg bd for 7.5 days. In addition, the adverse event profiles (secondary safety outcome) of the two treatments were similar. However, it was considered that Study 005, a safety study in a small number of healthy subjects, cannot support the therapeutic equivalence of Symbicort Rapihaler 100/3 and Symbicort 200/6 in adults and adolescents with asthma.

Symbicort Rapihaler 200/6 – Increased maximum dose in adults

The submission did not include a "stand alone" efficacy and safety study with Symbicort Rapihaler 200/6 at the proposed maximum dose in adults or a therapeutic equivalence study comparing the proposed maximum dose of this product with the approved corresponding dose of Symbicort Turbuhaler 400/12. The sponsor supported the application to increase the maximum dose by reference to a previously submitted

biopharmaceutical study [Study 730]. It can be inferred from Study 730 that the systemic bioavailabilities of budesonide and eformoterol are similar following 8 inhalations of Symbicort pMDI 200/6 and 4 inhalations of Symbicort Turbuhaler 400/12 in healthy adults. However, it was considered that the study cannot support the proposed increased maximum in adults with asthma as Study 730 was a "single dose" study in a small number (n=28) of healthy subjects. It was recommended that the application to register a new maximum dose of Symbicort Rapihaler 200/6 be rejected on the grounds of absence of studies establishing the efficacy and safety of the proposed dose in adults.

Recommendations

It was recommended that the application to register Symbicort Rapihaler 50/3 for asthma "maintenance therapy" in adults and adolescents (12 years and above) at the proposed doses be approved.

It was recommended that the application to register Symbicort Rapihaler 50/3 for asthma "maintenance and reliever" therapy in adults and adolescents (12 years and older) be rejected on the grounds that the submission included no clinical studies establishing the efficacy and safety of the product for this indication in the proposed patient group.

It was recommended that the application to register Symbicort Rapihaler 100/3 for "maintenance therapy" and "maintenance and reliever therapy" of asthma in adults and adolescents (12 years and older) be rejected on the grounds that the submission included no clinical studies establishing the efficacy and safety of the product for the proposed indications in the proposed patient group.

It was recommended that the application to register a new maximum dose of Symbicort Rapihaler 200/6 of 4 inhalations twice daily for "maintenance therapy" of asthma in adults (18 years and older) be rejected on the grounds that the submission included no clinical studies establishing the efficacy and safety of the product at the proposed dose, for the proposed indication, in the proposed patient group.

Sponsor response to the clinical evaluation report

Clarification of the bridging strategy

The sponsor acknowledged that the bridging strategy and rationale for this submission may have not been adequately presented in the submission materials, which were written to support approval of Symbicort Rapihaler (all strengths) in another major market. In particular, important *in vitro* data included in the quality documentation was not discussed within the clinical documentation and thus may not have been given appropriate consideration by the clinical evaluator.

The sponsor provided further clarification on the bridging strategy and the role in this submission of both *in vitro* and clinical data including the pivotal data which led to TGA's approval of Symbicort Rapihaler 100/6 and 200/6 presentations.

Both Symbicort Turbuhaler and Symbicort Rapihaler are currently approved for asthma treatment in Australia. However, the approved dosages/treatment regimens for the two actuation device Symbicort Rapihaler 100/6 and 200/6 do not completely match those approved for the one inhalation device Symbicort Turbuhaler 100/6, 200/6 and 400/12. The primary purpose of the current application was to register two new strengths of Symbicort Rapihaler (50/3 and 100/3) for both asthma "maintenance treatment" and "maintenance and reliever treatment". The registration of these strengths, combined with the requested increase in the asthma maintenance dose of Symbicort Rapihaler 200/6 to 4 inhalations bd, will allow a complete match between the Symbicort Turbuhaler and Symbicort Rapihaler approved asthma dosages/treatment regimens and physicians will

thus be able to prescribe either formulation at equivalent doses, according to individual patients' needs or preference.

Symbicort Rapihaler 100/3 for asthma "maintenance treatment"

The relationship between the currently approved Symbicort Turbuhaler strengths/maintenance doses and the Symbicort Rapihaler strengths/maintenance doses is presented in Table 5. This table shows that *in vivo* therapeutic equivalence between 2 actuations of Symbicort Rapihaler 50/3 bd and 1 inhalation of Symbicort Turbuhaler 100/6 bd has been accepted by the clinical evaluator, based on Study 003 in the current submission. In addition, *in vivo* therapeutic equivalence has already been accepted by the TGA for 2 actuations bd of Symbicort Rapihaler 100/6 versus 2 inhalations bd of Symbicort Turbuhaler 100/6 (Study 682) and 2 actuations bd of Symbicort Rapihaler 200/6 versus 2 inhalations bd of Symbicort Turbuhaler 200/6 (Study 681) (original Symbicort Rapihaler submission as cross-referenced within this submission). Thus, clinical therapeutic equivalence has been demonstrated for three of the Symbicort Rapihaler presentations, at both the bottom (50/3) and top (100/6 and 200/6) of the strength range.

