Australian Government

Department of Health and Ageing

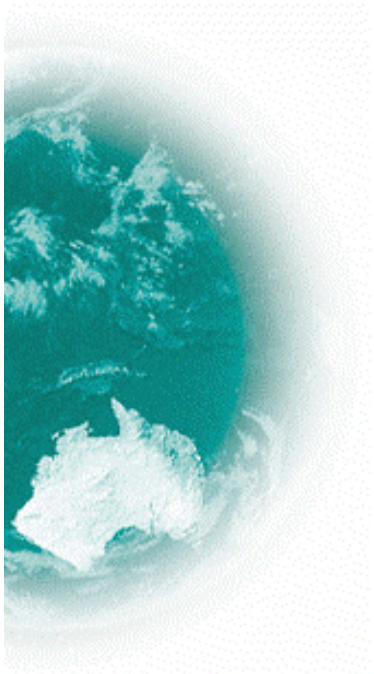
Therapeutic Goods Administration

# Australian Public Assessment Report for Budesonide/eformoterol fumarate dihydrate

**Proprietary Product Name: Symbicort Turbuhaler 200/6, 400/12 and Symbicort Rapihaler 200/6**

**Submission No: PM-2008-1992-5**

**Sponsor: AstraZeneca Pty Ltd**



***October 2010***

# Contents

# I. Introduction to Product Submission

## Submission Details

| | |
|---|---|
| *Type of Submission* | Extension of Indications |
| *Decision:* | Approved |
| *Date of Final Decision:* | 26 March 2010 |
| *Active ingredient(s):* | Budesonide/eformoterol fumarate dihydrate[1] |
| *Product Name(s):* | Symbicort Turbuhaler 200/6, 400/12 and Symbicort Rapihaler 200/6 |
| *Sponsor's Name and Address:* | AstraZeneca Pty Ltd<br>Alma Road<br>North Ryde NSW 2113 |
| *Dose form(s):* | Symbicort Turbuhaler; powder for inhalation |
| | Symbicort Rapihaler; inhalation pressurised |
| *Strength(s):* | Symbicort Turbuhaler; Budesonide 200 µg /eformoterol fumarate dihydrate 6 µg and 400 µg/12 µg |
| | Symbicort Rapihaler; Budesonide 200 µg /eformoterol fumarate dihydrate 6 µg[2] |
| *Container(s):* | Symbicort Turbuhaler; Inhaler – dry powder |
| | Symbicort Rapihaler; Inhaler – pressurised metered dose |
| *Pack size(s):* | Symbicort Turbuhaler; 200/6: 60 or 120 doses, 400/12: 1 x 60 doses or 2 x 60 doses |
| | Symbicort Rapihaler; 120 inhalations |
| *Approved Therapeutic use:* | Symbicort Turbuhaler and Rapihaler are indicated for the symptomatic treatment of moderate to severe COPD ($FEV_1 \leq 50\%$ predicted normal) in adults with frequent symptoms despite long-acting bronchodilator use, and/or a history of recurrent exacerbations. Symbicort Turbuhaler and Rapihaler are not indicated for the initiation of bronchodilator therapy in COPD. |
| *Route(s) of administration:* | Inhalation |

[1] Eformoterol is the preferred name used in Australia. It is synonymous with the name formoterol used overseas.
[2] Symbicort inhalers are labelled in terms of their metered dose in Australia. Delivered dose is frequently used in this document. Metered doses of 200/6 and 400/12 correspond to delivered doses of 160/4.5 and 320/9.

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|---|---|
| *Dosage:* | Adults:<br>*Symbicort Turbuhaler 200/6*<br>2 inhalations of Symbicort 200/6 twice daily. The maximum recommended daily dose is 4 inhalations (corresponding to 800 μg budesonide / 24 μg eformoterol).<br>*Symbicort Turbuhaler 400/12*<br>1 inhalation of Symbicort 400/12 twice daily. The maximum recommended daily dose is 2 inhalations (corresponding to 800 μg budesonide / 24 μg eformoterol).<br>*Symbicort Rapihaler 200/6*<br>2 inhalations of Symbicort 200/6 twice daily. The maximum recommended daily dose is 4 inhalations (corresponding to 800 μg budesonide / 24 μg eformoterol). |
| *ARTG Number (s):* | 80876, 80877, 115555 |

## Product Background

This submission is to seek approval of a new indication in the treatment of chronic obstructive pulmonary disease (COPD) for the following Symbicort products:

- Symbicort Turbuhaler: budesonide 200 μg/eformoterol 6 μg for inhalation dry powder inhaler, AUST R 80876
- Symbicort Turbuhaler: budesonide 400 μg/eformoterol 12 μg powder for inhalation dry powder inhaler, AUST R 80877
- Symbicort Rapihaler: budesonide 200 μg/eformoterol 6 μg for inhalation pressurised metered dose inhaler AUSTR R 115555.

Symbicort is a fixed combination inhalation product containing budesonide (a glucocorticosteroid) and eformoterol fumarate dihydrate (a long-acting β2-agonist). There are two inhaler types: Symbicort Turbuhaler is a dry powder inhaler (DPI) and Symbicort Rapihaler is a pressurised metered dose inhaler (pMDI). The current indications are as follows:

Symbicort Turbuhaler 100/6 and 200/6: "indicated for the treatment of asthma where use of a combination (inhaled corticosteroid and long acting β2-agonist) is appropriate. 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 alternative treatment regimens: Symbicort maintenance and reliever therapy; Symbicort maintenance therapy."

Symbicort Turbuhaler 400/12: "indicated for the regular treatment of asthma where use of a combination (inhaled corticosteroid and long acting β2-agonist) is appropriate. This includes: patients who are symptomatic on inhaled corticosteroid therapy; patients who are established on regular long acting β2-agonist and inhaled corticosteroid therapy. Symbicort 400/12 should only be used in patients aged 18 years and older."

Symbicort Rapihaler 100/6 and 200/6: "indicated for the regular treatment of asthma where use of a combination (inhaled corticosteroid and long acting β2-agonist (LABA)) 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."

The proposed extension of indications to COPD is as follows:

*Symbicort (Turbuhaler* 200/6 and 400/12 *and Rapihaler* 200/6*) is indicated for the maintenance treatment of moderate to severe COPD ($FEV_1$ ≤50% predicted normal) in subjects with frequent symptoms and/or history of exacerbations, where use of a combination (inhaled corticosteroid and long-acting ß2-agonist) is appropriate. The proposed COPD dosage consists of a total daily dose of 800 µg budesonide and 24 µg eformoterol, administered in divided doses twice daily.*

Chronic obstructive pulmonary disease is defined as a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual subjects. Its pulmonary component is characterized by airflow limitation, that is, not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

The pathophysiology of COPD involves both inflammatory and bronchoconstrictive components and so it is expected that glucocorticosteroids (GCS) and bronchodilator therapy would be beneficial. The spirometric classification of COPD severity includes four stages: Stage I - mild, Stage II - moderate, Stage III - severe and Stage IV - very severe (Table 1).

Table 1: Spirometric severity of chronic obstructive pulmonary disease based on postbronchodilator $FEV_1$

| | | |
|---|---|---|
| Stage I | Mild | $FEV_1/FVC$ <0.70<br>$FEV_1$ ≥80% predicted |
| Stage II | Moderate | $FEV_1/FVC$ <0.70<br>50% ≤ $FEV_1$ <80% predicted |
| Stage III | Severe | $FEV_1/FVC$ <0.70<br>30%≤ $FEV_1$<50% predicted |
| Stage IV | Very Severe | $FEV_1/FVC$ <0.70<br>$FEV_1$ <30% predicted or $FEV_1$ <50% predicted plus chronic respiratory failure |

$FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO2) <8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO2 (PaCO2) >6.7 kPa (50 mm Hg) while breathing air at sea level.

## Regulatory Status

Symbicort Turbuhaler has been available for many years and Symbicort Rapihaler received Australian registration in February 2006.

In June 2003 AstraZeneca (AZ) submitted an application to register the COPD indication for Symbicort Turbuhaler. This application was based on two clinical studies, Study SD-039-0629 (Study A) and Study SD-039-0670 (Study B). The application was rejected by the TGA Delegate, consistent with the advice of the Australian Drug Evaluation Committee (ADEC), on the basis of inadequate evidence for the clinical efficacy of the budesonide component of the combination; however, the Clinical Evaluator had concluded that 'efficacy has been confirmed in two large cohorts with COPD without evidence of safety concerns'. AstraZeneca withdrew the application on 16 April 2004.

This current application has been submitted on the basis that, according to the sponsor:

- Many of the factors that contributed to the original TGA/ADEC's recommendation (in April 2004) have changed. The role of LABA/inhaled glucocorticosteroids (IGCS) combinations in

the management of COPD has now been firmly established in current clinical practice, which is evident in the current recommendations for LABA/IGCS combinations in the latest international and local COPD guidelines (such as GOLD and COPD-X).

- Two new studies have been completed recently that investigated the efficacy and safety of Symbicort Rapihaler in subjects with moderate and severe COPD. The studies were randomised, double-blind, placebo-controlled clinical studies, in COPD patients treated for 6 months ('SHINE' or D5899C00002 study) and 12 months ('SUN' or D5899C00001 study), in a total of 3668 COPD patients.
- Symbicort has consistently been shown to reduce the frequency of exacerbations, improve lung function and improve symptoms and quality of life in subjects with moderate and severe COPD. The safety profile of budesonide, eformoterol and their fixed combination (Symbicort) has been extensively studied and well-established in asthma. No further safety issues have been identified in the COPD populations of all Symbicort studies (Studies A and B, as well as the two new Rapihaler studies, SUN and SHINE) compared to what is already known about budesonide, eformoterol or Symbicort.

Symbicort Turbuhaler

Currently Symbicort Turbuhaler is approved for use in COPD in 99 countries including the European Union (approved 7 February 2003), New Zealand (approved 19 February 2004) and Canada (5 August 2009). These approvals were based on data from the two pivotal studies (Studies A and B).

Symbicort Rapihaler

Currently, Symbicort Rapihaler is approved for maintenance treatment of COPD in 3 countries world-wide (USA, Mexico and Venezuela). The current COPD submission for Symbicort Rapihaler contains the two new pivotal studies: D5899C00001 (SUN) and D5899C00002 (SHINE). This submission was approved in USA on 27 February 2009. There have been no withdrawals, deferrals or rejections of this new dossier that includes the two pivotal pMDI studies.

### Product Information

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

## *II. Quality Findings*

### Drug Substances (active ingredients)

Budesonide (CAS number 51333-22-3)

Budesonide is a non-halogenated glucocorticosteroid (GCS) structurally related to 16 α-hydroxyprednisolone. The chemical name is 16α, 17α–22 R, S-propylmethylenedioxypregna -1, 4-diene-1ß, 21-diol-3, 20-dione.

Eformoterol fumarate dihydrate (CAS number 43229-80-7)

Eformoterol is a long-acting β2-agonist. The chemical name is (R*R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)- 1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate.

### Drug Product

Symbicort Rapihaler contains budesonide and formoterol fumarate dihydrate as the active ingredients. Symbicort Rapihaler also contains the inactive ingredients povidone (polyvinylpyrolidone K25), macrogol (polyethylene glycol) 1000, and apaflurane (known as

hydrofuroalkane (HFA)-227). Symbicort Turbuhaler contains budesonide and formoterol fumarate dihydrate as the active ingredients and the inactive ingredient lactose.

### Quality Summary and Conclusions

There was no requirement for a quality assessment in a submission of this type.

## III. Nonclinical Findings

There was no requirement for a nonclinical assessment in a submission of this type.

## IV. Clinical Findings

### Introduction

The current application was supported by data from two Phase I bioavailability (BA) studies, one Phase II pharmacodynamic study and two Phase III efficacy and safety studies which were identified as pivotal studies. In addition, one of the Phase IIIA studies (Study D5899C00002; SHINE) included an assessment of pharmacokinetics (PK) in a subset of subjects. Although this application relates to the combination of budesonide 160 μg and eformoterol 4.5 μg delivered by pMDI (Symbicort Rapihaler), it also includes the combination of budesonide 160 μg and eformoterol 4.5 μg delivered by dry powder inhaler (Symbicort Turbuhaler). The latter is supported by two Phase III clinical trials which have been published.[3,4] The TGA Clinical Evaluator's Report for the 'Application to extend registration of Symbicort (budesonide/eformoterol) Turbuhaler 200/6 for use in chronic obstructive pulmonary disease (COPD)' from 2004 was also available for review. The reports for these two trials (in the previous application in 2003) were not provided, but they were discussed in the sponsor's *Integrated Summary of Efficacy* and were reviewed in the sponsor's *Expert Commentary* in the current application.

The two Phase III pivotal studies in the current submission evaluated the efficacy and safety of two dosage strengths of Symbicort Rapihaler (80/4.5 μg and 160/4.5 μg per actuation), each administered as 2 actuations twice daily (bd). These studies were placebo and active-controlled and were conducted at investigative sites within and outside the US. Treatment duration was 6 months in one and 12 months in the other.

The Phase I studies evaluated the relative systemic BA of budesonide and eformoterol in subjects with COPD when given either as Symbicort pMDI or as a combination of the monoproducts used as active comparators in the Phase IIIA safety and efficacy studies, that is, budesonide pMDI and eformoterol Turbuhaler.

The PK analysis in the SHINE study measured plasma concentrations over 12 hours at steady state to assess the systemic exposure to budesonide and eformoterol following administration of Symbicort pMDI 80/4.5 μg, Symbicort pMDI 160/4.5 μg, budesonide pMDI 160 μg and eformoterol Turbuhaler 4.5 μg (when taken together and separately).

One Phase II pharmacodynamic study D5899C00748 compared the early bronchodilating effects of Symbicort pMDI, Seretide pMDI and Ventolin pMDI and the bronchodilating effects of these treatments through 180 minutes post-dose. The Phase IIIA COPD program for Symbicort pMDI was designed to characterize the efficacy and safety of Symbicort as maintenance therapy in subjects with COPD, and to demonstrate that Symbicort satisfies the combination rule.

There were two studies identified as pivotal:

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[3] Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003;21: 74-81.

[4] Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 2003 ; 22: 912-9.

Study D5899C00001 entitled 'A 12-Month Double-blind, Double-dummy, Randomised, Parallel group, Multicentre Efficacy & Safety Study of Symbicort pMDI 2 x 160/4.5 µg bd and 2 x 80/4.5 µg bd Compared to Formoterol Turbuhaler 2 x 4.5 µg bd and Placebo in Patients with COPD' (SUN).

Study D5899C00002 entitled 'A 6-Month Double-blind, Double-dummy, Randomised, Parallel group, Multicentre Efficacy & Safety Study of Symbicort pMDI 2 x 160/4.5 µg & 80/4.5 µg bd Compared to Formoterol Turbuhaler, Budesonide pMDI (& the combination) & placebo in COPD Patients (SHINE)'.

Both of the pivotal studies were randomised, double-blind, placebo-controlled, parallel-group, multicentre studies; in both studies Symbicort was administered as a pMDI (Rapihaler).

### Pharmacokinetics

There were two pharmacokinetic studies presented for evaluation in support of this application:

Study D5899C00006 and study SD-039-0738. Both studies examined the systemic BA of budesonide and formoterol administered by Symbicort pMDI and the monocomponents budesonide pMDI and formoterol Turbuhaler administered sequentially. Study D5899C00006 examined the pharmacokinetics over a period of 36 hours and study SD-039-0738 over a period of 12 hours. In addition the systemic BA of budesonide and formoterol in asthma subjects was compared to COPD subjects for Symbicort in study D5899C00006.

**SHINE study**. Pharmacokinetic (PK) testing was planned for a subgroup of approximately 180 subjects in the US, Poland, and the Czech Republic. These subjects underwent serial $FEV_1$ measurements at Visit 6; blood specimens were obtained pre-dose and 10, 20, 40, 60, 120, 240, 360, 540 and 720 minutes after the start of inhalation of study medication. Testing was performed for plasma levels of budesonide and formoterol. This study was not designed or intended to be a bioequivalence study; therefore there was no decision rule associated with these data. All budesonide-containing treatment groups were compared for all budesonide PK analyses and all formoterol-containing treatment groups were compared for all formoterol PK analyses.

The data were given only as a summary as follows: Exposure to budesonide (area under the curve from time zero to 12 hours [$AUC_{0-12}$] and the maximal plasma concentration [Cmax] at Month 6) was similar for subjects in the Symbicort pMDI 160/4.5, budesonide 160, and budesonide 160 plus formoterol 4.5 treatment groups and approximately 2-fold higher in the Symbicort pMDI 160/4.5 group compared with the Symbicort pMDI 80/4.5 group. The median time to maximal plasma concentration [Tmax] was approximately 20 to 40 minutes for each of these 4 treatment groups. Exposure to formoterol, based on $AUC_{0-12}$ and Cmax at Month 6, was slightly higher in the Symbicort pMDI 160/4.5 compared with the formoterol 4.5 treatment group but generally similar compared with Symbicort pMDI 80/4.5 and budesonide 160 plus formoterol 4.5. Formoterol Cmax values were similar amongst the 4 treatment groups. Results indicated a median Tmax of 40–60 minutes in the Symbicort pMDI groups and of 10–20 minutes in the budesonide 160 plus formoterol 4.5 and formoterol 4.5 groups.

**Study D5899C00006** was an open-label study of the relative systemic bioavailability of budesonide and formoterol in subjects with chronic obstructive pulmonary disease following single dose inhalation of Symbicort pMDI compared with budesonide pMDI plus formoterol Turbuhaler and in moderate asthma subjects following single dose inhalation of Symbicort pMDI.

The primary objective of this study was to estimate the relative systemic BA of budesonide and formoterol when inhaled from Symbicort compared with budesonide pMDI plus formoterol Turbuhaler in subjects with COPD; to compare the pharmacokinetics of budesonide and formoterol when inhaled from Symbicort in subjects with COPD versus subjects with asthma. The secondary

objective was to assess the safety and tolerability of single doses of Symbicort and budesonide pMDI plus formoterol Turbuhaler in subjects with COPD and Symbicort in subjects with asthma.

This was a Phase I open-label crossover study carried out at a single centre in the USA. Subjects with COPD were administered single doses of Symbicort 960/54 μg and budesonide 960 μg plus formoterol 54 μg; subjects with asthma were administered a single dose of Symbicort 960/54 μg. The COPD portion of the study comprised four visits. Visit 1 was for eligibility; treatments were given at Visits 2 and 3; Visit 4 was a follow up visit. Patients remained in the Clinical Pharmacology Unit for 36 hours during which time bloods were drawn. The following two single-dose treatments were separated by a washout period of ≥3 days and ≤14 days:

(1) Symbicort, budesonide/formoterol 80/4.5 μg per actuation; 12 actuations corresponding to a single dose of 960/54 μg.

(2) Oxis Turbuhaler, formoterol 4.5 μg/actuation 12 inhalations followed by budesonide pMDI 80 μg /actuation 12 inhalations, also corresponding to a single dose of budesonide 960μg and formoterol 54 micrograms.