The development of the new strengths (50/3 and 100/3), was based on the approved higher strength Rapihaler products (100/6 and 200/6). The sponsor provided comment on the similarities of the four Symbicort Rapihaler strengths in terms of formulation, device (including valve) and delivered dose. The sponsor also provided further comment on the *in vitro* data which was provided in the quality section of the current submission which demonstrated that all four Symbicort Rapihaler strengths give a linear response in terms of fine particle fraction, and thus further confirms that Symbicort Rapihaler 100/3 performs in accordance with its nominal dose.

Symbicort Rapihaler was developed in accordance with the TGA-adopted EU guidance.[8] which states that *"In cases where different dose strengths of the same product contain a well-known active substance are sought, it can be sufficient to state the therapeutic equivalence clinically in vivo with one of those dose strengths. Thereafter it is necessary to give proof of a linear dose deposition relationship in vitro for each of the other dose strengths performed with a multistage impactor."*

Based on this guidance, the sponsor contended that given the combination of proven *in vivo* therapeutic equivalence for the strengths that bracket Symbicort Rapihaler 100/3 (50/3, 100/6, and 200/6) and the linear dose relationships for both active ingredients from all strengths, there is sufficient and adequate evidence to justify the equivalence/bridging between Symbicort Rapihaler and Symbicort Turbuhaler for all relevant (that is, nominally equivalent) doses, including to claim therapeutic equivalence of 2 actuations bd of Symbicort Rapihaler 100/3 and 1 inhalation bd of Symbicort Turbuhaler 200/6, and thus satisfactorily establish the safety and efficacy of Symbicort Rapihaler 100/3 for asthma "maintenance treatment".

Symbicort Rapihaler 50/3 and 100/3 for asthma "maintenance and reliever therapy"

The sponsor stated that the safety and efficacy of asthma "maintenance and reliever therapy" had previously been demonstrated in a robust clinical development program, including 5 large, long term Phase III studies with Symbicort Turbuhaler and this alternative asthma dosing regimen had been accepted by the TGA (previous TGA evaluations cross-referenced). Based on the proven *in vivo* therapeutic equivalence and additional *in vitro* data discussed above, the sponsor considered Symbicort Rapihaler and Symbicort Turbuhaler to be interchangeable at nominally equivalent doses and thus it is appropriate to use Symbicort Rapihaler 50/3 and Symbicort Rapihaler 100/3 as asthma "maintenance and reliever therapy".

Increase in the maximum dose of Symbicort Rapihaler 200/6

The sponsor considered that the increase in maximum dose of Symbicort Rapihaler to 4 actuations bd was also supported by the established efficacy and safety of this daily dose via clinical trials with Symbicort Turbuhaler (SD-039-0689 – as previously evaluated by TGA including cross-reference to submission), combined with the proven *in vivo* therapeutic equivalence of Symbicort Rapihaler 200/6 and Symbicort Turbuhaler 200/6 (Study 681).

The sponsor also provided a summary of the study design and results for Study 689 (as per the approved Symbicort Turbuhaler PI) which concluded that when administered twice daily, Symbicort 400/12 is a more effective treatment for the majority of clinical endpoints than the corresponding budesonide dose.

Conclusion

Regulatory guidance has suggested that a stepwise approach be taken to establish therapeutic equivalence. First a pharmaceutical approach utilising *in vitro* comparisons, followed by a clinical approach if the *in vitro* comparisons alone are not convincing enough to provide substantive evidence of therapeutic equivalence. Consistent with this TGA adopted EU guidance, the sponsor has performed both pharmaceutical *in vitro* analysis that confirms all Symbicort Rapihaler strengths perform according to their nominal dose and clinical studies that have proven therapeutic equivalence across the range of strengths.[8,10] Based on the above, the sponsor considered the Symbicort Rapihaler and Symbicort Turbuhaler formulations as interchangeable and thus it was appropriate to approve the entirety of the registration request in the current application, including the Symbicort Rapihaler 100/3 for asthma "maintenance treatment", Symbicort Rapihaler 50/3 and 100/3 for asthma "maintenance and reliever therapy", and an increase in maximum dose for Symbicort Rapihaler 200/6 to 4 actuations bd in asthma "maintenance treatment".

No formal response to this clinical evaluation report response was issued by the TGA.

V. Pharmacovigilance findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The chemistry aspects were sufficient to recommend registration.

The recommendation of the Pharmaceutical Subcommittee (PSC) was limited to acknowledging that *in vitro* data supported linear delivery of drug from the different strengths of Rapihaler but not *in vitro* equivalence of Rapihaler and Turbuhaler.

The PSC agreed that the issues of concern in relation to comparative data on the aerosol particle size distribution profiles raised at its first consideration had been adequately resolved. The *in vitro* data were consistent with dose linear delivery of drugs from the different strengths of the Rapihaler pressurised metered dose inhalers.

The Committee however noted the absence of *in vivo* data to support the *in vitro* characteristics of the product. The PSC considered that the sponsor should be asked to provide FEV data if available.

The PSC reiterated its recommendation that the sponsor had not provided sufficient *in vitro* evidence to justify any claim of *in vitro* equivalence between any doses of Symbicort Rapihaler (pressurised metered dose inhaler) and Symbicort Turbuhaler (dry powder inhaler).

The PSC therefore concluded that the issues in relation to switching between Symbicort Rapihaler and Symbicort Turbuhaler dose forms is a clinical issue and should be addressed by clinical data. The PSC therefore concluded that approval of this application should be based on clinical data.

It is therefore relevant to consider the supporting clinical data.

Nonclinical

The nonclinical evaluator noted that the new strength would increase the exposure to excipients, if used to achieve the maximal daily dose. Symbicort Rapihaler contains povidone, macrogol 1000 and apaflurane as excipients. Doses of these excipients at the maximum recommended dose are increased up to sixfold relative to the currently registered Symbicort Rapihaler formulations, due to a sixfold increase in the maximum recommended number of actuations per day, from 4 with the current formulations to 24 with the proposed new strengths.

There is an adequate margin of safety based upon extant toxicology data, however.

The evaluator concluded that,

> "... greater doses of these excipients are provided by another currently registered product ... Moreover, the animal data from the previous submission and from the newly submitted studies in rats and dogs (6–24 months in duration) in the current submission did not show toxicities attributable to the excipients, at doses equivalent to or greater than at the maximum recommended clinical dose of the proposed formulations. Therefore, there is not likely to be any significant risk to patients due to the increased exposure to these excipients arising from the use of the newly proposed strengths."

Little concern was felt about leachable chemicals in the Rapihaler presentation, based on their low observed levels.

Registration was not opposed on nonclinical grounds.

Clinical

Overview

The clinical evaluator noted that, at the time of application, the Symbicort pMDI 50/3 and 100/3 strengths were not registered in any foreign country.

Three clinical studies not previously evaluated by the TGA were included in the current submission D5897C00003 (*003*), D5897C00004 (*004*) and D5897C00005 (*005*). Study 003 was considered to be of pivotal significance in support of the efficacy and safety of the Rapihaler 50/3 strength as maintenance therapy. No study examined reliever therapy. The evaluator found that the submission did not include pivotal or adequate supportive studies to support approval of the Symbicort Rapihaler 100/3.

The two new Symbicort Rapihaler lower strengths of 50/3 and 100/3 were proposed to improve dosing flexibility and allow the Symbicort Rapihaler range to deliver the same asthma dosage range and treatment regimen as that approved for Symbicort Turbuhaler 100/6 and 200/6 in adults and adolescents (aged 12 and over). As mentioned above, this is because doses of Symbicort Rapihaler should always be given in multiples of two actuations to ensure adequate dose uniformity, while Symbicort Turbuhaler can be given as single inhalations.

New strengths

Efficacy studies

Study 003 was considered by the evaluator to be the pivotal efficacy and safety study supporting approval of the Symbicort Rapihaler 50/3. The study was of Phase III, multicentre, randomised, double dummy, active controlled (Pulmicort Turbuhaler) and parallel group (n=3) design.

The primary efficacy variable was the change in morning peak expiratory flow (mPEF) from baseline (mean of the 10 last days of the run-in period) to the treatment period (mean of the 6 week treatment period).

The primary objective was to demonstrate that Symbicort pMDI 40/2.25 [50/3] μg two actuations bd was more efficacious than Pulmicort Turbuhaler 100 μg one inhalation bd. The secondary objectives of this study were: (i) a therapeutic equivalence analysis of Symbicort pMDI 40/2.25 [50/3] μg two actuations bd (n=253) and Symbicort Turbuhaler 80/4.5 [100/6] μg one inhalation bd (n=245) over a 6 week treatment period in adolescents and adults with asthma and (ii) to compare the safety profiles of Symbicort pMDI 40/2.25 [50/3] μg two actuations bd, Symbicort Turbuhaler 80/4.5 [100/6] μg one inhalation bd and Pulmicort Turbuhaler 100 μg one inhalation bd. Non-inferiority (NI) was considered established if the lower limit of the 95%CI of the difference between Symbicort pMDI and Symbicort Turbuhaler was > -15 L/min. Therapeutic equivalence was considered established if the 95% CI of the difference in mPEF was contained entirely within the equivalence limits ± 15 L/min.