The asthma portion of the study comprised three visits; eligibility assessments were performed at Visit 1; Visit 2 was the treatment visit and Visit 4 was a follow-up visit and occurred 3-14 days after Visit 2. There was no Visit 3 for asthma subjects. The following single dose treatment was administered: Symbicort, budesonide/formoterol 80/4.5 μg per actuation; 12 actuations corresponding to a single dose of 960/54 μg.

*Inclusion and exclusion criteria*. The study aimed to recruit subjects with COPD of either sex, aged ≥40 years who had been symptomatic for ≥2 years and were ex- or current smokers with a ≥10 pack year smoking history. Patients were allowed to continue smoking for the course of the study. The body mass index (BMI) had to be 18–30 kg/m$^2$. Prebronchodilator $FEV_1$ was between 20–70% predicted and the prebronchodilator $FEV_1$/FVC ratio was ≤70%. Subjects were excluded if they had experienced an exacerbation of their COPD within 6 weeks before the first dose of study drug. An exacerbation of COPD was defined as a worsening of symptoms of COPD requiring drug therapy in addition to the usual COPD medications. Other key exclusion criteria were onset of COPD symptoms before age 35 years, $SaO_2$ <88%, use of domiciliary oxygen, or a history of asthma or significant heart disease. Electrocardiograms were obtained at Visit 1 (enrolment) and at pre-dose and one and 6 hours post-dose. Inclusion criteria for asthma subjects were diagnosed asthma of ≥6 months duration, aged ≥18 years of either sex with a BMI of 18–30 kg/m$^2$. They had to have a postbronchodilator (approximately 6 hours after SABA or LABA) 60–90% predicted and reversibility of ≥12% and ≥200 ml. They must have been taking IGCS for 3 months and the dose had to be stable 30 days before inclusion and at a minimum dose equivalent to at least budesonide 400 μg/day for the previous 30 days. The asthma had to be well controlled on current medications, as assessed by the investigator. Exclusion criteria for asthmatic subjects included smoking within 6 months before Visit 1.

*COPD subjects*. All COPD subjects received both treatments. The order in which subjects received each treatment was randomised in a crossover, balanced design. COPD subjects were randomised strictly sequentially as subjects were eligible for enrolment/randomisation. Bloods for PK assessment were obtained at baseline (approximately 15 minutes before inhalation) and at 15, 30, 45, and 60 minutes and 2, 4, 6, 8, 10, 12 16 20, 24, 30 and 36 hours after inhalation. For both COPD and asthma subjects bloods for chemistry and haematology were drawn at Visit 1 and Visit 4 and in addition serum magnesium, glucose and potassium were measured at 2 and 24 hours after drug inhalation. Electrocardiograms were obtained at baseline and at 45 minutes and 6 hours after study drug and at Visit 4 follow up. The protocol for this study was modified from a previous study in COPD subjects (Study SD-039-0738) to include a higher dose of formoterol and longer plasma sampling time for both formoterol and budesonide. This was done in an attempt to decrease the extrapolated portion of the AUC (AUC ext) to <20%. In the current study all AUCext values for

budesonide were < 20%; for formoterol all AUCext values were less than 20% in subjects with asthma; in COPD <10% of values for AUCext exceeded 20%. All asthma subjects received a single dose of Symbicort, 960/54 µg. Asthma subjects were entered strictly sequentially as subjects were eligible for enrolment.

*Primary variable*. The primary measurement was plasma concentration of budesonide and formoterol. The primary outcome variable was the plasma concentration $AUC_{0-\infty}$ for budesonide and formoterol. The study was descriptive and did not aim to prove any hypothesis. The lower limit of quantification (LOQ) for budesonide in human plasma was 0.010 nmol/L and for formoterol was 5 pmol/L. The study aimed to randomise 26 COPD and 26 asthma subjects with an expectation that 24 in each group would complete the study. In a previous study[5] in healthy subjects which compared relative systemic BA when administering a single dose of 1280/36 µg from Symbicort and Symbicort Turbuhaler, the within-subject standard deviation for log-transformed AUC0-∞ was 0.25 for budesonide and 0.30 for formoterol. With this variability and 24 COPD subjects completing the study, the 90% CI for the relative BA, of Symbicort versus the monoproducts, for budesonide and formoterol would range from 0.89 to 1.13 times the observed mean relative BA of budesonide and 0.87 to 1.15 times the observed mean relative BA of formoterol respectively. In the same study the between-subject SD for log-transformed AUC was 0.27 for budesonide and 0.34 for formoterol. With this variability and 24 subjects of each type completing the study the 90% confidence intervals for the $AUC_{0-\infty}$ ratios between COPD and asthma subjects for budesonide and formoterol would range from 0.88 to 1.14 times the observed mean ratio for budesonide and 0.85 to 1.17 times the observed mean ratio for formoterol. 58 subjects were enrolled of whom 52 received study treatment (26 COPD and 26 asthma). The full analysis set (FAS) consisted of all 52 randomised subjects, all of whom completed the study. All subjects had plasma concentration data for all treatment periods. The pharmacokinetic evaluation is therefore based on 52 subjects, 26 COPD subjects and 26 asthma subjects.

**Primary outcome variable $AUC_{0-\infty}$**

(1) Plasma concentration of budesonide in chronic obstructive pulmonary disease subjects.

Mean $AUC_{0-\infty}$ was similar between Symbicort 940/54 µg and budesonide pMDI 960 µg plus formoterol Turbuhaler 54µg: 14.08 and 14.49 nmol/L.h respectively. The $AUC_{0-\infty}$ budesonide concentration was nearly identical between the two treatments with a treatment ratio of 0.97. In summary, the relative BA of budesonide when inhaled from Symbicort compared with budesonide 160 plus formoterol 4.5 was estimated to be 97% (based on $AUC_{0-\infty}$).

(2) Plasma concentrations of formoterol in COPD subjects.

Mean $AUC_{0-\infty}$ (nmol/L.h) for Symbicort and budesonide 960 µg plus formoterol 54 µg were 945 and 801 respectively. Comparing Symbicort and budesonide plus formoterol Turbuhaler, $AUC_{0-\infty}$, $AUC_{0-t}$ and Cmax were greater after Symbicort compared to budesonide 960 µg plus formoterol 54 µg with treatment ratios of 1.18, 1.22 and 1.22 respectively for Symbicort versus budesonide. The relative BA of formoterol when inhaled with Symbicort compared with budesonide plus formoterol was estimated to be 118% (based on $AUC_{0-\infty}$); $t_{1/2}$, Tmax and MRT were similar for the two treatments.

*Secondary variables*. $AUC_{0-t}$ and Cmax were nominated as key secondary variables.

Mean $AUC_{0-t}$ in mmol/L.h was 13.90 and 14.31 for Symbicort and budesonide 960 µg plus formoterol 54 µg respectively; mean Cmax (nmol/L) was 3.30 and 3.18 for Symbicort and budesonide 160 plus budesonide 960 µg plus formoterol 54 µg respectively. Both variables were nearly identical between the two treatments with a ratio of 0.97 and 1.04 respectively. Other

[5] Clinical study SD-039-0730, an open label, randomised, three-way, crossover study in healthy subjects of the relative systemic bioavailability of budesonide and formoterol

secondary end points (Mean Residence Time [(MRT], $t_{1/2}$ and Tmax) were similar between the two treatments.

The limits for bioequivalence are given as 80–125% and if this is the case then for budesonide there is bioequivalence in between the two modes of administration.

*Asthma versus COPD subjects*. Budesonide mean plasma concentrations were higher in COPD subjects than in asthma subjects except for the first hour. The between-patient variability was smaller in asthma subjects. Mean $AUC_{0-\infty}$ was higher in COPD subjects; mean Cmax was higher in asthma subjects. Mean half-life ($t_{1/2}$), median tmax and mean MRT were longer in COPD subjects than in asthma subjects. Mean plasma concentrations of formoterol were slightly higher in COPD subjects compared with asthma subjects (data not given). Both $AUC_{0-\infty}$ and Cmax were slightly higher in COPD subjects than in asthma subjects. The between-patient variability in AUC0-∞ for budesonide was smaller in asthma subjects (CV =24%) than in COPD subjects (CV = 41%) whereas Cmax showed no such difference. For formoterol there was no difference in variability in $AUC_{0-\infty}$ or Cmax between asthma or COPD subjects.

*Summary.* In COPD subjects the relative systemic BA of budesonide when inhaled from Symbicort compared with budesonide pMDI plus formoterol Turbuhaler was estimated to be 97% (based on $AUC_{0-\infty}$). For $AUC_{0-\infty}$, $AUC_{0-t}$ and Cmax the 90% CI for the mean treatment ratios were within the established bioequivalence limits of 80–125%. In COPD subjects the relative systemic BA of formoterol when inhaled from Symbicort compared with budesonide pMDI plus formoterol Turbuhaler was estimated to be 118% (based on $AUC_{0-\infty}$); $AUC_{0-t}$ and Cmax showed similar relationships.

**Study SD-039-0738** was an open-label, two-way crossover study in subjects with chronic obstructive pulmonary disease of the relative systemic BA of budesonide and formoterol when inhaled as a single dose of 1280/36 µg from Symbicort· pMDI compared with budesonide pMDI plus formoterol Turbuhaler (Oxis).

The primary objective of this study was to estimate the relative systemic BA of budesonide when inhaled from Symbicort compared with budesonide pMDI and of formoterol when inhaled from Symbicort compared to Oxis Turbuhaler in subjects with COPD. The secondary objective was to assess the safety and tolerability of single doses of Symbicort and budesonide pMDI plus formoterol Turbuhaler in subjects with COPD. This was a Phase I study, randomised, open-label, two-way crossover study carried out at a single centre in the USA. Subjects with COPD were administered single doses of Symbicort (1280/36 µg) and budesonide 160 µg plus formoterol 4.5 µg (1280/36 µg). The study comprised four visits: Visit 1 was for eligibility; treatments were given at Visits 2 and 3, and Visit 4 was a follow up visit. At Visits 2 and 3 subjects remained in the Clinical Pharmacology Unit for 12 hours during which time bloods were drawn. The two single dose treatments were separated by a washout period of between 3 and 14 days inclusive. Visit 4 occurred between 5–14 days after Visit 3.

Subjects were randomised to receive:

- Symbicort pMDI, budesonide/formoterol 160/4.5 µg per actuation; 8 actuations corresponding to a single dose of 1280/36 µg.
- Oxis Turbuhaler, formoterol 4.5 µg per inhalation, plus budesonide pMDI, 160 µg per actuation. A single dose of formoterol 36 µg and budesonide 1280 µg was achieved by 8 inhalations from formoterol Turbuhaler and 8 actuations from budesonide pMDI directly after each other and in this order.

The inclusion and exclusion criteria were the same as the study D5899C00006 except that the age limit was 40–80 years inclusive and prebronchodilator $FEV_1/FVC$ ratio was ≤65%. All subjects received both treatments. Bloods for PK assessment were obtained at baseline (approximately 15

minutes before inhalation) and at 10, 20, 40, 60 minutes and 2, 4, 6, 8, 10, and 12 hours after inhalation of study medication. Chemistry and haematology bloods were drawn at Visit 1 and Visit 4 and in addition serum magnesium, glucose and potassium levels were measured at 1 and 12 hours after drug inhalation. Electrocardiograms were obtained at Visit 1, baseline, and at 30 minutes and 1, 2, 6 and 12 hours after study drug and at Visit 4 follow up. The primary variable was plasma concentration of budesonide and formoterol. The primary outcome variable was the plasma concentration AUC0-12 for budesonide and formoterol. Secondary variables were the same as in Study D5899C00006. A total of 34 subjects were enrolled of whom 30 were randomised and received study treatment. There were 22 women and 8 men; 17 were Caucasian and 13 were Black; the mean age (range) was 52.8 years (43–67); mean $FEV_1$ was 1.1 L (0.67–1.56); baseline FVC was 2.12 L (1.28–3.17) and the mean BMI was 26.2 $kg/m^2$ (19.5– 30). All subjects completed the study and all had data for budesonide AUC for both treatments. In addition because of technical reasons the measurement of plasma concentrations of formoterol was considered unreliable and therefore data for formoterol will not be discussed further.

*Primary outcome variable* $AUC_{0-\infty}$

(1) Plasma concentrations of budesonide.

The geometric mean of AUC for Symbicort was higher than that for budesonide pMDI (21.5 nmol.h/L (66.3) versus 19.2 (58.2)). The ratio of Symbicort to budesonide was 1.12 (90% CI 0.98 to 1.28). $AUC_{0-t}$ (area under the curve from time 0 to the last value above LOQ) and Cmax were nominated in the sponsor's *Clinical Study Report* as the key secondary variables. These pharmacokinetic parameters were also higher for Symbicort compared to budesonide pMDI; for $AUC_{0-t}$ (mmol/L.h) the means were 17.0 (40) and) 15.8 (42.3) for Symbicort and budesonide pMDI respectively with ratio 1.08 (0.97–1.19). The means for Cmax were nmol/L 4.92 (39.2) and 4.55 (42.2) for Symbicort and budesonide respectively (ratio1.08 (0.93–1.25).

## Drug Interactions

No drug interactions studies were submitted with the application.

## Pharmacodynamics

### Study D5899C00748

A randomised, placebo-controlled, double-blind, double-dummy, crossover study to assess the onset of action of two inhalations of Symbicort pMDI 160/4.5 µg, compared with two inhalations of Seretide pMDI (salmeterol/fluticasone) 250/25 µg, two inhalations of Ventolin (salbutamol) 100 µg, and placebo, delivered by pressurised metered dose inhalers, in subjects with chronic obstructive pulmonary disease (COPD).

The primary objective of this study was to evaluate the efficacy (bronchodilatation) within 180 minutes of Symbicort 160/4.5 µg two inhalations, Seretide pMDI 250/25 µg, 2 inhalations, Ventolin pMDI 100 µg, 2 inhalations and placebo in subjects with COPD. This study consisted of a screening visit and four randomised visits. The study aimed to recruit subjects of both sexes, with a diagnosis of COPD, symptomatic for >2 years, aged ≥40 years and who were current or ex-smokers with a smoking history of ≥10 pack years. Specific spirometric inclusion criteria were: evidence of airflow limitation and significant reversibility 15 minutes after inhaling two doses of 0.5 mg terbutaline administered by Turbuhaler; prebronchodilator $FEV_1$ 30–70% predicted (≤85% postbronchodilator) and prebronchodilator $FEV_1$/FVC ratio ≤70%. Patients who had a history of asthma or allergic rhinitis over the previous 20 years and had suffered an exacerbation <30 days before study entry were excluded.

This was a multicentre study conducted in Sweden (10 centres) and Hungary (9 centres). The study comprised 6 visits; Visit 1 was a screening visit and at Visit 2 (approximately 7 days after Visit 1) eligible subjects had spirometric reversibility repeated and were randomised to receive treatment on

four separate occasions (Visits 3, 4, 5 and 6) with two inhalations of Symbicort 160/4.5 µg, Seretide, 250/25 µg, Ventolin 100 µg or placebo. The treatment visits were separated by a washout period of ≥three days. Because the three inhalers (Symbicort, Seretide and Ventolin differed in appearance) subjects took two inhalations from each of three inhalers at each visit. Thus, on three of the visits one device contained active compound and two contained placebo, and on one of the visits all three inhalers contained placebo. At Visits 3–6 spirometry (measuring $FEV_1$) was performed just before and at 3, 5, 10, 20, 30, 60, 120 and 180 minutes after inhalation of study drug. Inspiratory capacity (IC) was obtained before and 15, 35, 65, 125, 185 minutes after inhalation and the Perception of Onset of Effect (POE) questionnaire was administered immediately before the measurement of $FEV_1$ at each time point, pre- and post-administration of drug.

*Primary outcome variable*. The primary outcome variable was $FEV_1$ 5-minutes (5 min $FEV_{1)}$ after administration of randomised treatment expressed as a percentage of baseline. The primary comparison was between Symbicort 160/4.5 µg and Seretide 250/25 µg. This was a superiority study and the aim was to show that Symbicort was superior to Seretide in onset of bronchodilatation at 5 minutes. The ratio of $FEV_1$ at 5 min/ $FEV_1$ baseline expressed as a percentage was compared between treatments using a multiplicative analysis of variance (ANOVA) model with patient, period and treatment as fixed factors and the baseline $FEV_1$ before drug intake as a covariate; measurements including the covariate were log-transformed and then analysed in an additive ANOVA and the estimates were then back transformed by exponentiation; 95% confidence intervals were calculated, all expressed as percentage. For the measurement of 5-min $FEV_1$, assuming 80 subjects and a residual standard deviation of 0.083 (logarithmic scale), a difference of 4.4 % in $FEV_1$ would be detected with 90% power using a t-test. No subject was excluded from the full analysis set because of protocol deviations. There were no issues of multiplicity.

*Perception of Onset of Effect (POE) questionnaire*. This was self-administered during Visit 3-6. The patient was to answer yes or no to a question as to whether he or she felt that the study medication was working. If the answer was yes, the patient was to choose between given alternatives for reasons that led him or her to answer yes to the first question. The POE question was answered immediately prior to the $FEV_1$ measurements at 3, 5, 10, 20, 30, 60, 120, and 180 minutes after inhalation of investigational product. The outcome variable was the first time point that the answer was "yes" in minutes relative to inhalation of study drug. For subjects reporting no perception of onset of effect any time point, the time 180 minutes was used. The time to first POE was compared between treatments using a Wilcoxon signed-rank test and the difference was described by the Hodge-Lehmann estimate and its associated 95% confidence interval. Kaplan-Meier plots were created for time to onset in POE.

*Study subjects*. 90 subjects were randomised and allocated a treatment sequence and 89 subjects took study medication; one patient had data post inhalation from only one study period so that the FAS consisted of 88 subjects. Three subjects discontinued the study prematurely: two for adverse effects (AE) and one for other reasons. Of the randomised subjects 50 (56%) were male, the mean age was 61.7 years (41–79) and all were Caucasian. The mean (range) BMI ($kg/m^2$) was 26.3 (18–40); 54 (60%) were ex smokers, 3 (3%) were occasional smokers and 33 (37%) were current habitual smokers. The median pack-years number was 35 (10–114); 44 subjects (49%) were taking IGCS at a mean dose of 633.4 µg/day. The spirometric characteristics (mean (range) were: vital capacity (L) 2.96 (1.7–5.5); $FEV_1$ 1.32 L (0.50–2.36); predicted $FEV_1$ 47.8 (30–69); $FEV_1$/FVC ratio 45.5% (range 24–68); reversibility (%PN) 12.5 (9–24), absolute value = 0.034L (18–68).

*Primary efficacy variable*. Geometric mean $FEV_1$, 5-min post-dose, increased by 15.33%, 9.83% and 16.64% for Symbicort 160/4.5 µg, Seretide 250/25 µg and Ventolin 100 µg respectively. $FEV_1$ 5-min post-dose for placebo was virtually unchanged (difference <0.50%). Symbicort 160/4.5 µg produced greater bronchodilatation compared to Seretide 250/25 µg (ratio 105% (95% CI 102.57–107.49); p=0.0001). Furthermore all of the 'active treatments' were significantly better than

placebo: Symbicort versus placebo 115.88% (113.19, 118.63); Seretide versus placebo 110.36% (107.8, 112.98) and Ventolin versus placebo 117.19% (114.48, 119.98), all p <0.0001. The effect of Symbicort was not significantly different from Ventolin (ratio 98.88% (91.98–96.41) p=0.3464); Ventolin was superior to Seretide (Seretide/Ventolin ratio 94.17% (91.98, 96.41); p <0.0001).