The study did not compare Symbicort 40/2.25 [50/3] μg and Symbicort Turbuhaler 80/4.5 [100/6] μg as reliever therapy on an "as needed" basis. Instead, patients used short acting β_2-agonists as reliever (that is, rescue) medication when experiencing asthma symptoms. Consequently, it was considered by the evaluator that this therapeutic equivalence study can only be used to support Symbicort Rapihaler 50/3 for asthma "maintenance therapy" and not for asthma "maintenance and reliever therapy".

As described by the evaluator:

“The primary efficacy objective was to show that Symbicort pMDI 40/2.25 [50/3] μg two actuations bd was more efficacious than Pulmicort Turbuhaler 100 μg one inhalation bd over a 6 week treatment period in adolescents and adults with asthma as assessed by change in mPEF. The adjusted mean mPEF increased by 12.2 L/min with Symbicort pMDI, 4.15 L/min with Pulmicort Turbuhaler, and 13.1 L/min with Symbicort Turbuhaler. The results showed that the mean change from baseline in mPEF was greater with Symbicort pMDI than with Pulmicort Turbuhaler, and that the mean difference was statistically significant” (Table 7).

The evaluator remarked:

“The difference in mPEF between Symbicort pMDI 40/2.25 [50/3] μg two actuations bd and Pulmicort Turbuhaler 100 μg one inhalation bd was about 8 L/min. This figure was lower than the 13 L/min difference specified in the sample size calculations.”

In terms of secondary outcomes (Table 8), equivalence was established.

As might be expected, the results for the asthma symptom scores showed no statistically significant difference between the two Symbicort treatments, while the difference between Symbicort Turbuhaler and Pulmicort Turbuhaler were statistically significant for all four variables (Symbicort Turbuhaler superior) and the difference between Symbicort pMDI and Pulmicort Turbuhaler were statistically significant for three of the four variables (Symbicort pMDI superior). Rescue medication use was higher with Pulmicort.

The evaluator concluded that the study provides evidence of clinical equivalence for "maintenance" therapy only. For therapeutic equivalence, the study is rather short: 6 weeks and not the normative three months as recommended in the TGA-approved EU guideline.[17] Comparisons with the previous Study 681 suggest a smaller benefit was obtained over inhaled corticosteroid alone in Study 003 than in Study 681. Study 004 was considered by the evaluator not to be directly relevant to the submission as it included efficacy and safety data on Symbicort pMDI 40/2.25 [50/3] μg administered with (n=55) and without (n=52) spacer over a 4 week open label treatment period to children with asthma aged 6 to 11 years.

The primary objective was to show that Symbicort pMDI 40/2.25 [50/3] μg four actuations bd with a spacer (n=55) and without a spacer (n=52) had similar systemic steroid potencies in children aged 6 to 11 years with asthma. The primary outcome variable was a pharmacodynamic (safety) variable, namely 24 hour urinary free cortisol (UFC). The results showed that there was no statistically significant difference between the two treatment groups in change in 24 hour UFC levels. In the Symbicort pMDI with spacer group, the 24 hour UFC decreased by 6.4% and in the Symbicort pMDI without space group it increased by 7.6%. The ratio of the two treatments indicates that the 24 hour UFC level in the Symbicort pMDI with spacer group was 13% lower than in the Symbicort pMDI without spacer group.

The secondary objectives were to compare the clinical efficacy and safety of Symbicort pMDI 40/2.25 [50/3] μg four actuations bd, with or without a spacer. There was no statistically significant difference in the FEV_1 change from Visit 3 (baseline) to Visit 5 (last).

The evaluator had three reasons for critiquing the relevance of this study:

- The study has little relevance to the current Australian submission as it included only children aged 6 to 11 years with asthma and none of the currently registered Symbicort formulations are approved for this condition in this age group.
- The sponsor was not seeking to extend the currently approved indications for Symbicort to this age group.
- The effects of Symbicort pMDI 40/2.25 [50/3] μg four actuations bd administered with or without a spacer on 24 hour UFC levels in children is of doubtful relevance to treatment of adolescents or adults with this product.

Study 005 was considered by the evaluator to be of marginal relevance to the submission. It compared the safety of the maximum recommended dose in thirty healthy adult volunteers (that is, delivered dose 1280/36 μg [metered dose 1600/48 μg]) administered Symbicort pMDI 80/2.25 μg [100/3] eight actuations bd and Symbicort Turbuhaler 160/4.5 μg [200/6] four inhalations bd with each treatment being administered for 7.5 days in a three period, crossover design, at a single centre.

The primary safety (pharmacodynamic) outcome aimed to demonstrate that the systemic effects (plasma cortisol concentration) of 8 actuations of Symbicort pMDI 80/2.25 [100/3]

[17] EMEA, Committee for Proprietary Medicinal Products (CPMP), 22 April 2004. CPMP Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) CPMP/EWP/4151/00.

μg bd were not greater than those of 4 inhalations of Symbicort Turbuhaler 160/4.5 [200/6] μg bd. The primary safety (pharmacodynamic) variable was the 24 hour plasma cortisol concentration measured before and after treatment. Plasma cortisol suppression after treatment was 38.9% with Symbicort pMDI, 59.7% with Symbicort Turbuhaler and 3.2% with no-treatment. Suppression after Symbicort pMDI was about one third less than after Symbicort Turbuhaler. The results for 24 hour plasma concentration showed that Symbicort Rapihaler was non-inferior to Symbicort Turbuhaler (lower 95% CI of the estimated ratio >0.8), but that the two active treatments were not equivalent (95% CI for the estimated ratio outside the prespecified equivalence interval of 0.8 – 1.25). The secondary safety (pharmacodynamic) variable was plasma cortisol concentration after an ACTH stimulation test undertaken to detect impairment of adrenal activity. The protocol specified that on the morning on Day 8 of each treatment period, immediately after dosing, 1 μg of ACTH (Synacthen) was to be injected intravenously. The estimated mean geometric ratio between Symbicort pMDI and Symbicort Turbuhaler was 1.125 (that is, the plasma cortisol concentration after ACTH stimulation was 12.5% higher after Symbicort pMDI than after Symbicort Turbuhaler). Compared to no-treatment there was some suppression by 12.6% after Symbicort pMDI and by 22.3% after Symbicort Turbuhaler.

The evaluator concluded that plasma cortisol suppression was statistically significantly lower after Symbicort pMDI than after Symbicort Turbuhaler measured both as an average 24 hour plasma cortisol concentration and as plasma cortisol after ACTH stimulation. The study showed that in healthy young adults Symbicort pMDI at the maximum recommended dose plasma cortisol suppression was not greater than Symbicort Turbuhaler at the same dose.

The evaluator recorded the sponsor's reasoning for this outcome: the mean delivered dose of budesonide for the Symbicort pMDI and Symbicort Turbuhaler batches used in the study were 161 μg and 151 μg, respectively, and the corresponding fine particle doses were 72 μg and 90 μg. Both batches were within the specification acceptance ranges for mean delivered dose.

The Delegate noted that by implication, the sponsor claims that a bioassay system (human volunteers) is sensitive enough not only to support bioequivalence but to detect within-specifications variations in the fine particle dose.

In consideration of the use of Rapihaler 200/6 for an increase in new maximum dose for the currently registered asthma maintenance therapy (in line with that approved for Symbicort Turbuhaler 400/12), the evaluator could not locate adequate data in the submission. The evaluator considered that the submission does not include pivotal or adequate supportive studies to support approval of the new maximum dose of Symbicort Rapihaler 200/6 in adults with asthma.

Safety

The evaluator had no safety concerns arising from the submitted studies.

Evaluator's recommendations

The Delegate noted the evaluator's recommendations.

Response by sponsor to clinical evaluation report

The Delegate noted that the sponsor had provided a detailed commentary upon the evaluation report which indicated that the bridging strategy and rational may not have been adequately presented in the submission materials.

The Delegate also commented that the sponsor had explained the utility of having the new strengths and indications granted.

The Delegate noted that part of the justification relies on *in vitro* data and that he considered that this had been addressed by the quality evaluator and by the PSC. The clinical evaluator's comments on adopted guidelines were not disputed. Study 003 is a little short and there was no study on the 100/3 strength nor is there an alternative bridging study using the 50/3 strength and the registered strength (that is, 200/6) that would be supported by *in vitro* data for all three strengths.

Data limitations

These have been made clear by the clinical evaluator. Adequate clinical equivalence studies against other Symbicort presentations have not been done and the 100/3 strength has no clinical data.

Risk-benefit analysis

Delegate considerations

The study of most relevance to the new strength pMDIs (50/3 and 100/3) (Study 003) has a relatively short study duration. The evaluator discussed whether a 6 week trial period is sufficient. As asthma is a disease of some variability, the normative 12 week period would have provided greater security than 6 weeks about the claim of adequacy of Rapihaler 50/3 in maintenance therapy. The Delegate directed the following questions to the Advisory Committee on Prescription Medicines (ACPM):

1. Dependent on statistical considerations (which were subsequently found to be acceptable) to be discussed by the sponsor in the pre-ACPM response, Study 003 might support the registration of Rapihaler 50/3.
    a. Does Study 003 conclusively support clinical equivalence of Rapihaler 50/3 and Turbuhaler 100/6 as "maintenance" therapy?
    b. Can this be extended to "reliever" therapy?
2. Given the lack of support by the PSC for the claim that particle size data alone can support the interchangeable nature of Rapihaler and Turbuhaler presentations, can the submitted clinical data support the suggestion that the various strengths of Turbuhaler and Rapihaler be seen as interchangeable in the treatment of asthma? It would seem at present that there is no clinical support for the registration of the Rapihaler 100/3 presentation and data on the interchangeable nature of Rapihaler and Turbuhaler presentations in asthma are not available.