*Secondary efficacy variables*. These were $FEV_1$ at 3 and 180 minutes, maximal $FEV_1$ and $FEV_1$ (0–180 minutes) (AUC). At 3 minutes post-dose, all of the active treatments produced significantly greater bronchodilatation compared to placebo: Symbicort/placebo ratio 111.67% (p<0.0001); Seretide pMDI/placebo 105.50% (p<0.0001); Ventolin pMDI/placebo 113.44% (p<0.0001). Treatment with Symbicort gave 5.85% higher $FEV_1$ compared to treatment with Seretide (<0.0001). Symbicort did not differ significantly from Ventolin (p=0.1709).

(1) The maximal $FEV_1$ did not differ significantly between any of the active treatments. The $FEV_1$ was higher after inhalation of Symbicort, Seretide and Ventolin compared to placebo (increases of 13.46%, 12.14% and 13.53% for Symbicort, Seretide and Ventolin respectively; all p<0.0001).

(2) $FEV_1$ (0–180 minutes) AUC findings were qualitatively similar to maximal $FEV_1$, that is, no differences between the active treatments but all three were significantly different to the placebo (increases of 16.09%, 14.68% and 15.65; all p<0.0001 for Symbicort, Seretide and Ventolin versus placebo respectively). At 15 minutes IC increased by 14 to 15% from baseline for the three active treatments and no differences could be detected between these treatments; however, they were all superior to placebo, with differences of approximately 11 to 12% versus placebo. Maximal IC was higher following Symbicort on average compared to treatment with Seretide pMDI (3.6% (p=0.0184). For average IC during the 185 minutes observation interval after study drug administration, no differences could be shown between the three active treatments, but they were all superior to placebo with increases of 13.93%, 11.21% and 12.46% for Symbicort pMDI, Seretide pMDI and Ventolin pMDI versus placebo respectively (all p<0.0001).

Perception of Onset of Effect. The proportions of subjects reporting 'yes' to the POE question were 84%, 81%, 84% and 61% for Symbicort, Seretide, Ventolin and placebo respectively. The median time to POE for the active treatments was 5 versus 20 minutes for placebo. The differences between the active treatments were not significant but the median times were significantly less compared to placebo for all active treatments (p≤0.0006).

## Efficacy

**Study D5899C00001 (SUN).** A 12-Month Double-blind, Double-dummy, Randomised, Parallel group , Multicentre Efficacy & Safety Study of Symbicort pMDI 2 x 160/4.5 µg bd and 2 x 80/4.5 µg bd compared to Formoterol Turbuhaler 2 x 4.5 µg bd and Placebo in Patients with COPD(SUN).

This was identified as a pivotal study conducted at a total of 237 sites in US and 8 other countries. The following treatments were used in adults with COPD:

(1) Symbicort, 2 x 160/4.5 µg bd

(2) Symbicort, 2 x 80/4.5 µg bd

(3) Formoterol Turbuhaler, 2 x 4.5 µg bd

(4) placebo

To maintain the double-dummy blinding of study medication, subjects randomised to active treatment delivered by a pMDI device (that is Symbicort) also received placebo delivered by a Turbuhaler device. Subjects randomised to active treatment delivered by a Turbuhaler device (that is formoterol) also received placebo delivered by a pMDI device. Subjects randomised to placebo received placebo pMDI plus placebo Turbuhaler. The study was of 52 weeks duration and the potential treatment period was 365±7 days.

The study consisted of a screening visit (Visit 1), a 2 week run-in period followed by randomisation at Visit 2 and then a 52 week treatment period. There were 6 visits during the treatment period, at 1, 2, 4, 6 and 12 months. There was a telephone follow-up 4 weeks after completion of the study. Spirometry was obtained at each visit before the study medication was taken and at one hour post dose. In addition serial spirometry and inspiratory capacity over 12 hours were obtained in a subgroup of subjects at randomisation and after 6 and 12 months of treatment. Diary assessments were collected at each visit. The St. George's respiratory questionnaire (SGRQ) was administered (before all other procedures) at Visit 1 and all other visits except the four months Visit.[6] For safety assessments, routine bloods were obtained at Visit 1 and end of treatment (EoT). Electrocardiograms were obtained at randomisation and after 2, 6 and 12 months of treatment. In addition Holter monitoring was carried out in a subgroup of subjects at baseline and after 1 and 4 months of treatment. Twenty four hour urinary collection for cortisol measurements was obtained before randomisation and before the 6 and 12 months visits. Bone mineral density was measured in a subgroup at randomisation and after 12 months of treatment; ophthalmologic examination was carried out in a subgroup at baseline and after 6 and 12 months of treatment. The entry criteria were designed to recruit a representative population of subjects with moderate to very severe COPD (prebronchodilator $FEV_1$ ≤50% predicted $FEV_1$/FVC <70%) who had experienced exacerbations, whose disease burden was significant (assessed by MRC dyspnoea score ≥2 and documented use of short acting β2-agonist or anticholinergic) and who were likely to be candidates for an IGCS/LABA combination product. In order to be as inclusive as possible of the COPD population as a whole, COPD subjects with stable co-morbid conditions were recruited and there was no upper age limit.

*Co-primary variables*. The primary outcome variables were pre-dose $FEV_1$ to assess the budesonide component and 1-hour (1-h) post dose $FEV_1$ to assess the formoterol component. The primary analysis was change from baseline to the average of the randomised period using the Efficacy Analysis Set (EAS). The change in pre-dose $FEV_1$ from baseline to the average of the randomised treatment period (with no imputation of missing data), was assessed using an ANCOVA model, adjusting for the fixed factors of treatment and country and for the covariate of baseline pre-dose $FEV_1$. Treatment comparisons were made by formulating contrasts within the context of this model. The baseline was the last available $FEV_1$ before the first inhalation of randomised treatment. Additional analyses performed were change from baseline for each visit and change from baseline to EoT. End of treatment was the last observed value during the randomised period. All other time points were analysed as a change from baseline using similar methods. Analysis of 1-h post-dose $FEV_1$ was similar to that described here for pre-dose $FEV_1$.

Three key secondary variables were identified namely dyspnoea score, SGRQ total score and number of COPD exacerbations.

*Exacerbations*. A COPD exacerbation was defined as worsening of COPD that required a course of oral steroids for treatment and/or hospitalisation. The start date was defined as the start of treatment with oral glucocorticosteroid (OGCS) for the exacerbation or date of hospitalisation for treatment of the exacerbation, whichever occurred first. The end-date was defined as the date of completion of treatment with OGCS; for subjects not treated with OGCS, the end date was defined as the date of discharge from the hospital. If hospitalisation was prolonged for reasons other than COPD exacerbation, the exacerbation end-date was determined by the investigator. The main outcome variable was the number of exacerbations per patient-treatment years.

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[6] *SGRQ total score*. The SGRQ consists of 3 domains: symptoms (distress due to respiratory symptoms); activity (disturbance of physical activity), and Impacts (overall impact on daily life and well-being). Together, they comprise the total score. The main outcome assessed was the change from baseline to EoT.

For all secondary variables including those identified as key secondary variables, the primary analysis was Symbicort versus placebo.

*Other secondary variables*. The BCSS is a three-item, self-administered diary designed to evaluate the severity of 3 symptoms associated with COPD: breathlessness (using the Breathlessness Diary), cough, and sputum. Each of the 3 symptoms assessed by the measure is represented by a single item. Subjects were asked to evaluate each symptom or item on a Likert-type scale ranging from 0 to 4, with higher scores indicating a more severe manifestation of the symptom. A total symptom score (TSS) is expressed as the sum of three item scores, with a range of 0 to 12. The minimal clinically important difference (MID) is a change >0.30 on the BCSS total score.

Night-time awakening scores (also called the sleep score) were recorded every day from Visit 1 to Visit 8 in the diary cards prior to the morning dose of study drug. Night-time awakenings were assessed with a score of 0 to 4 with higher scores indicating more sleep disturbances. Only night-time awakenings caused by symptoms of COPD were to be recorded.

Morning and evening peak expiratory flow (ePEF) were analysed individually using a change from baseline to the average of the randomised treatment period (with no replacement of missing data); baseline was defined as the mean of the last 10 days of run-in, excluding Day 1. The randomised treatment period was defined as the day after the first dose of randomised treatment (study Day 2) to the last day of randomised treatment, inclusive.

**Results**

**Primary variables pre-dose and post-dose $FEV_1$**

a) Pre-dose $FEV_1$ increased significantly from baseline to the average of the randomised treatment period in all of the active treatments groups. Symbicort 160/4.5 least squares (LS) mean = 0.10 L; Symbicort 80/4.5 LS mean = 0.08 and formoterol 4.5 LS mean = 0.06. The placebo did not change significantly (LS mean = 0.01). One hour post-dose $FEV_1$ also increased significantly from baseline in the three "active" treatments but did not change significantly for placebo: Symbicort 160/4.5 LS mean = 0.21; Symbicort 80/4.5 LS mean = 0.19; formoterol 4.5 LS mean = 0.18; placebo LS mean = 0.02.

b) Symbicort 160/4.5 produced a significantly greater increase in post-dose $FEV_1$ compared to placebo (LS mean = 0.18, $p<0.001$). The increase in pre-dose $FEV_1$ from baseline to average of randomised period was also significantly greater for Symbicort 160/4.5 compared to placebo (LS mean = 0.09, $p <0.001$). Symbicort 160/4.5 produced a significantly greater increase in pre-dose $FEV_1$ compared to formoterol 4.5 (LS mean = 0.04, $p=0.008$). For pre-dose $FEV_1$, the increase from baseline in the formoterol 4.5 group was significantly greater than placebo ($p<0.001$); Symbicort 160/4.5 was not statistically significant from Symbicort 80/4.5 ($p=0.206$). For post-dose $FEV_1$ the change from baseline in the formoterol group was also greater than placebo ($p<0.001$); the two Symbicort treatments did not differ significantly ($p=0.144$); however, Symbicort 160/4.5 differed significantly from formoterol 4.5 ($p=0.023$).

c) For Symbicort 80/4.5, pre-dose $FEV_1$ and post-dose $FEV_1$ increased significantly from baseline to the average of the randomised treatment period. For the primary variables the change from baseline to average of randomised period for pre-and post-dose $FEV_1$ was greater compared to placebo (LS mean = 0.07, $p<0.001$) and LS mean = 0.16 ($p<0.001$) for pre- and post-dose $FEV_1$ respectively). However, pre-dose $FEV_1$ for Symbicort 80/4.5 was not statistically significantly different compared to formoterol 4.5 (LS mean = 0.02, $p=0.161$).

The clinical evaluator decided that the analysis for the key secondary variables was descriptive only[7].

**Key secondary variables**

*Dyspnoea index*

The primary analysis was change from baseline to the average of the randomised treatment period with no replacement of missing data. Treatment mean scores averaged over the randomised treatment period decreased significantly from base line for all the groups including placebo (Symbicort 160/4.5 LS mean = -0.37; Symbicort 80/4.5 LS mean = -0.32; formoterol 4.5 LS mean = -0.29; placebo LS mean = -0.17).

The decrease in the Symbicort 160/4.5 group was significantly more than in the placebo and formoterol 4.5 groups: LS mean = -0.20 ($p<0.001$) and LS mean = -0.08 ($p = 0.0302$) respectively. The decrease in the formoterol 4.5 group was greater than placebo (LS mean = -0.12, $p=0.003$). 55.8% of subjects who received Symbicort 160/4.5 had clinically significant improvement compared to 40.5% for placebo (OR 1.88, $p<0.001$); 51.9% of subjects in the formoterol 4.5 group had clinically significant improvement and this was significantly more than placebo (OR 1.6, $p<0.001$).

Symbicort 80/4.5 differed significantly from placebo (LS mean = -0.15, $p< 0.001$) but was not significantly different from formoterol 4.5 (LS mean = -0.04, $p=0.348$). 54.7% had a clinically important improvement compared to 40.5% of placebo (OR 1.8, $p<0.001$); 17.6% had clinically significant worsening compared to 24% of placebo subjects.

*SGRQ total score*

There was a significant decrease from baseline to EoT in all of the active treatment groups: Symbicort 160/4.5 (LS mean = -3.6); Symbicort 80/4.5 (LS mean = -4.84); formoterol 4.5 (LS mean = -2.50). Placebo did not change significantly from baseline to EoT (LS mean = -1.18). The change in the Symbicort 160/4.5 group was significantly different from placebo (LS mean = -2.39 [$p=0.006$]) but the magnitude of the change was not clinically significant. Symbicort 160/4.5 did not differ significantly from formoterol 4.5; formoterol 4.5 did not differ significantly from placebo and the two Symbicort doses did not differ significantly from each other. The domain scores were qualitatively similar expect that for the symptoms domain, Symbicort 160/4.5 was significantly different to formoterol 4.5 (LS mean = -2.83, $p=0.015$).

More subjects in the Symbicort 160/4.5 group achieved the MID for SGRQ total score compared to the placebo group but this difference was not statistically significant (45.2% versus 40.4%; OR 1.22, $p=0.163$); the proportions of subjects who worsened did not differ significantly either (25.6% versus 30.6% for Symbicort versus placebo). Regarding categories of clinical improvement, there were no significant differences for any of the other between group comparisons.

The change from baseline to EoT in the Symbicort 80/4.5 group was significantly greater than placebo (LS mean = -3.66, $p<0.001$) and formoterol 4.5 (LS mean = -2.33, $p=0.006$).

*Exacerbations*

- In the Symbicort 160/4.5 group 30.8% of subjects experienced one or more exacerbations (0.626/patient-treatment year). Corresponding data for the other groups were: Symbicort 80/4.5, 32.6% (0.584 /patient-treatment year); formoterol 4.5, 35.8% (0.826 /patient-treatment year); placebo 37.2% (0.963 /patient-treatment year).

[7] In the final outcome, after appeal evaluation (see p 47) it was accepted that the secondary analyses in SUN are statistically valid, that is, not "descriptive only". Different views on the validity of the secondary analyses occur in this AusPAR because of an anticipatory change in the statistical analysis plan before unblinding the study.

- The majority of exacerbations were treated with oral glucocorticosteroids (OGCS): Symbicort 160/4.5, 96.5%; Symbicort 80/4.5, 94.1%; formoterol 95.7%; placebo 97.4%. A much smaller proportion required hospitalisation for treatment of the exacerbations. 146 (7.4%) subjects who had a COPD exacerbation required hospitalisation with the lowest proportion of subjects reported in the placebo group (6.2%) and the highest reported in the formoterol 4.5 group (8.1%).
- Symbicort 160/4.5 and Symbicort 80/4.5 demonstrated statistically significant reductions in the exacerbation rate compared to placebo (37% and 41% respectively, rate ratio [RR] versus placebo 0.632 and 0.593 respectively, both p<<0.001). In addition both Symbicort doses significantly reduced the exacerbation rate compared to formoterol 4.5 (ratio 0.751 [p=0.004] and 0.706 [p <0.001]) for Symbicort 160/4.5 and 80/4.5 respectively representing a reduction of 24.9% and 13.9% respectively).
- The significant reduction in protocol-defined exacerbations per subject-treatment year seen with Symbicort was driven by the subset of the exacerbations treated with OGCS with or without hospitalisation. Rates for the formoterol group though less were not statistically significant compared to placebo RR = 0.841, p=0.060. The two Symbicort groups did not differ significantly from each other. Small non-significant increases in the rate of hospitalisations per subject-treatment year due to COPD exacerbation were observed in all active treatment groups, compared to placebo (Symbicort 160/4.5, 0.091; Symbicort 80/4.5, 0.088; formoterol 4.5, 0.094; placebo 0.084).
- Symbicort 160/4.5 and Symbicort 80/4.5 significantly prolonged the time to first exacerbation, compared with placebo, as analysed using log-rank test or a Cox proportional hazards model. Additionally Symbicort 160/4.5 significantly prolonged the time to first exacerbation compared to formoterol 4.5.

**Other secondary efficacy variables**

(a) $FEV_1$ at EoT: Symbicort 160/4.5 demonstrated significantly greater improvements in pre-dose $FEV_1$ from baseline to EoT compared to placebo (LS mean = 0.09 (p<0.001) but not significantly different compared to formoterol 4.5 (LS mean = 0.03, p=0.150). The increase in post-dose $FEV_1$ from baseline to EoT for Symbicort 160/4.5 compared to placebo was also significant (LS mean = 0.18, p<0.001). Symbicort 160/4.5 did not differ significantly from formoterol 4.5 for change in post-dose $FEV_1$ from baseline to EoT. Formoterol 4.5 demonstrated a highly statistically significant increase from baseline in 1-hour post-dose $FEV_1$ compared with placebo. (LS mean = 0.16, p<0.001).

(b) Serial spirometry. At Visits 2, 6, and 8, $FEV_1$ was measured pre-dose and at 5, 15, 30, 60, 120, 180, 240, 360, 480, 600 and 720 minutes post-dose in a subset of 491 subjects. $FEV_1$ was expressed as percentage change from baseline $FEV_1$. For each treatment group the percent reversibility to albuterol at screening (Visit 1) was greater in the serial spirometry set than in the efficacy analysis set, with the 2 Symbicort groups showing the greatest difference between the 2 analysis sets, and the formoterol 4.5 group showing the least. Therefore, within the serial spirometry analysis set, but not the overall EAS, the Symbicort and placebo groups were more reversible than the formoterol 4.5 group.

(c) 15% onset of action of bronchodilatation. On the day of randomisation (DoR), the median time to 15% onset of action was 4.2, 4.8 and 6.0 minutes for Symbicort 160/4.5, Symbicort 80/4.5 and formoterol respectively. All three of these groups were significantly earlier compared to placebo (all p<0.001). At EoT, the median time to 15% onset of action was 4.5 minutes 4.3 minutes and 16.3 minutes for Symbicort 160/4.5, Symbicort 80/4.5 and formoterol 4.5 respectively; all p<0.001 compared to placebo. The proportion of subjects who did not achieve a response of 15% within 60

minutes after dosing was numerically lower for Symbicort 160/4.5 (20.7%) and Symbicort 80/4.5 (23.3%) compared with formoterol 4.5 (33.1%).

(d) Maximum $FEV_1$. On the DoR, all of the groups including placebo showed significant bronchodilatation as assessed by the maximum $FEV_1$: Symbicort 160/4.5 LS mean = 0.37 L; Symbicort 80/4.5, LS mean = 0.34 L; formoterol 4.5 LS mean = 0.29 L; placebo LS mean = 0.18; both Symbicort doses and formoterol were significantly different from placebo (all <0.001). Symbicort 160/4.5 demonstrated statistically significant increases compared to formoterol 4.5

(e) $FEV_1$ at the 12-hour time point. On the DoR all of the active treatments caused significant bronchodilatation (that is improved from baseline) but not the placebo. Symbicort 160/4.5 and Symbicort 80/4.5 demonstrated statistically significant increases compared with placebo and formoterol 4.5. Formoterol 4.5 did not demonstrate a significant difference for $FEV_1$ at 12 hours compared with placebo. At EoT, both Symbicort doses produced significant increases from baseline but placebo and formoterol did not. Symbicort 160/4.5 and Symbicort 80/4.5 demonstrated statistically significant increases for $FEV_1$ at 12 hours compared with placebo.