The Delegate was unable to make a definite recommendation concerning the registration of the Symbicort Rapihaler 50/3 presentation in the absence of clarification by the sponsor of the statistical plan (which was subsequently found to be acceptable).

The Delegate proposed that (taking into account the sponsor's answers concerning the statistical plan – which was subsequently found to be acceptable) the application to register a new strength, Symbicort Rapihaler 50/3, for asthma "maintenance therapy" in adults and adolescents (12 years and above) at the proposed doses be approved/be rejected on the grounds of inadequate pharmaceutical and clinical equivalence data to relate both new strengths to registered Symbicort presentations.

The application to register a new indication, asthma "maintenance and reliever therapy", for Symbicort Rapihaler presentations, in adults and adolescents (12 years and above)

should be rejected due to a lack of efficacy and safety data in the asthma patient population, including comparative studies against the Turbuhaler presentations.

The application to register a new strength, Symbicort Rapihaler 100/3, for asthma "maintenance therapy" and "maintenance and reliever therapy" in adults and adolescents (12 years and above) at the proposed doses should be rejected because the submission included no clinical studies establishing the efficacy and safety of the product for the proposed indications in the proposed patient group and on the grounds of incomplete pharmaceutical and inadequate clinical equivalence data to relate both new strengths to registered Symbicort presentations.

The application to register a new maximal dose of Symbicort Rapihaler 200/6 - 4 inhalations twice daily for "maintenance therapy" of asthma in adults (18 years and older) should be rejected because the submission included no clinical studies establishing the efficacy and safety of the product at the proposed dose, for the proposed indication, in the proposed patient group.

Response from Sponsor

The main points of the sponsor's pre-ACPM submission were as follows:

Bridging strategy

The rationale of the bridging strategy is based on the stepwise approach suggested in the TGA adopted CPMP guidance which states that "*In cases where different dose strengths of the same product contain a well-known active substance are sought, it can be sufficient to state the therapeutic equivalence clinically in vivo with one of those dose strengths. Thereafter it is necessary to give proof of a linear dose deposition relationship in vitro for each of the other dose strengths performed with a multistage impactor.*"[8,10]

The pharmaceutical/clinical bases of the bridging strategy are outlined in Table 3.

1. Therapeutic equivalence between Symbicort Rapihaler and Symbicort Turbuhaler has been established and accepted by the Australian Drug Evaluation Committee (ADEC) (which preceded ACPM), which resulted in the original TGA approval of Symbicort Rapihaler 100/6 and 200/6 in asthma maintenance treatment, with the same maximum recommended doses as those for Symbicort Turbuhaler (100/6 and 200/6; Studies 681 and 682).

   Similarly, therapeutic equivalence between Symbicort Rapihaler (200/6) and Symbicort Turbuhaler (200/6 and 400/12) was recently accepted by TGA in the approval of COPD indication for Symbicort Rapihaler and Symbicort Turbuhaler, with the same dosage (800/24 daily dose) recommended for the two delivery systems.[6]

   Thus, both the 100/6 and 200/6 Symbicort Rapihaler and Symbicort Turbuhaler (100/6, 200/6 and 400/12) have already been accepted by TGA as interchangeable for both asthma maintenance and COPD indications.

2. The development of the new strengths (Symbicort Rapihaler 50/3 and 100/3) was based on the approved higher strength Symbicort Rapihaler products (100/6 and 200/6), which are pharmaceutically very similar. For the two new lower strengths of Symbicort Rapihaler (50/3 and 100/3) in this application, in terms of the pharmaceutical aspects, the quality evaluator concluded that "Registration is recommended with respect to chemistry and biopharmaceutic aspects".

   The PSC has accepted that "*in vitro* data were consistent with dose linear delivery of drugs from the different strengths of the Rapihaler". This supports that the different strengths of the Rapihaler are interchangeable (as shown by the *in vitro* data). The PSC concluded that "approval of this application should be based on clinical data".

3. Three clinical studies (Studies 681, 682 and 003) have already demonstrated *in vivo* therapeutic equivalence between Symbicort Turbuhaler and Symbicort Rapihaler. These studies involved the lowest strength (50/3) and the two highest strengths (100/6 and 200/6), that bracket Symbicort Rapihaler 100/3.
4. The safety and efficacy of Symbicort "maintenance and reliever therapy" had been previously demonstrated in a robust clinical development program with Symbicort Turbuhaler (100/6 and 200/6), and was subsequently approved by the TGA in 2006. It is intended for the same asthma patient population and has the same indication as for Symbicort maintenance treatment. It is an improved dosing regimen in which patients receive improved asthma control with the lowest effective doses of Symbicort.
5. The proposed increased maximum dose of Symbicort Rapihaler 200/6 (from 2 to 4 inhalations bd) is further supported by the biopharmaceutic Study 730 which showed that the relative systemic bioavailability of budesonide and eformoterol (at proposed total daily dose of 1600/48) was comparable between Symbicort Rapihaler 200/6 and Turbuhaler 200/6, and also Symbicort Turbuhaler 200/6 and 400/12.
6. Based on the above, the sponsor considered that Symbicort Rapihaler and Symbicort Turbuhaler formulations are interchangeable and the pharmaceutical and clinical evidence fully support this application for:
   - the registration of the two new strengths of Symbicort Rapihaler (50/3 and 100/3) for both asthma maintenance treatment" and Symbicort "maintenance and reliever therapy" in asthma; and
   - the increase in the maximum dose of Symbicort Rapihaler 200/6 to 4 inhalations twice daily, to match an equivalent dose currently approved for Symbicort Turbuhaler 400/12 (of 2 inhalations twice daily) in asthma "maintenance therapy".

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to this document, made the following recommendations:

- approval of the submission to register a new strength of budesonide / eformoterol (Symbicort Rapihaler) pressurised inhaler 50/3 μg for the indication:

  For the maintenance therapy of asthma where use of a combination (inhaled corticosteroid and long-acting β2 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 β2 agonist and inhaled corticosteroid therapy.
- rejection of the application to register a new strength and indication for budesonide / eformoterol (Symbicort Rapihaler) pressurised inhaler 100/3 μg, on the grounds that insufficient evidence of efficacy and safety was demonstrated for maintenance therapy in the proposed population group.
- rejection of the submission to register a new dosage regimen for budesonide / eformoterol (Symbicort Rapihaler) pressurised inhaler 200/6 μg, to include a higher daily dose, on the grounds that insufficient evidence of efficacy and safety was demonstrated for maintenance therapy in the proposed population group.

- rejection of the submission to register budesonide / eformoterol (Symbicort Rapihaler) pressurised inhaler presentations [50/3 and 100/3] for the indication to include *maintenance and reliever therapy*, on the grounds that insufficient evidence of efficacy and safety was demonstrated for maintenance therapy in the proposed population group.

The ACPM encouraged the sponsor to undertake specific clinical trials in the asthma patient population, to support the proposed indication of *maintenance and reliever therapy* for Symbicort Rapihaler presentations, in adults and adolescents including comparative studies against the Turbuhaler presentations.

Initial outcome

Based on a review of quality, safety and efficacy, the TGA issued four separate decisions.

1. The TGA approved the registration of Symbicort Rapihaler containing budesonide/eformoterol fumarate dihydrate 50/3 pressurised metered dose inhaler, indicated for:
    - *the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β_2-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 β_2-agonist and inhaled corticosteroid therapy.*

2. The application to register Symbicort Rapihaler containing budesonide/eformoterol fumarate dihydrate 100/3 pressurised metered dose inhaler for asthma maintenance therapy was rejected.
3. The proposed extension of registered indications (asthma "maintenance and reliever therapy") that would have applied to Symbicort Rapihaler containing budesonide/eformoterol fumarate dihydrate 100/6 pressurised metered dose inhaler and to the proposed new strengths, Symbicort Rapihaler containing budesonide/eformoterol fumarate dihydrate 50/3 pressurised metered dose inhaler and Symbicort Rapihaler containing budesonide/eformoterol fumarate dihydrate 100/3 pressurised metered dose inhaler were rejected.[1]
4. The application to register a new maximal dose of Symbicort Rapihaler containing budesonide/eformoterol fumarate dihydrate 200/6 pressurised metered dose inhaler involving 4 inhalations twice daily for 'maintenance therapy' of asthma in adults (18 years and older) was rejected.