(f) Baseline-adjusted average 12-hour $FEV_1$. On the DoR, all of the active treatments were significantly better than placebo: Symbicort 160/4.5 LS mean = 0.17, p<0. 001; Symbicort 80/4.5 LS mean = 0.14, p<0.001; formoterol 4.5 LS mean = 0.09, p<0.001. At EoT, the results were qualitatively similar, that is, the active treatments had maintained their effects.

(g) Peak Expiratory Flow. The three active treatments showed significant increases in morning peak expiratory flow (mPEF) from baseline to the average of the randomised period as follows: Symbicort 160/4.5, LS mean = 21 L/min; Symbicort 80/4.5, LS mean = 15.9 L/min; formoterol 4.5, LS mean = 10.54 L/min; placebo group did not change significantly, LS mean = 2.68 L/min. The results for ePEF were qualitatively similar and the changes were slightly less than the mPEF. The increases caused by the active treatment groups were significantly greater compared to placebo: Symbicort 160/4.5, LS mean 18.43 L/min; Symbicort 80/4.5, LS mean = 13.21 L/min; formoterol, LS mean = 7.86 L/min (all p<0.001); the ePEF data for comparisons with placebo were qualitatively similar.

(h) Symptom variables. Within treatment differences from baseline to the average of the randomised treatment period all improved significantly including placebo for BCSS: Symbicort 160/4.5>Symbicort 80/4.5>formoterol 4.5 >placebo (LS mean from -0.85 (Symbicort 160/4.5) to -0.38 for placebo). Sleep score (0-4) all improved significantly including placebo: Symbicort 80/4.5 (LS mean = -0.26) >Symbicort 160/4.5 >formoterol 4.5 > placebo (LS mean = -0.09). The awakening free nights (%) and β2-agonist use (puffs/day) followed a similar pattern except that for placebo; rescue medication use did not change significantly from baseline. For the above variables, all the active treatments were significantly better than placebo.

**Study D5899C00002 (SHINE).** A 6-Month Double-blind, Double-dummy, Randomised, Parallel group, Multicentre Efficacy & Safety Study of Symbicort pMDI 2 x 160/4.5 µg & 80/4.5 µg bd Compared to Formoterol Turbuhaler, Budesonide pMDI (& the combination) & placebo in COPD Patients (SHINE).

This study was conducted at a total of 194 sites in the US and 4 other countries. The study design, inclusion and exclusion criteria, primary end-points and data analysis were identical to the SUN study. The study had a 6 months treatment period and was randomised, double-blind, placebo-controlled, multicentre and parallel-group in design. After a screening visit (Visit 1) subjects entered a run-in period of 2 weeks. At Visit 2 (end of run-in) they were randomised to receive one of 6 treatments for 26 weeks:

- Symbicort 160/4.5 µg per actuation, 2 actuations bd–277 subjects
- Symbicort 80/4.5 µg per actuation, 2 actuations bd–281 subjects

- budesonide pMDI 160 µg per actuation, 2 actuations bd–275 subjects
- formoterol Turbuhaler 4.5 µg per actuation, 2 actuations bd –272 subjects
- combination budesonide pMDI 160 µg plus formoterol Turbuhaler –287 subjects
- placebo—300 subjects

*Outcome variables*. The primary outcome variables were pre-dose $FEV_1$ and 1-h post dose $FEV_1$. Dyspnoea, SGRQ total score and the number of exacerbations were identified as key secondary variables.

**Results**

**Primary outcome variables: pre-dose and post-dose $FEV_1$**

(a) Pre-dose $FEV_1$ increased significantly from baseline to treatment average in the Symbicort 160/4.5 (LS mean = 0.08), Symbicort 80/4.5 (LS mean = 0.06), budesonide 160 plus formoterol 4.5 (LS mean = 0.07) and formoterol 4.5 (LS mean = 0.04) groups. Note that budesonide and placebo did not change significantly from baseline to the average of the randomisation period. For post dose $FEV_1$, there was a significant increase from baseline to treatment average as follows: Symbicort 160/4.5 LS mean = 0.2; Symbicort 80/4.5 LS mean = 0.19; budesonide 160 plus formoterol 4.5 LS mean = 0.19; budesonide, LS mean = 0.03; formoterol LS mean = 0.17. Placebo did not change significantly from baseline.

(b) Symbicort 160/4.5 produced a significantly greater change in pre-dose $FEV_1$ compared to formoterol (LS mean = 0.04, p=0.026). Symbicort 160/4.5 produced a significantly greater change in post-dose $FEV_1$ compared to budesonide (LS mean = 0.17, p<0.001).

(c) The post-dose $FEV_1$ change from baseline for Symbicort 80/4.5 was significantly greater than budesonide 160 (LS mean = 0.16, p<0.001) but Symbicort 80/4.5 was not significantly different to formoterol 4.5 regarding pre-dose $FEV_1$.

Therefore the primary objectives were met for Symbicort 160/4.5; however, the primary objectives were not met by the Symbicort 80/4.5 group so that the presentation of the findings regarding the key secondary end points were considered descriptive only for this dose of Symbicort.

(d) Other pre-specified comparisons for pre-dose and post-dose $FEV_1$ (L) were:

· Post-dose $FEV_1$ formoterol 4.5 minus placebo LS mean = 0.14, p<0.001

· Pre-dose $FEV_1$ Symbicort 160/4.5 and 80/4.5 minus placebo LS mean = 0.08 (p=0.001) and LS mean = 0.05 (p=0.002) respectively

· Post-dose $FEV_1$ Symbicort 160/4.5 and 80/4.5 minus placebo LS mean= 0.17 (p<0.001) and LS mean = 0.16 (p<0.001) respectively

· The Symbicort dosages did not differ significantly from each other for pre and post-dose $FEV_1$

· Symbicort 160/4.5 did not differ significantly from budesonide 160 plus formoterol 4.5 for pre- or post-dose $FEV_1$ indicating that the effects of Symbicort were not dependent on the delivery device.

**Key secondary variables**

*Dyspnoea score.*

The dyspnoea score decreased significantly from baseline to the average of the randomised period for all of the treatment groups including placebo; Symbicort 160/4.5, LS mean = -0.34; Symbicort 80/4.5, LS mean = -0.34; budesonide 160 plus formoterol 4.5, LS mean = -0.39; budesonide 160, LS mean = -0.21; formoterol 4.5, LS mean = -0.24; placebo, LS mean = -0.18. The within-treatment changes from baseline to average of treatment for Symbicort 160/4.5 and 80/4.5 were greater than the MID.

Symbicort 160/4.5 and Symbicort 80/4.5 both demonstrated a statistically significant reduction from baseline in dyspnoea scores compared with placebo (both LS mean = 0.16, p=0.001) but the pre-specified MID was not achieved. Symbicort 160/4.5 also demonstrated statistically significant reductions in dyspnoea scores from baseline compared with the monoproducts formoterol 4.5 and budesonide 160. Neither formoterol 4.5 nor budesonide 160 demonstrated statistically significant differences from baseline in dyspnoea scores compared to placebo. Symbicort 160/4.5 did not demonstrate a statistically significant difference for change from baseline in dyspnoea scores compared with the free combination of budesonide 160 plus formoterol 4.5 or Symbicort 80/4.5.

During the randomised treatment period 55.4% and 48.4% of the Symbicort 160/4.5 and 80/4.5 groups respectively had a decrease in the dyspnoea score of ≥0.2 (improvement) compared to placebo 35.4% (odds ratio [OR] 2.30 [p<0.001]) and 1.74 (p=0.001) for Symbicort 160/4.5 and 80/4.5 respectively); budesonide 160 (44.1% subjects) and formoterol 4.5 (50.0% subjects) also had a significantly greater proportion of subjects who had an improved dyspnoea score compared to placebo (budesonide 160 versus placebo, OR 1.46 (p=0.034) and formoterol 4.5 versus placebo, OR 1.81 (p<0.001)); formoterol 4.5 versus placebo, OR 1.81, p<0.001. A statistically significant smaller percentage of subjects taking Symbicort 160/4.5(13.3%) and Symbicort 80/4.5 (17.6%) experienced a worsening (increase ≥0.2) in dyspnoea compared with placebo (22.5%; p<0.001 and p=0.013 respectively)

*SGRQ*

Symbicort 160/4.5 significantly decreased the total score from baseline to EoT (LS mean = -5.16); Symbicort 80/4.5 also decreased significantly (LS mean = -4.99). All of the groups had a significant change from baseline to EoT with the groups receiving both budesonide and formoterol showing numerically greater changes. Note that only the groups who received both budesonide and formoterol had a change >MID.

For the key treatment comparisons, Symbicort 160/4.5 and Symbicort 80/4.5 produced a greater decrease compared to placebo (LS mean = -3.12 [p=0.003] and LS mean = -2.95 [p=0.005] respectively). The monocomponents were not significantly different from placebo. Both Symbicort 160/4.5 and Symbicort 80/4.5 were also significantly different from the monocomponents budesonide 160 or formoterol 4.5. Symbicort 160/4.5 did not differ significantly from budesonide 160 plus formoterol 4.5 or Symbicort 80/4.5.

A statistically significant greater proportion of subjects taking Symbicort 160/4.5 and Symbicort 80/4.5 achieved the MID for SGRQ total score compared with placebo (45.5%, 41.4% and 35% respectively; Symbicort 160/4.5/placebo, OR = 1.55 (1.08, p=0.018) and Symbicort 80/4.5/placebo, OR = 1.55 (p=0.016)).

The number of subjects who showed a significant improvement in the budesonide 160 plus formoterol 4.5, (41.4%), budesonide 160 (37.0%) and formoterol 4.5 (37.5%) groups did not differ significantly from placebo (35%). A statistically significantly smaller proportion of subjects taking Symbicort 160/4.5 and Symbicort 80/4.5 worsened (increases ≥4.0) compared with placebo (22.5%, 23.3% and 31.1% respectively; p=0.027 and p=0.047 respectively).

*COPD exacerbation*

- In the Symbicort 160/4.5, Symbicort 80/4.5 and placebo groups, 25.1%, 25.7% and 26.4% of subjects experienced at least one exacerbation. The subject-treatment years did not differ very much between groups. The rates (subject-treatment year) were 0.786, 0.769 and 1.08 for Symbicort 160/4.5, 80/4.5 and placebo respectively. The majority of exacerbations were treated with OGCS: Symbicort 160/4.5, 92.9%; Symbicort 80/4.5, 97%; placebo 96%.
- There were no statistically significant differences in the exacerbation rates between any of the treatment groups. However, for the Symbicort 160/4.5 group there was a statistically

significantly higher rate of hospitalisation for exacerbation (0.158/subject-treatment year compared to placebo (0.108/subject-treatment year, p=0.05).

- The percentage of subjects with at least one episode of COPD worsening treated with antibiotics alone (mild exacerbations) was numerically greater for the Symbicort 160/4.5 treatment group compared with the placebo group (10.9% and 5.4%, respectively). The number of subjects with at least one episode of COPD worsening with antibiotics alone was the same for Symbicort 80/4.5 and placebo (5.4%).

In summary, for the higher dose of Symbicort 160/4.5 the primary objectives were met; for the key secondary variables there was a significant improvement over placebo for dyspnoea and SGRQ score but not for exacerbation rate[8].

*Other secondary variables*.

(a) Pre-dose and post-dose $FEV_1$ at EoT. Symbicort 160/4.5 increased significantly from baseline to the EoT LS mean = 0.07; the change was significantly greater than placebo (LS mean = 0.06, p=0.004). Symbicort 160/4.5 was also significantly greater than Formoterol 4.5 (LS mean = 0.04, p=0.044). The change from baseline to EoT for Symbicort 80/4.5 did not differ significantly from placebo. For post-dose $FEV_1$ from baseline to EoT, Symbicort 160/4.5 was significantly greater than placebo (LS mean = 0.16, p<0.001) and also budesonide 160 (LS mean = 0.17, p<0.001). Formoterol 4.5 was also significantly greater than placebo (LS mean = 0.12, p<0.001).

(b) 12-hour serial $FEV_1$ assessments. For all 12-hour serial $FEV_1$ assessments in this section, Symbicort 160/4.5 did not show a statistically significant difference compared with the free combination of budesonide 160 plus formoterol 4.5. Additionally, Symbicort 160/4.5 and Symbicort 80/4.5 were not statistically significantly different from each other.

(c) Mean percentage change from baseline over 12 hours. On the DoR all of the formoterol containing treatments had significant bronchodilatation within 5 minutes with a maximum occurring at 2–3 hours and this was maintained over the 12 hours. At EoT, results for Symbicort 160/4.5 and the combination of monocomponents were similar to those on DoR.

(d) 15% onset of action of bronchodilatation. On the DoR, the median time to 15% onset of action was 6.8 minutes for Symbicort 160/4.5, 4.9 minutes for Symbicort 80/4.5, 6.2 minutes for the free combination of budesonide 160 plus formoterol 4.5 and 9.0 minutes for formoterol 4.5. Median time for budesonide 160 and placebo could not be estimated due to the fact that fewer than 50% of subjects achieved a 15% improvement within 60 min. Symbicort 160/4.5 and Symbicort 80/4.5 demonstrated a highly statistically significantly earlier time to 15% onset of action compared with placebo and budesonide 160 (p<0.001 for all comparisons). At EoT, the median time to 15% onset of action was 4.3 minutes for Symbicort 160/4.5, 6.2 minutes for Symbicort 80/4.5, and 10.8 minutes for the free combination of budesonide 160 plus formoterol 4.5. Thus the median times for 15% onset of action for both doses of Symbicort at the EoT were similar to the DoR; formoterol 4.5 demonstrated a statistically significant difference for time to 15% onset of action compared with placebo on the DoR (p<0.001). At the EoT, formoterol 4.5 showed a prolonged time to 15% onset of action (18 min) compared to the DoR, but maintained statistically significant differences compared to placebo.

(e) Maximum $FEV_1$ (L). On the DoR, the maximum $FEV_1$ achieved was significantly greater for Symbicort 160/4.5, Symbicort 80/4.5 and formoterol 4.5 compared to placebo (LS mean = 0.15, 0.14 and 0.11 (all p<0.001) respectively). The data at EoT were qualitatively similar. Symbicort 160/4.5 demonstrated statistically significant increases compared with placebo and budesonide

[8] The lack of statistically demonstrable differences with regard to exacerbation rate was not unexpected since the study had a duration of 6 months only and was not powered to detect these differences.

160, but not compared with formoterol 4.5 at EoT. The results for $FEV_1$ at the 12-h time points were similar.

(f) Baseline-adjusted average 12-hour $FEV_1$ (L). The treatments containing formoterol showed a significant increase of $AUC_{0-12}$ from baseline: Symbicort 160/4.5, LS mean = 0.17; Symbicort 80/4.5, LS mean = 0.16; formoterol 4.5, LS mean = 0.13; budesonide 160 plus formoterol 4.5, LS mean = 0.13. The budesonide 160 and placebo groups did not change significantly. Results for within treatment changes from baseline to EoT were qualitatively similar. On DOR, Symbicort 160/4.5, Symbicort 80/4.5 and formoterol 4.5 caused significantly greater bronchodilatation compared to placebo (LS means 0.16, 0.15 and 0.12 for Symbicort 160/4.5, 80/4.5 and formoterol 4.5 respectively). The effect of budesonide 160 was not statistically significantly different from placebo. Treatment comparisons for change of $FEV_{10-12}$ from baseline to EoT were qualitatively similar: Symbicort 160/4.5 minus placebo LS mean = 0.13 L ($p<0.001$); Symbicort 80/4.5 minus placebo LS mean = 0.08 ($p=0.012$); formoterol 4.5 minus placebo LS mean = 0.06 ($p=0.043$); budesonide 160 did not differ significantly from placebo (LS mean = -0.01, $p=0.683$).

(g) Peak expiratory flows. Symbicort 160/4.5 increased PEF from baseline to the treatment period, to a greater extent than placebo (LS mean = 18.91 L/min for mPEF and LS mean = 15.30 L/min for ePEF).

(h) Symbicort 160/4.5 was significantly better than placebo in improving the outcomes of BCSS; sleep score, awakening free nights and β2-agonists. For COPD symptoms and rescue medication use, there were no significant differences between Symbicort 160/4.5 and the free combination of budesonide 160 plus formoterol 4.5 or between the two dosage strengths of Symbicort. This indicates the effects of Symbicort are not device dependent. COPD resource utilisation: the only significant difference for both dosages of Symbicort compared to placebo for both was the number of home visits by a physician.

## Safety

### Study D5899C00001 (SUN)

A total of 1964 subjects who received at least one dose of study drug and provided data after randomisation, were included in the safety analysis set. Details are shown in Table 2.

*Adverse events by MedDRA system organ class*

The most commonly reported System Organ Class (SOC) categories during randomised treatment were: *Infections and Infestations* (34.4%); *Respiratory, Thoracic, and Mediastinal Disorders* (25.6%); *Musculoskeletal and Connective Tissue Disorders* (10.4%); *Gastrointestinal Disorders* (9.9%); *Cardiac Disorders* (7.8%); and *Nervous System Disorders* (6.2%). The percentage of subjects reporting AE within each SOC and the rate of adverse events per subject-treatment year were higher in the Symbicort and formoterol 4.5 groups compared to placebo. In the SOC *Infections and Infestations*, the percentage of subjects was highest in the Symbicort 80/4.5 group (39.9%) and lowest in the placebo (27.2%) group; Symbicort 160/4.5 was second highest (39.1%). The rate of AE per subject-treatment year for these groups was also higher (0.80, 0.74, 0.65, and 0.62 for Symbicort 160/4.5, Symbicort 80/4.5, formoterol 4.5 and placebo respectively). The incidence of *Respiratory, Thoracic, and Mediastinal* SOC adverse events was similar across treatment groups.

Regarding the *Cardiac Disorders* SOC: adverse events/subject-treatment year were highest in the Symbicort 80/4.5 group (0.17) followed by formoterol 4.5 (0.14), Symbicort 160/4.5 (0.13) and placebo 0.08. Regarding the *Nervous System Disorders* SOC, the percentage of subjects with an AE within this SOC was higher in the Symbicort 160/4.5 (8.1%), Symbicort 80/4.5 (6.1%) and formoterol 4.5 groups (6.1%) compared to the placebo group (4.6%).