Final outcome

Following the initial decision described above, the sponsor:

- Accepted the approval of Symbicort Rapihaler 50/3 for asthma maintenance therapy,
- Appealed the 3 negative decisions under Section 60 of the Therapeutic Goods Act whereby a review of the initial decisions can be conducted by the Minister. The main concerns raised by the sponsor in the Section 60 appeal were as follows:

  Considering that all four Symbicort Rapihaler strengths contain the same drugs, have the same formulation, are delivered by the same device, produce the same particle size profiles for both active ingredients, and are supported by three therapeutic equivalence studies with corresponding Turbuhaler products in asthma (and clinical

equivalence having been demonstrated for each device in COPD), compliance with the TGA adopted CPMP OIP guidelines would appear to have been conclusively established.8,10 Consequently, if the requirements of these guidelines had been used to assess the application, it is difficult to understand how the statutory test for efficacy and safety was failed to be met. Instead it appears that the Delegate has evaluated the proposed products as if they were completely new delivery devices with new active ingredients. The four Symbicort Rapihaler strengths (three of which are now registered) do not contain new active ingredients with a new delivery device, and no justification or explanation has been provided to justify the need for provision of additional clinical data to support registration of the three aspects rejected by the Delegate (that is, a new strengths – 100/3, an increased dose for 200/6, and an alternative dosing regimen for "maintenance and reliever therapy" [50/3 and 100/3 only]).

As the sponsor did not receive notice of the decision of the Minister within 60 days of the appeal, the Minister was taken to have confirmed the initial decisions.

Subject to the *Administrative Appeals Tribunal Act 1975*, the sponsor appealed to the Tribunal for review of the 3 negative Minister's decisions.[18]

Following further TGA review of the data submitted by the sponsor and on advice from an expert in the field, the TGA reached agreement with the sponsor regarding the 3 negative decisions prior to a full hearing by Administrative Appeal Tribunal.

Administrative Appeals Tribunal decision

On 19 June 2012, by consent the Tribunal decided, in accordance with subsection 42C(1) and pursuant to subsection 42C(2) of the *Administrative Appeals Tribunal Act 1975*, that;

A. Symbicort Rapihaler budesonide/eformoterol fumarate dihydrate 100/3 pressurised metered dose inhaler (Rapihaler 100/3)

1. the decisions of 28 March 2011 rejecting the application to register:

   1.1. Symbicort Rapihaler budesonide/eformoterol fumarate dihydrate 100/3 pressurised metered dose inhaler for maintenance therapy in asthma is set aside; and,

   1 .2. Symbicort Rapihaler budesonide/eformoterol fumarate dihydrate 100/3 pressurised metered dose inhaler for maintenance and reliever therapy in asthma is set aside;

2. the decisions under review are substituted by decisions that Rapihaler 100/3 (as described in the "Provisional ARTG Records" and "Product Details" at attachment 1[19]) is approved under section 25(1) of the *Therapeutic Goods Act 1989* for registration of the following indication:

   "Symbicort Rapihaler is indicated for the treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β2-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 β2- agonist and inhaled corticosteroid therapy.*

[18] This AusPAR was updated on 26 February 2013 with the AAT decision.

[19] Attachment 1 of the AAT Consent Order is not included in this AusPAR.

There are two alternative treatment regimens:

- *Symbicort maintenance and reliever therapy;*
- *Symbicort maintenance therapy";*

B. Symbicort Rapihaler budesonide/eformoterol fumarate dihydrate 50/3 pressurised metered dose inhaler (Rapihaler 50/3)

3. the decision of 28 March 2011 rejecting the application to register Symbicort Rapihaler budesonide/eformoterol fumarate dihydrate 50/3 pressurised metered dose inhaler for maintenance and reliever therapy in asthma is set aside;
4. the decision under review is substituted by a decision that Rapihaler 50/3 is approved under section 25(1) of the *Therapeutic Goods Act 1989* for registration of the following indication:

   "Symbicort Rapihaler is indicated for the treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β2- 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 β2-agonist and inhaled corticosteroid therapy.*

   There are two alterative treatment regimens:

   - Symbicort maintenance and reliever therapy;
   - Symbicort maintenance therapy";

C. Symbicort Rapihaler budesonide/eformoterol fumarate dihydrate

200/6 pressurised metered dose inhaler (Rapihaler 200/6)

5. the decision of 28 March 2011 rejecting the application to register Symbicort Rapihaler budesonide/eformoterol fumarate dihydrate 200/6 pressurised metered dose inhaler for maintenance therapy at a higher dose in asthma is set aside;
6. the decision under review is substituted by a decision that Rapihaler 200/6 is approved under section 25(1) of the *Therapeutic Goods Act 1989* for registration of the following indication:

   "*Symbicort Rapihaler is indicated for the treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β2-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 β2-agonist and inhaled corticosteroid therapy"*

   but with an increased maximum dosage so that for adults 18 years and over who require a higher daily maintenance dose (as compared to 2 inhalations twice daily), the maximum recommended maintenance dose may be increased to 4 inhalations of Symbicort Rapihaler 200/6 twice daily (corresponding to 1600 μg budesonide/48 μg eformoterol).

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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