Table 2: Summary of adverse events during randomised treatment period in study D5899C00001

| | Treatment group | | | |
|---|---|---|---|---|
| | SYMB 160/4.5[a)] N=494 | SYMB 80/4.5[a)] N=494 | Form 4.5[a)] N=495 | Placebo N=481 |
| Mean (SD) exposure days | 305 (115) | 299 (118) | 289 (127) | 270 (139) |
| >48 weeks treatment n (%) subjects | 373 (75.5) | 359 (72.7) | 344 (69.5) | 307 (63.8) |
| Subjects with at least one adverse event (AE) | 322 (65.2) | 323 (65.4) | 299 (60.4) | 268 (55.7) |
| Total AE | 1061 | 976 | 898 | 733 |
| Mild | 556 (52.4) | 475 (48.7) | 446 (49.7) | 359 (49.0) |
| Moderate | 381 (35.9) | 389 (39.9) | 343 (38.2) | 302 (41.2) |
| Severe | 124 (11.7) | 112 (11.5) | 109 (12.1) | 72 (9.8) |
| AE/subject-treatment year | 2.6 | 2.4 | 2.3 | 2.1 |
| Serious adverse event (SAE) n (%) subjects | 79 (16.0) | 69 (14.0) | 89 (18.0) | 62 (12.9) |
| Total SAE | 113 | 110 | 117 | 88 |
| SAE/subject-treatment year | 0.27 | 0.27 | 0.30 | 0.25 |
| Deaths | 3 | 6 | 2 | 4 |
| DAE n (%) subjects | 56 (11.3) | 61 (12.3) | 61 (12.3) | 60 (12.5) |
| Number of DAE | 75 | 71 | 72 | 72 |
| DAE/subject-treatment years | 0.18 | 0.18 | 0.18 | 0.20 |
| Study-drug related AE n (%) subjects | 63 (12.8) | 51 (10.3) | 42 (8.5) | 30 (6.2) |
| Total study drug-related AE | 96 | 81 | 58 | 53 |
| Subjects with study drug related SAE | 5 | 3 | 7 | 0 |

DAE: discontinuation adverse event, SYMB = Symbicort, Form = formoterol
[a)] Note this denotes dosage strength. The actual dose was 2 actuations of the dosage strength administered bd.

*Adverse events by MedDRA preferred terms*

Adverse events by intensity: In each treatment group, most AE were rated as mild or moderate in intensity. The distribution of severity grading (mild, moderate, or severe) was generally similar across treatment groups. Overall, 14.5% of randomised subjects experienced at least one severe AE; however, there was a slight increase both in the incidence of severe events and in the number of subjects experiencing at least one severe event in all active treatment groups compared with

placebo. The incidence of severe events was low across all Preferred Terms (PTs) except for COPD (5.7% of subjects), the PT with the highest incidence of severe events; and pneumonia (1.3% of subjects). 26 (14.0%) of subjects experienced 27 AE of severe intensity. There were more severe intensity events in all active treatment groups compared with placebo. Most frequent adverse events are shown in Table 3 and adverse events of interest are shown in Table 4.

Table 3: Most frequently reported adverse events in study D5899C00001 (reported by at least 3% of subjects in any treatment group) by MedDRA preferred term, during randomised treatment (Safety analysis set)

| | Treatment group | | | |
|---|---|---|---|---|
| | SYMB 160/4.5[a)] N=494 | SYMB 80/4.5[a)] N=494 | Form 4.5[a)] N=495 | Placebo N=481 |
| Mean (SD) exposure days | 305 (115) | 299 (118) | 289 (127) | 270 (139) |
| MedDRA preferred term | Number (%) of subjects | | | |
| Subjects with ≥1 AE | 322 (65.2) | 323 (65.4) | 299 (60.4) | 268 (55.7) |
| COPD | 66 (13.4) | 93 (18.8) | 83 (16.8) | 77 (16.0) |
| Nasopharyngitis | 35 (7.1) | 44 (8.9) | 30 (6.1) | 22 (4.6) |
| Bronchitis | 24 (4.9) | 22 (4.5) | 24 (4.8) | 18 (3.7) |
| Viral upper respiratory tract infection | 21 (4.3) | 22 (4.5) | 22 (4.4) | 17 (3.5) |
| Pneumonia | 15 (3.0) | 15 (3.0) | 17 (3.4) | 23 (4.8) |
| Oral candidiasis | 36 (7.3) | 21 (4.3) | 2 (0.4) | 8 (1.7) |
| Sinusitis | 19 (3.8) | 19 (3.8) | 19 (3.8) | 8 (1.7) |
| Back pain | 18 (3.6) | 5 (1.0) | 14 (2.8) | 11 (2.3) |
| Upper respiratory tract infection | 14 (2.8) | 16 (3.2) | 10 (2.0) | 5 (1.0) |
| Muscle spasms | 16 (3.2) | 16 (3.2) | 4 (0.8) | 6 (1.2) |
| Dysphonia | 16 (3.2) | 6 (1.2) | 1 (0.2) | 4 (0.8) |

SYMB = Symbicort, Form = formoterol

[a)] Note this denotes dosage strength. The actual dose was 2 actuations of the dosage strength administered bd

Table 4: Adverse events of interest in study D5899C00001 (multiple preferred terms in each category). Adverse events reported during randomised treatment (Safety analysis set)

| | Treatment group | | | |
|---|---|---|---|---|
| | SYMB 160/4.5[a)] N=494 | SYMB 80/4.5[a)] N=494 | Form 4.5[a)] N=495 | Placebo N=481 |
| | Number (%) subjects unless otherwise specified | | | |
| Pneumonia-related PTs[b)] | 20 (4.0) | 17 (3.4) | 17 (3.4) | 24 (5.0) |
| Steroid class effects | | | | |
| Candidiasis and voice effects (multiple PT) | 10.3 % | 5.7 % | 0.6 % | 2.5 % |
| Osteoporosis and bone fractures | 2.4 % | 0 | 0.6 % | 1.7 % |
| β2-agonist class effects | 9.5% | 8.9% | 6.5% | 4.8% |
| Subjects (%) with ≥1 cardiac related AE | 56 (11.3) | 53 (10.7) | 52 (10.5) | 33 (6.9) |
| Cardiac disorders SOC | 38 (7.7) | 42 (8.5) | 35 (7.1) | 24 (5.0) |
| Atrial fibrillation | 6 (1.2) | 11 (2.2) | 4 (0.8) | 0 |

SYMB = Symbicort, Form = formoterol

[a)] Note this denotes dosage strength. The actual dose was 2 actuations of the dosage strength administered bd

[b)] Preferred terms: pneumonia, bronchopneumonia, lobar pneumonia, pneumonia staphylococcal

*Study drug-related adverse events.*

The overall percentage of subjects with ≥1 AE study drug-related was higher in all active treatment groups; the most common study drug-related AEs were disease under study (DUS) related PTs and oral candidiasis. For AE reported in ≥1% of subjects, oral candidiasis, dysphonia and muscle spasms were reported most frequently in the Symbicort 160/4.5 group; atrial fibrillation was reported only in the active treatment groups. 26 (14.0%) of subjects experienced 27 AE of severe intensity. There were more severe intensity events in all active treatment groups compared with placebo. Forty eight per cent of the severe-intensity, study drug-related AE were COPD exacerbation or deterioration. None of the 15 deaths that occurred during randomised treatment or the 15 deaths that occurred post-randomised treatment was considered to be study drug-related. Fifteen subjects had ≥1 non-fatal SAE considered to be study drug-related and 60 subjects had a DAE considered to be study drug-related. There were no study drug-related SAE in the placebo group.

*Adverse Events of Special Interest*

Systemic steroid class effects and $\beta_2$-agonist class effects

Note that during the randomised period, 32.7% of subjects used oral, parenteral rectal or systemic glucocorticosteroids. The AE categories of bone effects, diabetes control, skin effects, weight gain, ocular effects, taste effects and adrenal suppression, were taken to represent multiple PTs for possible systemic steroid class effects. These AE, both individually and combined, were reported with a low incidence across all 4 treatment groups (2.6% for formoterol 4.5 to 4.5% for Symbicort 80/4.5). The incidence was slightly higher for both doses of Symbicort compared to formoterol 4.5 and placebo. The category of systemic effects with the highest overall incidence was bone effects (osteoporosis and bone fractures) with the highest incidence in the Symbicort 160/4.5 group (2.4%)

and the lowest in the formoterol 4.5 group (0.6%); however, the incidence in the placebo group (1.7%) was only slightly less than Symbicort 160/4.5.

Oral candidiasis was more frequent in the Symbicort 160/4.5 (7.3%) and Symbicort 80/4.5 (4.3%) groups compared to placebo (1.7%), with a dose-ordered response observed for budesonide. The PTs nasopharyngitis, bronchitis, viral upper respiratory tract infection and sinusitis, in general, were more frequently reported in all active treatment groups compared to placebo.

The overall incidence of $\beta_2$-agonist class effects was 7.4% and there were increases in the three active treatment groups compared to placebo (see Table 4).

Pneumonia

The percentage of subjects reporting the PT pneumonia was lower in all active treatments compared to placebo (3.0%, 3.0%, 3.4% and 4.8% for Symbicort 160/4.5, Symbicort 80/4.5, formoterol 4.5 and placebo respectively); pneumonia was most frequently reported among subjects ≥75 years of age (4.1%). In total 78 subjects had at least one AE coded as a pneumonia-related PT (pneumonia, bronchopneumonia, lobar pneumonia, or pneumonia-staphylococcal). There were slightly fewer events on all active treatments: Symbicort 160/4.5, 4.0%; Symbicort 80/4.5, 3.4%; formoterol 3.4% and placebo 5.0%. Thirty three subjects had pneumonia-related SAEs during randomised treatment and 7 of these SAEs led to a DAE.

The percentage of subjects with ≥1 event for 'potential lung infections other than pneumonia preferred terms was higher in the Symbicort 160/4.5 group compared to the Symbicort 80/4.5, formoterol 4.5 and placebo groups (8.1% 6.9% 7.1% and 6.2% respectively). Combining these two categories indicates that the incidence of pneumonia and respiratory infections other than pneumonia were similar in all the treatment groups: Symbicort 160/4.5, 12.1%; Symbicort 80/4.5, 10.3%; formoterol 4.5, 10.5% and placebo 11.2%.

Deaths

A total of 15 subjects died from an SAE with onset during the randomised treatment period (from date of first dose through the day after the last dose): 3 in the Symbicort 160/4.5 group, 6 in the Symbicort 80/4.5 group, 2 in the formoterol 4.5 group, and 4 in the placebo group. The most frequent SAEs leading to death during randomised treatment were cancer (n=4) and nervous system disorders (n=2); the remaining SAEs leading to death were isolated in nature with 6 deaths having a respiratory component, 2 deaths that were cardiac-related and 3 deaths that were sudden deaths at home with no autopsy reported.

Cardiac-related events

Twelve-lead electrocardiograms (ECGs) were performed pre-dose and 1-hour post-dose on all subjects at DoR (Visit 2), end of Month 2 (Visit 4), end of Month 6 (Visit 6) and end of Month 12 (Visit 8). Cardiac related events were predefined as events in the *Cardiac Disorders* SOC, cardiac related investigations and chest pain but excluding the terms tachycardia and palpitation.

The overall percentages of subjects reporting AEs in the *Cardiac Disorders* SOC were higher in the active treatment groups compared to placebo (Symbicort 160/4.5, 8.7%; Symbicort 80/4.5, 9.3%; formoterol 4.5, 7.9%. placebo 5.4%). The most common PTs in the *Cardiac Disorders* SOC were angina pectoris (1.2%), atrial fibrillation (1.1%), ventricular extrasystoles (0.6%), and cardiac failure (0.5%). Percentages of subjects reporting cardiac-related AEs were as follows: Symbicort 160/4.5, 11.3%; Symbicort 80/4.5, 10.7%; formoterol 4.5, 10.5%; placebo 6.9%).

Atrial fibrillation

There was a higher percentage of subjects with ≥1AE for the PT atrial fibrillation in all active treatment groups compared with placebo (Symbicort 160/4.5, 1.2%; Symbicort 80/4.5, 2.2%; formoterol 4.5, 0.8%); there were no events in the placebo group. Ten of these events (in 9 subjects)

were SAEs but no deaths occurred due to atrial fibrillation; 5 of the 21 cases had a medical history of atrial fibrillation, and 5 cases had atrial fibrillation at baseline before dosing based on ECGs and/or Holter examinations.

Therefore the majority of the adverse events of atrial fibrillation appeared to be of acute onset. The subjects were predominantly male with a mean age of 67 years and a high proportion reported hypertension (14 of 21), and ischaemic heart disease (9 of 21); 6 AEs of atrial fibrillation were concurrent with a COPD exacerbation.

Bone mineral density analysis

326 of subjects had baseline and post-baseline BMD results and were included in the BMD analysis set. Subjects were recruited from US centres (269 subjects) and Bulgaria (57 subjects). LS mean changes from baseline to EoT for lumbar spine and total hip BMD were close to zero and similar in each treatment group. There were nominally statistically significant differences between treatment groups but the treatment ratios were 0.98 – 0.99.

There were 14 subjects who shifted from normal to the osteopenic range and these were similarly distributed in each of the treatment groups. Nine subjects went from osteopenic to osteoporotic range and 18 subjects showed some improvement in T score(s).

No subjects with normal BMD shifted into the osteoporotic range for any of the treatments. For lumbar BMD and the Symbicort 160/4.5 group, 5 (10.6%) of subjects who were normal at baseline shifted into the osteopenic range; one subject shifted from osteopenic into the osteoporotic arrange. There were 11 subjects for hip BMD who went from normal to osteopenic and three went from osteopenic to osteoporotic. There were no clinically relevant differences between treatments.

24-hour urinary cortisol

Specimens were collected for analysis of urinary cortisol from a subgroup of 179 subjects at or prior to Visit 2 (baseline) and within 1 week prior to Visits 6 (Month 6) and 8 (Month 12). Mean 24-h urinary cortisol at 6 months and EoT were lower in the Symbicort 160/4.5 and Symbicort 80/4.5 compared to formoterol and placebo group (LS means (nmol/24 h) at EoT = 36.66, 44.91, 55.15 and 52.60 for Symbicort 160/4.5, Symbicort 80/4.5, formoterol 4.5 and placebo respectively). This is in spite of the fact that mean values (nmol/24-h) in the placebo group were lower at baseline compared to the other treatments: Symbicort 160/4.5, 48.68; Symbicort 80/4.5, 43.74; formoterol 4.5, 47.72 and placebo 36.58. Statistically significant differences were seen for the reduction due to Symbicort 160/4.5 versus placebo at 6 months (ratio 0.66, p=0.035) and for Symbicort 160/4.5 versus formoterol 4.5 at EoT (ratio 0.66, p=0.044). No other between group comparison was statistically significant. Only four subjects had a shift from normal at baseline to low (<5.5 nmol/24-h) on treatment and they were evenly distributed across treatment groups.

**Study D5899 C00002 (SHINE)**

The section on safety was both thorough and extensive. The potential exposure for the study was 180 ±7 days from Visit 2. A total of 1704 subjects received at least one dose of study-drug and provided data after randomisation. The majority of the subjects in each treatment group received randomised treatment for at least 168 days (24 weeks) and completed the planned 6-month treatment. Details are shown in Table 5.

Table 5: Adverse events during the randomised treatment period in study D5899C00002

| | Treatment group | | | | | |
|---|---|---|---|---|---|---|
| | SYMB 160/4.5[a)] N=277 | SYMB 80/4.5[a)] N=281 | Budes 160 plus Form 4.5[a)] N=287 | Budes 160[a)] (N=275) | Form 4.5[a)] (N=284) | Placebo N=300 |
| Mean (SD) exposure days | 166.5 (41.29) | 168.3 (37.73) | 164.6 (40.28) | 157.1 (51.31) | 156.3 (53.22) | 150.0 (60.15) |
| Treatment >24 weeks | 86.6 % | 87.5 % | 82.2 % | 78.5 % | 79.2 % | 76.0 % |
| Treatment duration >0–≤8 weeks | 5.1 % | 4.6 % | 5.2 % | 9.1 % | 11.3 % | 16.0 % |
| Any AE n (%) subjects | 159 (57.4) | 147 (52.3) | 142 (49.5) | 158 (57.5) | 161 (56.7) | 152 (50.7) |
| Total AE | 364 | 345 | 327 | 343 | 369 | 320 |
| Mild | 187 (51.4) | 172 (49.9) | 183 (56.0) | 155 (45.2) | 198 (53.7) | 167 (52.2) |
| Moderate | 131 (36.0) | 126 (36.5) | 107 (32.7) | 145 (42.3) | 120 (32.5) | 117 (36.6) |
| Severe | 46 (12.6) | 47 (13.6) | 37 (11.3) | 43 (12.5) | 51 (13.8) | 36 (11.3) |
| AE/subject-treatment year | 2.9 | 2.7 | 2.5 | 2.9 | 3.0 | 2.6 |
| SAE n (%) subjects | 33 (11.9) | 34 (12.1) | 26 (9.1) | 28 (10.2) | 24 (8.5) | 26 (8.7) |
| Total SAE | 42 | 44 | 30 | 42 | 30 | 34 |
| SAE/subject-treatment year | 0.33 | 0.34 | 0.23 | 0.35 | 0.25 | 0.28 |
| SAE leading to death n (%) subjects | 3 (1.1) | 4 (1.4) | 0 | 2 (0.7) | 1 (0.4) | 1 (0.3) |
| SAE not leading to death n (%) subjects | 31 (11.2) | 30 (10.7) | 26 (9.1) | 26 (9.5) | 23 (8.1) | 25 (8.3) |
| SAE leading to DAE n (%) subjects | 10 (3.6) | 10 (3.6) | 7 (2.4) | 7 (2.5) | 7 (2.5) | 6 (2.0) |
| DAE n (%) subjects | 19 (6.9) | 19 (6.8) | 13 (4.5) | 25 (9.1 ) | 32 (11.3) | 25 (8.3) |
| Number of DAE | 19 | 25 | 14 | 29 | 36 | 30 |
| DAE/subject-treatment years | 0.15 | 0.19 | 0.11 | 0.24 | 0.30 | 0.24 |
| Study drug-related AE n (%) subjects | 24 (8.7) | 24 (8.5) | 17 (5.9) | 22 (8.0) | 22 (7.7) | 18 (6.0 |
| Total study drug-related AE | 39 | 36 | 25 | 34 | 38 | 28 |
| Study drug-related SAE n (%) subjects | 1 (0.4) | 2 (0.7) | 0 | 0 | 1 (0.4) | 0 |
| Study drug-related AE leading to DAE n (%) subjects | 3 (1.1) | 5 (1.8) | 1 (0.3) | 2 (0.7) | 10 (3.5) | 6 (2.0) |

SYMB = Symbicort, Form = formoterol, Budes = budesonide, DAE = discontinuation adverse event

[a)] Note this denotes dosage strength. The actual dose was 2 actuations of the dosage strength administered bd

*Summary of system organ class (SOC) categories (reported by at least 3% of subjects in any treatment group), during randomised treatment (Safety analysis set)*

The incidence of AE within each SOC was generally similar across treatment groups. The most commonly reported system organ class (SOC) categories during randomised treatment were: *Infections and Infestations* (26.4%); *Respiratory, Thoracic, and Mediastinal Disorders* (20.5%); *Gastrointestinal Disorders* (6.9%); *Musculoskeletal and Connective Tissue Disorders* (6.6%); *Nervous System Disorders* (4.6%); and *Cardiac Disorders* (4.0%). No other SOC was reported in more than 4.0% of the subjects overall.

*Most frequently reported adverse events (reported by at least 3% of subjects in any treatment group) by MedDRA Preferred Term, during randomised treatment (Safety analysis set)*

COPD

COPD was the most frequently reported AE, with the highest incidence in the formoterol 4.5 group (17.7%), and a slightly higher incidence in the Symbicort 160/4.5 group (13.4%) compared to placebo (11.7%). The incidence of bronchitis was higher in the Symbicort 160/4.5 (3.6%) and the free combination of budesonide 160 plus formoterol 4.5 groups (3.5%) compared to placebo (2.0%). The incidence of oral candidiasis and sinusitis was higher in the Symbicort 160/4.5, Symbicort 80/4.5 and budesonide 160 plus formoterol 4.5 groups, compared to placebo (oral candidiasis 3.6%, 2.5%, 2.8% and 2.0% for Symbicort 160/4/5, 80/4.5, budesonide 160 plus formoterol 4.5 and placebo respectively) (see Table 6). Note however that when one considers the PTs which could represent local steroid effects including multiple terms for candidiasis, the percentages were much higher (see Table 7).

Table 6: Most frequently reported adverse events in study D5899C00002 (reported by at least 3% of subjects in any treatment group) by MedDRA Preferred Term, during randomised treatment (Safety analysis set).

| | Treatment group | | | | | |
|---|---|---|---|---|---|---|
| MedDRA preferred term | SYMB 160/4.5[a)] N=277 | SYMB 80/4.5[a)] N=281 | Budes 160 plus Form 4.5[a)] N=287 | Budes 160[a)] (N=275) | Form 4.5[a)] (N=284) | Placebo N=300 |
| | Number (%) subjects unless otherwise specified | | | | | |
| Mean (SD) exposure days | 166.5 (41.29) | 168.3 (37.73) | 164.6 (40.28) | 157.1 (51.31) | 156.3 (53.22) | 150.0 (60.15) |
| At least one AE n (%) | 159 (57.4) | 147 (52.3) | 142 (49.5) | 158 (57.5) | 161 (56.7) | 152 (50.7) |
| COPD | 37 (13.4) | 34 (12.1) | 30 (10.5) | 34 (12.4) | 50 (17.6) | 35 (11.7) |
| Nasopharyngitis | 21 (7.6) | 11 (3.9) | 12 (4.2) | 9 (3.3) | 15 (5.3) | 16 (5.3) |
| Oral candidiasis | 10 (3.6) | 7 (2.5) | 8 (2.8) | 12 (4.4) | 7 (2.5) | 6 (2.0) |
| Bronchitis | 10 (3.6) | 4 (1.4) | 10 (3.5) | 8 (2.9) | 8 (2.8) | 6 (2.0) |
| Sinusitis | 8 (2.9) | 9 (3.2) | 9 (3.1) | 4 (1.5) | 5 (1.8) | 6 (2.0) |
| Diarrhoea | 3 (1.1) | 5 (1.8) | 4 (1.4) | 3 (1.1) | 9 (3.2) | 1 (0.3) |

SYMB = Symbicort, Form = formoterol, Budes = budesonide
[a)] Note this denotes dosage strength. The actual dose was 2 actuations of the dosage strength administered bd

Table 7: Adverse events of interest in study D5899C00002 (multiple preferred terms in each category). Adverse events reported during randomised treatment (Safety analysis set).

| | Treatment group | | | | | |
|---|---|---|---|---|---|---|
| MedDRA preferred term | SYMB 160/4.5[a)] N=277 | SYMB 80/4.5[a)] N=281 | Budes 160 plus Form 4.5[a)] N=287 | Budes 160[a)] (N=275) | Form 4.5[a)] (N=284) | Placebo N=300 |
| | Number (%) subjects unless otherwise specified | | | | | |
| Steroid class effects<br>Oral candidiasis/voice effects (multiple PTs) | 6.9% | 3.2% | 3.1% | 5.5% | NA | 2.3% |
| Pneumonia/bronchopneumonia/ pneumonia pneumococcal | 3 (1.1) | 7 (2.5) | 3 (1.0) | 5 (1.8) | 5 (1.8) | 4 (1.3) |
| Pneumonia SAE (total 13) (pneumonia, bronchopneumonia, pneumococcal pneumonia) | 1 | 3 | 2 | 3 | 3 | 1 |
| Bronchitis/ lower respiratory tract infection/lower respiratory tract infection bacterial/lower respiratory tract infection viral/lung infection | 21 (7.6) | 9 (3.2) | 18 (6.3) | 17(6.2) | 13 (4.6) | 10 (3.3) |
| | | | | | | |
| General $\beta_2$-agonist class effects | 5.8% | 7.5% | 4.9% | 6.5% | 5.3% | 5.7% |
| Cardiac-related AE | 14 (5.1) | 15 (5.3) | 19 (6.6) | 18(6.5) | 13 (4.6) | 12 (4.0) |
| Non-fatal cardiac related SAE | 3 | 4 | 3 | 5 | 5 | 4 |

SYMB = Symbicort, Form = formoterol, Budes = budesonide, NA = not assessed
[a)] Note this denotes dosage strength. The actual dose was 2 actuations of the dosage strength administered bd

Pneumonia and potential lung infections

There were 27 subjects who had an AE of pneumonia-related preferred terms. There were no clinically important differences seen with the overall incidence across the treatment groups ranging from 1.0% (free combination of budesonide 160 plus formoterol 4.5) to 2.5% (Symbicort 80/4.5), but with no consistent dose-ordering for budesonide. Pneumonia was most frequently reported among subjects aged ≥75 years, and taking xanthines, cardio-selective β-blockers or ipratropium. Among the 27 subjects with pneumonia, 13 were reported as an SAE, all of which were confirmed radiologically. All of the PTs which could represent lung infections other than pneumonia-related PTs were grouped together and the percentage of subjects with these adverse events was highest in the Symbicort 160/4.5 group (7.6% versus placebo 3.3%).

Local steroid effects

The AE categories of candidiasis and voice effects, each representing multiple preferred terms for possible local steroid class effects, were reported with a slightly higher incidence in the Symbicort

160/4.5 (6.9%), Symbicort 80/45 (3.2%), budesonide 160 plus formoterol 4.5 (3.1%) and budesonide 160 (5.5%) groups than in the placebo group (2.3%).

General β2-agonist class effects

The overall incidence was low (5.9%) and there were no clinically important differences across the treatment groups in the incidence of AE potentially associated with β2-agonist class effects (headache, sleep effects, cramp, anxiety, serum potassium decrease, serum glucose increase, palpitation, tremor, tachycardia, and agitation).

Summary of Cardiac-related events

The percentage of subjects with an AE within the SOC of *Cardiac Disorders* was slightly higher in the formoterol 4.5 group (4.9%) than in any other treatment groups: Symbicort 160/4.5 and placebo both 4.0%; however, there was no trend for any specific abnormality or type of abnormality. The percentage of subjects with an AE within the SOC of *Investigations*, which includes abnormalities found on ECGs, was similar across all treatment groups.

Disease under study events

There were no clinically important differences across the treatment groups in the incidence of DUS events (AE categories of COPD, bronchitis, cough, dyspnoea, wheezing, and increased sputum; each representing multiple preferred terms for possible COPD events), with an overall incidence across all treatment groups of 20.1%. The incidence of DUS-related AE was slightly higher in the Symbicort 160/4.5 group (22.24%) than in the placebo group (19.3%), and was slightly lower in the Symbicort 80/4.5 group (17.1%). Chronic obstructive pulmonary disease was the most frequently reported severe intensity AE; it was also the AE reported second-most frequently as study drug-related.

Drug-related adverse events

The overall percentage of subjects with one or more AE considered study drug-related was higher in the Symbicort 160/4.5 (8.7%), Symbicort 80/4.5 (8.5%) and budesonide 160 (8.0%) groups compared to placebo (6.0%). For most individual PTs that were considered study drug-related, the incidence was generally low and similar across treatment groups. The percentage of subjects with study drug-related oral candidiasis was highest in the Symbicort 160/4.5 (7 subjects, 2.5%) and the budesonide 160 (8, 2.9%) groups compared to placebo (4 subjects, 1.3%). Dysphonia was reported more frequently in the Symbicort 160/4.5 group (4 subjects, 1.4%) compared to placebo (1 subject only). Pharyngeal candidiasis was reported in only two subjects, both in the Symbicort 160/4.5 group.

The majority of AEs that were considered study drug-related were mild or moderate in intensity; however, there were 15 subjects with study drug-related AE of severe intensity; these 15 subjects were distributed evenly across the treatment groups, both overall and within individual AE preferred terms. The majority (59%, 10/17) of the severe intensity study drug-related AE were COPD and the same number (10/17) had their onset within the first 15 days of treatment.

Deaths

None of the 11 deaths that occurred during randomised treatment or the 10 deaths that occurred post-randomised treatment was considered by the investigator to be study drug-related. Four subjects had a non-fatal SAE and 27 subjects had a DAE considered by the investigator to be study drug-related; three of the 4 study drug-related SAE occurred in the Symbicort groups, while the study drug-related DAE were distributed across the treatment groups (highest incidence was 3.5% of subjects in the formoterol 4.5 group).

24-hour urinary cortisol

This measurement was obtained at or prior to Visit 2 and within one week of EoT or 6 months termination in a subgroup of 437 subjects. All of the treatments containing budesonide showed a reduction from baseline to EoT whereas values in the formoterol 4.5 and placebo groups increased. At EoT, 24 hour urinary cortisol for Symbicort 160/4.5 was significantly less than placebo (treatment ratio = 0.74, p=0.023) and formoterol 4.5 (0.55, p<0.001) but did not differ significantly from the budesonide 160 or budesonide 160 plus formoterol 4.5 groups. The changes from baseline to EoT in the Symbicort 80/4.5 group did not differ significantly from placebo but was significantly less than formoterol 4.5 (ratio 0.63, <0.001).

More subjects (%) in the groups receiving budesonide (total dose 640 ug/day) in any form shifted from the normal range to below the normal range: Symbicort 160/4.5, 4/78 (5.9%); placebo 1/52 (1.8%); budesonide 160 plus form 4.5, 64 (4.7%); budesonide 160, 2/53 (3.8%); formoterol 4.5 none; Symbicort 80/4.5 none.

**Study D5899C00006**

There were no SAEs, DAEs or deaths reported in this study. The most common AEs reported were tremor, headache and dizziness. For COPD subjects after administration of Symbicort, 11 (42%) of subjects experienced 16 AEs (12 mild and four severe; maximum 2/subject). For COPD after administration of budesonide 160 plus formoterol 4.5, 13 (50%) of subjects experienced 19 AEs (13 mild, 5 moderate and one severe; maximum 4/subject). For asthmatic subjects after administration of Symbicort, 7 (27%) of subjects experienced 10 AEs all judged as mild in severity (maximum 3/subject). Adverse events were reported most commonly in the SOC *Nervous System Disorders* (31%, 42% and 19% of COPD/Symbicort, COPD/budesonide 160 plus formoterol 4.5 and asthmatic subjects respectively). By MedDRA PT the most common adverse events reported were tremor, dizziness and headache all of which were evenly distributed between groups.

**Study SD-039-0738**

Only four subjects experienced adverse events (3 Symbicort (tremor, headache and sinus headache) and 1 budesonide/formoterol Turbuhaler (tremor)). There were no SAEs or DAEs reported. The cases of tremor occurred five days after study drug administration and the headache occurred after four days. The investigator considered each case of tremor and headache as possibly study drug-related. The sinus headache was not considered study drug-related. Clinical laboratory evaluations did not yield any significant safety concerns.

**Post marketing data are presented as part of the Integrated Summary of Safety**

An overview of all post-marketing reports received by AZ through 31 December 2007 revealed 372 reports (29 serious reports, 343 non-serious reports). These reports included 52 serious events and 575 non-serious events. Of the 372 reports, 253 are medically confirmed, including 22 of the 29 serious reports. There are no safety concerns which need to be flagged from these data. Most of the adverse events reported were related to expected effects of β2-agonists and/or IGCS.

## Clinical Summary and Conclusions

The submission generally was well organised and presented. The safety assessment was exhaustive but at times was redundant particularly as regards the ECG data. There were no safety concerns raised by the studies submitted in this submission.

This was an application to register a new indication for the use of budesonide in combination with formoterol in the treatment of COPD. The application was for both Symbicort Rapihaler a pressurised metered dose inhaler and Symbicort Turbuhaler a dry powder inhaler; however, the current submission included the two Symbicort Rapihaler studies only. These were two Stage II pivotal studies submitted in support of this application, one of 12 months and the other of 6 months duration. The inclusion of Symbicort Turbuhaler relies on two studies both of 12 months duration,

which have been submitted previously. For the purposes of this application, these studies have been alluded to and summarised in the body of the sponsor's *Clinical Evaluation Report*.

The two pivotal studies (SUN and SHINE) studies were sound in their design and the co-primary endpoints (pre- and post-dose $FEV_1$) were suitable to test the hypotheses that both components of the combination treatment contributed to its effect, that is, fulfilled the requirements of the combination rule for pharmaceutical products. There were multiple secondary endpoints of which three, dyspnoea, SGRQ total score and exacerbations were nominated as key secondary variables. In addition serial spirometry was performed in a subgroup of subjects in both pivotal efficacy studies. These variables all contributed to an adequate global assessment for this current application for a new indication for the treatment of COPD.

Evidence was presented that the clinical effects of the combination treatment are not dependent on the device. In all comparisons there were no statistically significant differences between budesonide and formoterol when administered as a combination product (Symbicort) or budesonide and formoterol administered as the individual monoproducts together.

The therapeutics indications proposed in this application are:

Chronic Obstructive Pulmonary Disease (COPD)

*Symbicort (Turbuhaler and Rapihaler) is indicated for the maintenance treatment of moderate to severe COPD ($FEV_1$ ≤50% predicted normal) in subjects with frequent symptoms and/or a history of exacerbations, where use of a combination product (inhaled corticosteroid and long-acting beta2-agonist) is appropriate.*

The Australian COPD-X guidelines recommend inhaled glucocorticosteroids for subjects with a documented response to inhaled glucocorticoids or severe disease with frequent exacerbations.[9] These guidelines define severe disease as postbronchodilator $FEV_1$ <40% predicted and the presence of dyspnoea on minimal exertion and severe curtailment of daily activities. No specific indications are given for combination treatment with inhaled corticosteroids and LABA but the implication is that the indications are similar to those for inhaled corticosteroids alone. The GOLD guidelines suggest that regular treatment with inhaled glucocorticosteroids should be added to long-acting inhaled bronchodilators in subjects with a postbronchodilator $FEV_1$ <50% predicted (Stage III: severe COPD to Stage IV: very severe COPD) and a history of repeated exacerbations (for example, 3 in the last 3 years), in order to improve health status and reduce exacerbations.[10]

Therefore the above therapeutic indication proposed is similar to the recommendations in national and international guidelines. There is the potential for some confusion in that the definition of severe COPD in the COPD-X guidelines differs slightly from that in GOLD. It was assumed that the figure of ≤50% in the proposed indication is based on the inclusion criteria for the Symbicort COPD studies (the EU Summary of Product Characteristics (SPC) for Symbicort Turbuhaler states that the therapeutic indication is for symptomatic treatment of subjects with severe COPD ($FEV_1$ <50% predicted) and a history of repeated exacerbations who have significant symptoms despite regular treatment with regular long acting bronchodilators.

The NZ data sheet gives the indications as:

COPD

[9] David K McKenzie, Michael Abramson, Alan J Crockett, Nicholas Glasgow, Sue Jenkins, Christine McDonald, Richard Wood-Baker, Peter A Frith. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2007.

[10] Rabe KF, Hurd S Anzuetto A et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. GOLD Executive Summary. American Review of Respiratory and Critical Medicine 2007; 176: 532-555.

*Symbicort Turbuhaler is indicated in the regular treatment of subjects with moderate to severe chronic obstructive pulmonary disease (COPD) [$FEV_1$ ≤50% of predicted], with frequent symptoms despite beta2- agonist use and a history of exacerbations.*

Furthermore the pivotal studies recruited subjects aged ≥40 years. The NZ data sheet states that the dose for COPD is for adults aged 40 years and older. None of the Symbicort studies for the COPD indication included subjects aged <40 years.

In the opinion of the evaluator, before it is acceptable the therapeutic indication proposed by the Sponsor needs to be changed to specify adults aged 40 years or older, with $FEV_1$ ≤50% predicted (pre- or post need not be specified) with frequent symptoms and a history of frequent exacerbations.

*Contribution of individual components as assessed by $FEV_1$*

In both studies the contribution of budesonide was assessed by pre-dose $FEV_1$. In both studies Symbicort produced a significantly greater increase from baseline to the average of the randomised treatment period in pre-dose $FEV_1$ compared to formoterol. However in both studies the treatment differences were small and coincidentally identical (LS mean = 0.04 L). In the SUN study, Symbicort 160/4.5 and formoterol increased pre-dose $FEV_1$ by 9.7% and 5.8% respectively which is a treatment difference of approximately 3.8% over baseline. In the SHINE study the estimated treatment difference was approximately 3.9% above baseline. In the SUN study, the improvement in pre-dose $FEV_1$ at EoT for Symbicort did not differ significantly from formoterol (LS mean = 0.03 L, p=0.150).

Therefore although there is a statistically significant contribution of budesonide as assessed by pre-dose $FEV_1$, the absolute increase above that of formoterol alone is small. Furthermore subgroup analysis revealed a differential treatment-effect depending on the severity of COPD; the absolute magnitude of the treatment-effect decreased as severity increased.

*Exacerbations*

In the SUN study, Symbicort 160/4.5 reduced the exacerbation rate by 37% compared to placebo and by 24% compared to formoterol. Exacerbations were defined as those which required OGCS or hospitalisation for treatment. The significant reduction in protocol defined exacerbations was largely due to the reduction in the subset of subjects treated with OGCS (albeit this was the majority of them). A small increase in rate of hospitalisations for COPD exacerbations wase seen in the Symbicort 160/4.5 group compared to placebo. Similarly the number of subjects who were treated with antibiotics without OGCS or hospitalisation (so-called mild exacerbations) was higher in the Symbicort group (10.1%) compared to placebo (7.9%). In the SHINE study, Symbicort 160/4.5 reduced the exacerbation rate by 20.4% compared to placebo but this was not statistically significant (p=0.109). Furthermore in the Symbicort 160/4.5 group there was a statistically significant increase in hospitalisation for COPD exacerbation compared to placebo (0.158 and 0.108, p=0.05). The proportion of subjects who experienced at least one mild exacerbation was higher for Symbicort (10.9%) compared to placebo (5.4%).

The evaluator was mindful of the fact that only one of the two pivotal studies has provided evidence in support of the use of Symbicort Rapihaler in the treatment of COPD patients with frequent exacerbations. In Study B, Symbicort Turbuhaler prolonged the time to first exacerbation but the exacerbations rates did not differ between Symbicort and budesonide alone; in Study A, Symbicort Turbuhaler reduced the exacerbation rates compared to formoterol and placebo, but not compared to budesonide alone. Therefore only one of the four Symbicort studies (SUN) showed a significantly greater reduction in exacerbation rate for Symbicort compared to budesonide alone[11].

[11] The sponsor commented that this statement is factually incorrect. The SUN study did not include a 'budesonide' comparator group.

Therefore only one of the four Symbicort studies (SUN) showed a significantly greater reduction in exacerbation rate for Symbicort compared to budesonide alone.

There were no safety concerns raised by the studies submitted in this dossier.

For the reasons outlined above, the evaluator recommended that the current application not be approved.

## 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

There was no requirement for a quality assessment in a submission of this type.

### Nonclinical

There was no requirement for a nonclinical assessment in a submission of this type.

### Clinical

The two new Phase III pivotal studies in the current submission tested the efficacy and safety of two different dosage strengths of Symbicort (80/4.5 µg versus 160/4.5 µg delivered per actuation), each administered as 2 actuations bd. These studies were of placebo and active-controlled (double dummy) parallel group design and were conducted at multiple sites within and without the USA. Both had an initial screening visit followed by a run-in period of a fortnight, followed by randomisation to one of the studies' arms. Both studies included an active comparator arm (formoterol Turbuhaler, 4.5 µg per inhalation, administered as 2 actuations twice daily).

The studies were designed to assess the efficacy and safety of Symbicort at two dosage strengths in subjects with COPD and to compare Symbicort to the combination of the actives taken together as the single component products, and to one or other of the single components alone.

Treatment duration was 6 months in the first and 12 months in the second study.

The first study was Study D5899C00002 ("SHINE") which used Symbicort pMDI 2 x 160/4.5 µg & 80/4.5 µg bd. compared to formoterol Turbuhaler formoterol 4.5 µg per inhalation, administered as 2 actuations twice daily, budesonide pMDI 160 µg bd. (and these in combination i.e. 160 µg per actuation plus formoterol 4.5 µg per actuation, given as 2 actuations bd.) or placebo in COPD patients. SHINE had 1,704 randomised subjects. The study was conducted at 194 sites in 5 countries.

The second study was Study D25899C00001 ("SUN") which used Symbicort pMDI 2 x 160/4.5 µg bd. and 2 x 80/4.5 µg bd. compared to formoterol Turbuhaler 2 x 4.5 µg bd. and placebo in patients with COPD. It thus had four parallel groups. This study, a 12 month study, had a scheduled visit at 12 months (but none other after month 6). The SUN study had 1,964 randomised subjects. The study was conducted at 237 sites in 9 countries.

The studies had multiple endpoints. In both studies the primary outcome variables were pre-dose $FEV_1$ and 1-h post-dose $FEV_1$. Pre-specified comparisons were Symbicort versus formoterol for pre-dose $FEV_1$ (to assess the budesonide component) and Symbicort versus budesonide (or placebo) for post-dose $FEV_1$ to assess the formoterol component.

Three key secondary variables were identified: dyspnoea score (breathlessness diary), SGRQ total score and the number of exacerbations (defined as worsening of COPD which required a course of

oral corticosteroids for treatment and/or hospitalisations). The primary comparisons for the key secondary outcome variables were between Symbicort and placebo.

SUN Study results: The primary efficacy variable result was a dose dependent advantage regarding improvement from baseline shown for the higher Symbicort dose versus formoterol alone or placebo in terms of the averaged pre-dose $FEV_1$; this advantage was shared for all active treatments versus placebo in terms of post-dose $FEV_1$. The 95% CIs are broad. However, Symbicort 160/4.5 produced a statistically significant greater change from baseline in post-dose $FEV_1$ compared to placebo (LS mean = 0.18L, $p<0.01$). Symbicort 160/4.5 produced a significantly greater change from baseline in pre-dose $FEV_1$ compared to formoterol 4.5 (LS mean = 0.04 L, $p=0.008$). For Symbicort 80/4.5, pre-dose $FEV_1$ (L) increased significantly from baseline versus placebo (LS mean (95% CI) = 0.08 (0.06, 0.11)) and post-dose $FEV_1$ increased from baseline to average of the randomised period (LS mean = 0.19 (0.16, 0.21)).

Regarding the primary analysis, Symbicort 80/4.5 produced a significantly greater change in post-dose $FEV_1$ compared to placebo (LS mean = 0.16 ($p<0.001$); however the change in pre-dose $FEV_1$ was not significantly different to formoterol 4.5 (LS mean = 0.02; $p=0.161$). Due to the statistical plan having changed before breaking of the blind, the SUN study was still able to progress to secondary endpoint analyses.

In terms of secondary variables, the dyspnoea score reached a pre-specified clinically significant difference for Symbicort 160/4.5 which is a significantly greater decrease compared to placebo (55.8% versus. 40.5%); the SGRQ total score failed to show benefit; and the rate of exacerbations was Symbicort 160/4.5 - 30.8%, Symbicort 80/4.5 - 32.6%, placebo - 37.2%. The absolute rate of exacerbations in the SUN study's placebo group was 0.892 exacerbations per subject per treatment year. The absolute difference between placebo and either dose of Symbicort was about 40% of this, that is, about 0.35 exacerbations per subject per treatment year.

Safety in the SUN study raised no new qualitative information but, as stated by the evaluator, "The percentage of subjects with any SAE (fatal and non-fatal) was highest in the formoterol 4.5 group (18.0%) and lowest in the placebo group (12.9%) (Symbicort 160/4.5, 16%; Symbicort 80/4.5, 14%). Fifteen subjects had a fatal SAE during randomised treatment; the proportion of fatal SAE was not notably different across treatment groups." There is a suggestion that Symbicort is less well tolerated than placebo except in regard to "COPD" and, as expected, corticosteroid related adverse effects, including infections, were seen with both doses of Symbicort and there is a signal present in the data on 24 hour urinary cortisol excretion.[12]

SHINE Study results:

This was a six month study. Pre-dose $FEV_1$ increased significantly from baseline *to the average of the randomised period* in the Symbicort 160/4.5 (LS mean (95% CI) = 0.08 (0.06, 0.11); Symbicort 80/4.5 LS mean = 0.06, (0.03, 0.08), formoterol 4.5 LS mean = 0.04 (0.02, 0.07) and budesonide 160 plus formoterol 4.5 LS mean = 0.07 (0.04, 0.09) groups. Post-dose $FEV_1$ (L) increased significantly from baseline *to average of randomised period* in the Symbicort 160/4.5 LS mean = 0.2 (0.18, 0.23); Symbicort 80/4.5 (LS mean = 0.19 0.17, 0.22); budesonide 160 plus formoterol 4.5 LS mean = 0.19, (0.16, 0.21); budesonide 160 LS mean = 0.03, (0.01, 0.06) and formoterol 4.5 LS mean= 0.17 (0.14, 0.19) groups. Symbicort 160/4.5 was statistically superior to budesonide 160 with respect to post-dose $FEV_1$, to formoterol with respect to pre- dose $FEV_1$ – the evaluator finds this difference to be clinically insignificant.

[12] It should be noted that the clinical evaluator does not refer to a "signal" in urinary cortisol, and that in the conclusions of the sponsor's Clinical Evaluation Report it is stated that "There were no safety concerns raised by the studies in this dossier"

In terms of secondary variables, all groups improved with respect to dyspnoea but Symbicort 160/4.5 was superior to placebo. The same can be said in regard to the SGRQ total score.

Secondary endpoint analyses could not be formally performed for Symbicort 80/4.5. Symbicort 80/4.5 produced a significantly greater change in post-dose $FEV_1$ compared to budesonide 160 (LS mean = 0.06 ($p<0.001$); however the change in pre-dose $FEV_1$ was not significantly different to formoterol 4.5 (LS mean = 0.02; $p=0.335$). Therefore the analytical criteria (combination rule) were not met and consequently the applicant's analyses of the key secondary end points for this dosage of Symbicort are descriptive only.

The Delegate noted that the SHINE study is a failed study as far as the lower dose of Symbicort is concerned. There was no superiority versus formoterol with respect to pre-dose $FEV_1$ .

There was little difference in the number of patients that experienced at least one exacerbation; there was a non-significant trend to a lower rate of exacerbations that was not dose-dependent.

With regard to safety, the percentage of subjects with any SAE (fatal and non-fatal SAE) was highest in the Symbicort 160/4.5 (11.9%) and Symbicort 80/4.5 (12.1%) groups and lowest in the formoterol 4.5 group (8.5%). The overall percentage of subjects with non-fatal SAE during randomised treatment was higher in both Symbicort 160/4.5 (11.2%) and Symbicort 80/4.5 (10.7%) groups than in the four other treatment groups (8.1% to 9.5%). The evaluator was of the view that there was a clear cut dose ordering effect with budesonide for overall respiratory infections. Corticosteroid related adverse events and cortisol excretion data were broadly consistent with the SUN study.

The evaluator recommended rejection but also suggests a number of significant changes to the draft product information document and a narrower indication, if approved:

*Symbicort Rapihaler is indicated for the maintenance treatment of moderate to severe COPD (FEV1 ≤50% predicted normal) in adults ≥40 years of age with frequent symptoms despite long-acting bronchodilator use including long-acting $\beta_2$-agonists and/or a history of exacerbations (for example three in the last three years).*

### Risk-Benefit Analysis

As noted in the applicant's own clinical overview, Symbicort Rapihaler 160/9 bd (dosage strength 80/4.5), as used in SUN and SHINE, may have been a sub-therapeutic dose. SHINE's results were available before the blind was broken in the SUN study. There was anticipatory switching of the primary endpoints in SUN – from pre- and post-dose $FEV_1$ for both strengths - to the testing first of the higher strength only ("Efficacy will be determined by the co-primary endpoints of pre-dose $FEV_1$ and 1 hour post-dose $FEV_1$ compared to placebo and compared to formoterol for pre-dose $FEV_1$.") to be then followed by testing of the secondary endpoints (dyspnoea, SGRQ and exacerbations) for the higher dose only. This is arguably not appropriate[13].

It is problematical that the improvement in SGRQ was less significant than pre-specified in either SUN or SHINE and SHINE was not powered for a specific improvement in exacerbations or indeed for any secondary endpoint. Actually, it appears improper for the applicant to report significance for secondary endpoints in SHINE because the lower dose did not achieve significance in the primary endpoints. In SUN, the validity of statistically testing the third secondary endpoint (exacerbations) is questionable, given the lack of pre-defined benefit in the SGRQ (the preceding test).

In SHINE, the budesonide 160 single dose product was not superior to placebo with respect to pre-dose $FEV_1$.

[13] In the final outcome, after appeal evaluation (see page 47), it was accepted that that the secondary analyses in SUN are statistically valid and that the anticipatory switching of the primary endpoints was appropriate in this case.

Efficacy and safety in the present submission rest upon two large studies that included a 2-dose dose-ranging component. The higher dose was the only one to show statistically significant improvement for the primary endpoints in the six month SHINE study. Secondary endpoint analyses were therefore only exploratory in SHINE. The primary endpoints showed small changes for the higher dose.

The 12 month study, SUN, did not include a test of the lower dose of Symbicort Rapihaler owing to a change in the statistical plan. Three secondary endpoints were thus able to be tested for statistical significance in respect of the higher dose group. The second of the three included a predefined margin of improvement that was not met. The primary endpoints suggest minor absolute benefit in respect of pre- and post-dose $FEV_1$.

The safety data show no new signals but also suggest some burden of adverse events attributable to Symbicort, more so for the proposed higher dose.

The original submission included Turbuhaler studies. The issue at the time, as now, was the clinical significance of the benefit, in terms of primary and secondary endpoints.

The four pivotal studies (Turbuhaler submission and the current one for Rapihaler) span two delivery systems that have not been shown to be clinically equivalent.

The frequency of exacerbations has been explored in the current submission and the results are roughly similar to those previously regarded in Studies A and B, albeit cross-study comparisons are not reliable. In the original submission, the number needed to treat (NNT) was 2.13 to 2.3, indicating that 2-3 patients needed to be treated for one year to prevent one exacerbation, when compared to treatment with eformoterol alone. In SUN, as noted by the evaluator, "Overall 34.1% of subjects experienced 1159 exacerbations: Symbicort 160/4.5, 30.8%; Symbicort 80/4.5, 32.6%; placebo 37.2%." The crude difference is 6.4%, of which only the SUN results are statistically credible.

The applicant seeks an indication that is broad, including treatment in an unqualified form, "for the maintenance treatment of moderate to severe COPD". It might be more reasonable to specify "symptomatic" or "palliative" than "maintenance" since there is no convincing evidence of alteration of the natural history of the disease and the exacerbations data are weak, implying a large number needed to treat that might be unreliable. Symbicort cannot be said to be unequivocally effective in preventing exacerbations.

The basis of inflammatory processes in COPD is complex and it is not likely that ICS would be effective. No data exist to show that ICS/LABA combinations affect the natural history of COPD but some palliation of symptoms might be inferred from the primary endpoints in all studies and the first of the secondary endpoints in SUN (dyspnoea). The improvement in the primary endpoints is small, as noted by the evaluator.

None of the Symbicort studies for the COPD indication included subjects aged <40 years. There are no grounds for dissenting from the evaluator's advice that "Before it is acceptable the therapeutic indication proposed by the sponsor needs to be changed to specify adults aged 40 years or older, with $FEV_1$ ≤50% predicted (pre- or post need not be specified) with frequent symptoms and a history of frequent exacerbations**.**" Therefore a possible indication could be "Symbicort Rapihaler 200/6 is indicated for the symptomatic treatment of moderate to severe COPD ($FEV_1$ ≤50% predicted normal) in adults ≥40 years of age with frequent symptoms despite long-acting bronchodilator use including long-acting $\beta_2$-agonists and/or a history of exacerbations (for example three in the last three years)".

The Delegate posed the following questions to the ADEC:

1. Do SUN and SHINE contribute new, clinically meaningful information that builds confidence in regard to the results of studies that used Turbuhaler A and B?

2. Do the data available in the two submissions suggest more than minor symptomatic improvement in COPD?

3. Is there a signal of higher total adverse events attributable to Symbicort 200/6 than to the separate actives?

4. Can the data sets be seen as interchangeable, given the lack of clinical equivalence data for pMDI and Turbuhaler? If they are not, then the Turbuhaler presentations are not approvable even if the 200/6 Rapihaler presentation might be.

5. The options with this application are to reject due to limited evidence of efficacy or to accept that the spirometric data and results for dyspnoea in SUN support some symptomatic benefit, or to go further and entertain the other secondary endpoints. Are the data robust enough to support the latter?

6. The rational basis for the use of ICS in COPD has recently been strongly questioned and it may be the case that the nature of the inflammatory process is not amenable to the use of ICS.[14,15] However, there is some support for symptomatic benefit in the current data set. Do these doubts about medium to long term risk and benefit warrant post-market requirements for further studies?

Because of doubt about the approvability of this application, the Delegate proposed rejection, due to lack of clinically meaningful efficacy and added benefit over risk, but to leave open the possibility of a more restrictive indication.

*Symbicort (Turbuhaler and Rapihaler) may be registered for the indication, "Symbicort Rapihaler and Turbuhaler are indicated for the symptomatic treatment of moderate to severe COPD ($FEV_1$ ≤50% predicted normal) in adults ≥40 years of age with frequent symptoms despite long-acting bronchodilator use including long-acting $\beta_2$-agonists and/or a history of exacerbations (for example three in the last three years).*

Response from the sponsor

In its pre-ADEC response the sponsor addressed the questions posed by the Delegate to ADEC (as listed above). The sponsor agreed in principle with the Delegate's proposal, that Symbicort Turbuhaler and Symbicort Rapihaler (pMDI) should be registered for the treatment of COPD with a modified indication, although the readability of the indication could be slightly improved through further modifications.

The sponsor maintained that the scientific evidence clearly supports the efficacy and safety of Symbicort for the treatment of COPD. The following points summarise the sponsor's response to the respective questions put to the ADEC by the Delegate.

Q1. SUN and SHINE provide clinically meaningful results, including evidence that both budesonide and eformoterol contribute to the efficacy achieved with Symbicort. The improvements in lung function and the reduction in severe exacerbations seen are consistent with results achieved in the Turbuhaler studies.

Q2. In addition to clinically relevant improvements in lung function and symptoms, consistent reductions in COPD exacerbations, which is an important treatment goal, were seen in three 12-

[14] Suissa S, Barnes PJ. Inhaled corticosteroids in COPD: the case against. Eur Respir J 2009; 34: 13–16 DOI: 10.1183/09031936.00190908.

[15] Cosio MG. et al. Immunologic Aspects of Chronic Obstructive Pulmonary Disease. N Engl J Med 2009; 360:2445-54.

month clinical trials (studies A, B, and SUN), and thus represent important treatment for COPD patients.

Q3. Overall, Symbicort does not result in a higher incidence of adverse events and serious adverse events than seen in patients treated with either eformoterol or budesonide alone, when adjusted for exposure differences. Exposure time of Symbicort is greater, and this affects the absolute number of adverse events.

Q4. The TGA has previously accepted the therapeutic equivalence of the pMDI and Turbuhaler formulations in asthma patients, based upon pharmacokinetic results in healthy volunteers, pharmacodynamic results in healthy volunteers and asthma patients, and efficacy results in asthma patients. Based on European guidance, the COPD results from the two formulations can thus be considered as mutually supportive, and thus recent results from the pMDI formulation provide further evidence for the efficacy and safety of the Turbuhaler formulation.

Q5. In addition to being statistically robust, the totality of the efficacy results from the 4 large, well controlled Symbicort studies are clinically robust as well. The most significant clinical effect of Symbicort in the Turbuhaler and pMDI studies is the prevention of exacerbations, which has been consistently shown across all three 12-month studies (studies A, B, and SUN).

Q6. A positive benefit-risk relationship for Symbicort in the treatment of COPD has been shown based on extensive clinical experience with budesonide and eformoterol and clinical data from large, long-term, well controlled clinical trials. The literature cited by the Delegate does not change this assessment.

Recommendation from ADEC

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ADEC recommended rejection of the application for registration of budesonide with eformoterol fumarate dihydrate (Symbicort Turbuhaler 200/6, 400/12 and Symbicort Rapihaler 200/6) dry powder inhaler 200 μg/6 μg and 400 μg/12 μg and pressurised metered dose inhaler 200 μg/6 μg for the indication maintenance treatment of moderate to severe chronic obstructive pulmonary disease ($FEV_1$<50% predicted normal) in patients meeting certain criteria on the grounds that efficacy has not been adequately demonstrated.

In making this recommendation, the ADEC recalled that it had previously recommended rejection of an application seeking to register Symbicort Turbuhaler for use in the treatment of patients with moderate to severe chronic obstructive pulmonary disease on the grounds of inadequate efficacy of the budesonide component of the combination. Data on exacerbations were not regarded as clinically significant.

The current submission provides evidence from two new large Phase III efficacy studies, D5899C00002 (SHINE) and D5899C00001 (SUN). However neither study demonstrated a clinically meaningful improvement in the co-primary efficacy variable, $FEV_1$, at the proposed dose.

Additionally, although some new exploratory evidence was presented in the present submission that treatment with Symbicort may be associated with a clinically meaningful reduction in exacerbations compared with treatment with eformoterol alone, the ADEC did not consider these data sufficiently robust to support approval for this use. Of particular note is that only one of the two new Symbicort studies (SUN) presented to TGA in the two submissions showed a statistically significantly greater reduction in exacerbation rate for Symbicort compared to eformoterol alone and the exacerbation rate was the third of three secondary endpoints. There have now been four large clinical trials that have failed to show clinically relevant benefit. Thus ADEC considers further, specific studies are needed to confirm this finding.

## Initial Outcome

Based on a review of quality, safety and efficacy, TGA rejected the application to register an extension of registered indications for Symbicort Turbuhaler containing budesonide 200 µg/eformoterol 6 µg for inhalation dry powder inhaler, and budesonide 400 µg/eformoterol 12 µg powder for inhalation dry powder inhaler, and Symbicort Rapihaler containing budesonide 200 µg/eformoterol 6 µg for inhalation pressurised metered dose inhaler, indicated for:

*Symbicort Turbuhaler and Rapihaler are indicated for the symptomatic treatment of moderate to severe COPD (FEV1 ≤50% predicted normal) in adults ≥40 years of age with frequent symptoms despite long-acting bronchodilator use including long-acting β2-agonists and/or history of exacerbations (for example three in the last three years).*'

## Final Outcome

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

As the products are already registered on the ARTG for the management of asthma, it is evident that the quality of the product has been satisfactorily established, leaving the issues of efficacy and safety to be considered.

In determining whether safety has been established, the Delegate of the Minister noted that the clinical evaluator for the earlier application found no evidence of safety concerns in the two large cohorts of Studies A and B. In addition, no new safety concerns were subsequently detected by the clinical evaluator in the SUN and SHINE studies, and in commenting on adverse effects of special interest in this patient group, he noted:

> 'The percentage of patients with ≥1 event for 'potential lung infections other than pneumonia' was higher in the Symbicort 160/4.5 µg group compared to the Symbicort 80/4.5 µg, eformoterol 4.5 µg and placebo groups (8.1%, 6.9%, 7.1% and 6.2% respectively). Combining these two categories [that is, with subjects reporting pneumonia] indicates that the incidence of pneumonia and respiratory infections other than pneumonia were similar in all the treatment groups (12.1%, 10.3%, 10.5% and 11.2% respectively)'.

Given the inherent variability in the diagnosis of pneumonia, which was not standardized and left up to the discretion of the investigator, the Delegate of the Minister accepted these data as not indicating a significantly higher risk of pneumonia in patients in the Symbicort arms of studies SUN and SHINE.

The Delegate of the Minister further noted that no safety concerns were identified by the clinical evaluator in the post-marketing data submitted by the sponsor up to December 2007, with most of the adverse events reported related to expected effects of LABA and/or IGCS. The Delegate of the Minister noted also that a Product Safety Update Report was submitted to TGA on 21 October 2008, covering the period 25 August 2007 to 24 August 2008, which included a cumulative review of lower respiratory tract infections and pneumonia in asthma and COPD. This included clinical trial and post-marketing surveillance data, and identified no new concerns regarding safety.

A recent meta-analysis had been published in the Lancet, which examined the risk of pneumonia using pooled patient data from seven large clinical trials (including all four of the Symbicort pivotal trials discussed above) of inhaled budesonide (320-1280 µg/day), with or without eformoterol, versus control regimen (placebo or eformoterol alone) in patients with stable COPD and at least 6

months of follow-up.[16] Data was analysed from 7042 patients, and showed that budesonide was not significantly associated with 1-year risk of pneumonia, and that there was no evidence of a dose-dependent effect in increasing risk of pneumonia.

Taking all of the above into account, the Delegate of the Minister accepted that there are no significant safety concerns regarding the use of budesonide in patients with COPD that would prevent registration of a COPD indication for Symbicort Turbuhaler/Rapihaler on safety grounds.

Therefore, in making a decision, the critical issue is that of efficacy relative to the particular indication which has been sought. The Delegate of the Minister noted that he understood efficacy to infer that, on the evidence available, patients can expect to derive clinically meaningful benefit from the use of a product, with a degree of risk of adverse effects which is appropriate to the seriousness of the condition being treated. This definition would be accepted by most regulatory agencies with standards comparable to TGA, as well as most reasonable medical practitioners. This concept is quite distinct from that of 'statistical significance', which implies a measurable difference between study parameters which reaches a pre-determined level of probability such that it is unlikely to be a chance occurrence, but does not necessarily predict whether the patient will experience a perceptible incremental benefit in their condition.

There are difficulties in adequately defining what constitutes a response to a pharmacological intervention in COPD, and since the relationship between spirometry and symptoms appears to be poor, measures of lung physiology alone may not adequately describe either the social impact of COPD or the effectiveness of therapeutic interventions in individual patients.[17] Most researchers regard changes in patient-centred outcomes such as symptoms, exacerbations, exercise capacity and health-related quality of life to be essential in comprehensively assessing both disease progression and treatment efficacy.

The concept of minimal clinically important difference (MCID or MID) has therefore been proposed as a tool to assist clinicians and researchers in weighing the evidence from clinical trials. MID has been defined by a group of epidemiologists at McMaster University as 'the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, either beneficial or harmful, and which would lead the patient or clinician to consider a change in management'. In response to this challenge, the American Thoracic Society (ATS) and European Respiratory Society (ERS) have jointly created a Task Force on 'Outcomes for COPD pharmacological trials: from lung function to biomarkers' to inform the COPD research community about the possible use and limitations of current outcomes and markers when evaluating the impact of a pharmacological therapy.[18] The Delegate of the Minister utilised the definitions for MID for a variety of outcomes developed in this paper to assist in evaluating the clinical efficacy of Symbicort for COPD in the four pivotal trials which have been reviewed. This will be further discussed below.

These have been important considerations in how the Delegate of the Minister weighed the evidence.

Consideration of the appeal and the available evidence:

In considering the four pivotal Symbicort trials, in the view of the Delegate of the Minister, it was first necessary to determine whether the two different delivery systems (Turbuhaler DPI and

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[16] Sin DD, Tashkin D, Zhang X et al. Budesonide and the risk of pneumonia: a meta-analysis of individual patient data. Lancet 2009; 374: 712-9.

[17] Edwards N. A framework for future trials: Guidelines on Developing COPD Drugs. GCPJ 2004; 11: 1-5.

[18] Cazzola M, MacNee W, Martinez FJ et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008; 31: 416-68.

Rapihaler pMDI) are clinically equivalent, as this has a fundamental bearing upon whether all four trials can be considered together in assessing efficacy. The Delegate of the Minister noted that therapeutic equivalence between these delivery systems has previously been accepted for the treatment of asthma, based on pharmacokinetic and pharmacodynamic studies in healthy volunteers, and efficacy and safety studies in asthma patients.

In addition, the pharmacokinetic study D5899C00006 presented in the current submission has shown similar systemic exposure from Symbicort pMDI compared with budesonide pMDI plus eformoterol Turbuhaler DPI in COPD subjects. The other pharmacokinetic study in the present submission (SD-039-0738) compared relative systemic bioavailability of budesonide and eformoterol in COPD subjects when inhaled as a single dose of 1280/36 µg from Symbicort pMDI compared with budesonide pMDI plus eformoterol Turbuhaler DPI. Although there were some methodological difficulties encountered in this study, it was concluded by the clinical evaluator that bioavailability could be considered equivalent. There are no studies which demonstrate therapeutic equivalence directly between the two delivery systems.

Taking these findings into account, the Delegate of the Minister accepted that the Turbuhaler and Rapihaler presentations can be considered to be reasonably equivalent in therapeutic effect in COPD patients, hence both delivery systems are potentially registrable for this indication, and the data from all four pivotal trials can be considered together when evaluating efficacy.

Inclusion and exclusion criteria were very similar in all four pivotal studies (Studies A and B, SUN and SHINE), and baseline characteristics of patients enrolled were closely comparable, predominantly reflecting patients with moderate to severe COPD.

In Studies A and B, two co-primary endpoints were examined, with post-dose $FEV_1$ used in both to examine the eformoterol/LABA effect. In Study A, IGCS effect was examined by exacerbation rate, and in Study B, by time-to-first exacerbation. Exacerbations were defined by the need for oral steroids, and/or antibiotics, and/or hospitalization due to respiratory symptoms. It is noted that this definition differs from that used in the SUN and SHINE studies, where antibiotic treatment was not a part of the definition.

Although $FEV_1$ has been extensively used in clinical studies of COPD as a measure of lung function, it has statistically significant but weak correlations with other patient-centred outcomes such as dyspnoea. Despite its widespread use, there has been relatively little effort to determine a MID for $FEV_1$. However, the ATS/ERS Taskforce has recommended that an appropriate range for MID might be 100-140 mL.

For post-dose $FEV_1$, treatment with Symbicort Turbuhaler 160/4.5 µg, 2 inhalations bd, versus placebo resulted in statistically significant increases of 15% ($p<0.001$) and 14% ($p<0.001$) in Study A and B respectively, equivalent to absolute increases of 0.17 L and 0.14 L respectively. Significant increases in post-dose $FEV_1$ were also demonstrated in both studies versus budesonide of 9% ($p<0.001$) and 11% ($p<0.001$) respectively, confirming the LABA effect. There was no significant benefit in Study A versus the eformoterol arm, but a small effect was observed in Study B (5%, $p=0.002$). Hence the LABA component of Symbicort has been shown to have a small effect on post-dose $FEV_1$ consistent with the current definition of MID.

However, given that the indication sought is for the treatment of COPD patients who remain symptomatic despite long-acting bronchodilator use, arguably the most important consideration is whether Symbicort improves other patient-centred outcomes which reflect the budesonide IGCS component, in particular exacerbations. The ATS/ERS Taskforce suggest a MID of 22% change in exacerbations.

In Study A, number of exacerbations was tested as a co-primary outcome, and treatment with Symbicort Turbuhaler 160/4.5 µg, 2 inhalations bd, resulted in statistically significant reductions compared with both placebo (23%, $p=0.035$) and eformoterol (25%, $p=0.042$). Time-to-first

exacerbation was tested as a secondary endpoint, and was not statistically different for Symbicort versus any of the comparator arms.

In Study B, time-to-first exacerbation was tested as a co-primary outcome, and treatment with Symbicort Turbuhaler 160/4.5 µg, 2 inhalations bd, resulted in statistically significant reductions compared with both placebo (28%, p=0.006) and eformoterol (29%, p=0.003). Number of exacerbations was tested as a secondary endpoint, and resulted in statistically significant reductions compared with both placebo (24%, p=0.029) and eformoterol (25%, p=0.015).

In all cases, measurement of exacerbation rate ratios and hazard ratios shows modest but definite reductions with Symbicort Turbuhaler in comparison to both placebo and eformoterol arms, which marginally exceed the ATS/ERS Taskforce suggested MID of 22%. This translates into a Number Needed to Treat (NNT) of 2.1 and 2.4 for Study A and Study B respectively to prevent one exacerbation per year, which the Delegate of the Minister accepted to be relatively low.

Other secondary endpoints examined in Studies A and B included oral steroid courses required, St George's Respiratory Questionnaire (SGRQ), vital capacity (VC) and diary-card data. The clinical evaluator summarised these data by commenting:

> 'Symbicort achieved a significant improvement in primary and most secondary efficacy variables in both studies with no increased discontinuation rate or adverse event reporting.'

In the current application, the 12-month study SUN and 6-month study SHINE both used post-dose $FEV_1$ and pre-dose $FEV_1$ as co-primary endpoints, intended to examine effects of the LABA and IGCS components of Symbicort respectively, relevant to the appropriate comparators. For post-dose $FEV_1$, treatment with Symbicort Rapihaler 160/4.5 µg, 2 inhalations bd, resulted in statistically significant reductions compared with placebo of 0.18 L ($p<0.001$) and 0.17 L ($p<0.001$) in the SUN and SHINE studies respectively. No budesonide comparator was included in SUN, but comparison of Symbicort versus budesonide in SHINE showed an increase of 0.17 L ($p<0.001$). These results confirm the LABA component of Symbicort Rapihaler has been shown to have a small effect on post-dose $FEV_1$ consistent with the current definition of MID, which is consistent with that seen in the earlier Symbicort Turbuhaler Studies A and B.

For pre-dose $FEV_1$, treatment with Symbicort Rapihaler 160/4.5 µg, 2 inhalations bd, resulted in statistically significant reductions compared with placebo of 0.09 L ($p<0.001$) and 0.08 L ($p<0.001$) in the SUN and SHINE studies respectively, and compared with eformoterol of 0.04 L in both studies ($p=0.008$ and $p=0.026$). No budesonide comparator was included in SUN, but comparison of Symbicort versus budesonide in SHINE showed an increase of 0.17 L ($p<0.001$). These findings are consistent with only a modest effect of IGCS on pre-dose $FEV_1$ in comparison with eformoterol monotherapy, which is below the ATS/ERS suggested MID, and therefore does not demonstrate clinical efficacy.

In summary, although the post-dose $FEV_1$ and pre-dose $FEV_1$ measurements reach statistical significance, allowing testing of secondary endpoints, they do not give reasonable evidence of efficacy, which must therefore rely on secondary endpoints in the SUN and SHINE trials. The SHINE trial, being of only 6 months duration, is not powered to detect a treatment difference for exacerbations, and therefore the SUN trial is critical to determining efficacy in the current application.

For this reason, examination of the Statistical Analysis Plan (SAP) for SUN is of considerable importance. It has been noted that anticipatory switching of the primary endpoints in the original SAP for SUN occurred, from post-dose $FEV_1$ and pre-dose $FEV_1$ measurements for both dose levels, to testing the higher dose only first, followed if appropriate by testing of the secondary endpoints for the higher dose only. This resulted from availability of data from the SHINE study which showed that the lower dose of Symbicort Rapihaler (80/4.5 µg, 2 inhalations bd) was not effective, and the change in SAP was intended to improve the power of the trial to detect a

significant treatment effect at the higher dose level. This was undertaken prior to unblinding of the trial outcome, and was not influenced by any interim analysis of the data. The Delegate of the Minister therefore accepted that the subsequent analysis of primary and secondary endpoints remains statistically valid, provided that other pre-specified conditions of the hierarchical testing procedure were met.

In the SUN study, key secondary variables examined in order were dyspnoea, SGRQ and exacerbations.

Treatment with Symbicort 160/4.5, 2 inhalations bd, reduced mean scores for dyspnoea compared to placebo (LS mean = -0.27, p<0.001). 55.8% of subjects who received Symbicort had a clinically relevant improvement in the dyspnoea score (MID ≥0.02) compared to 40.5% in the placebo group (p<0.001).

This result allowed examination of the second key secondary variable, SGRQ. Total SGRQ score from baseline to end-of-treatment showed a significant decrease in patients treated with Symbicort 160/4.5, 2 inhalations bd, Least Square (LS) mean = -3.6 (95% CI: -4.991 -2.135). Compared to placebo, Symbicort produced a significantly greater reduction in SGRQ, LS mean = -2.39 (p=0.006), but in both comparisons this is less than the ATS/ERS suggested MID of ±4 units. Although this finding is relevant to interpretation of clinical efficacy, the Delegate accepted that the testing procedure was based solely on statistical significance, not MID, and that it is therefore valid to proceed to examine the third key secondary endpoint, exacerbations, on which the appeal has relied to demonstrate efficacy.

Exacerbations were analysed by number of exacerbations, and time-to-first exacerbation. Treatment with Symbicort 160/4.5 µg, 2 inhalations bd, reduced the number of exacerbations compared with both placebo and eformoterol by 37% (p<0.001) and 25% (p=0.004) respectively. With regard to time-to-first exacerbation, Symbicort reduced the risk of an exacerbation compared to placebo by 26% (p=0.009), but comparison with the eformoterol arm failed to achieve statistical significance (20%, p=0.056).

The Delegate of the Minister noted an expert report which was included with the appeal documents, in which a meta-analysis was undertaken of pooled data from all four pivotal trials to compare the incidence of exacerbation comparing Symbicort 200/6 µg (400/12 µg bd) [sic] with placebo, eformoterol 12 µg bd and budesonide 400 µg bd. The Delegate of the Minister expressed some reservations regarding the pooling of the results of Studies A and B, and SUN and SHINE, respectively, using a rate ratio, given the different definitions of exacerbations that were used in each pair of trials. Nonetheless, he accepted that the similarity of eligibility and exclusion criteria, treatment arms and baseline patient characteristics otherwise renders this series of trials suitable for meta-analysis.

Results of the expert's meta-analysis show a reduction in exacerbation rates in the Symbicort 200/6 µg (400/12 µg bd) treatment group compared to placebo with a rate ratio of 0.76 (95% CI: 0.64-0.91; p=0.0024) in the pooled data from Studies A and B, and 0.69 (95% CI: 0.56-0.87; p=0.0012) in the pooled data from SUN and SHINE. The overall pooling of all studies results in a rate ratio of 0.72 (95% CI: 0.64-0.80); p<0.00001).

Comparison of Symbicort with eformoterol also showed a reduced rate ratio of 0.76 (95% CI: 0.64-0.90; p=0.0016) in the pooled data from Studies A and B, and 0.77 (95% CI: 0.65-0.90; p=0.0012) in the pooled data from SUN and SHINE. The overall pooling of all studies results in a rate ratio of 0.76 (95% CI: 0.68-0.86); p<0.00001).

Comparison of Symbicort with budesonide were available for Studies A and B, and SHINE. No statistically significant reduction in exacerbation rate was evident for either the individual or combined studies.

Summary

In reviewing all of the above data, the Delegate of the Minister placed particular emphasis on comparisons of Symbicort treatment with eformoterol LABA monotherapy, given that the indication sought is for patients who have already been treated with a long-acting bronchodilator, and who remain symptomatic.

The $FEV_1$ data support modest clinical efficacy of the bronchodilator component of Symbicort (eformoterol) when used in combination with budesonide, which is of a similar order of magnitude to eformoterol LABA monotherapy. As has been noted above, long-acting bronchodilator therapy is already accepted as a recommended treatment option for this moderate to severe COPD patient group.

However, the critical question is regarding the efficacy and safety of the addition of the budesonide IGCS component to eformoterol in fixed combination therapy with Symbicort. In this regard, accepting reasonable therapeutic equivalence of the Turbuhaler and Rapihaler presentations, the Delegate found that the evidence from the four pivotal trials, when considered together, is sufficient to infer a modest clinical benefit especially in regard to exacerbations, which translates into a clinically meaningful improvement when measured against the ATS/ERS Taskforce suggested MID.

The Delegate of the Minister was cognizant of the difficulties in defining and measuring what constitutes a response to pharmacological intervention in COPD, which has led to exploration of a large number of lung function measures, patient-centred outcomes and biomarkers in clinical trials. Because of this it is unlikely that any single measure will provide certainty with regard to efficacy, and weighing clinical trial evidence will necessarily entail a degree of subjectivity due to differing trial designs.

The Delegate of the Minister further noted that a number of secondary endpoints have also been explored in Studies A and B which have shown statistically significant improvements, including Breathlessness, Cough and Sputum Scale (BCSS), reduced use of rescue medication, improvement in morning and evening peak flow rates (PFR), and sleep measures. Although none of these measures amount to unequivocal evidence of efficacy, they indicate biological plausibility of the exacerbation data.

In making his final decision, the Delegate of the Minister took into account the safety data, as discussed above, the relative paucity of alternative effective therapies for COPD, and the consequent symptomatic/palliative approach to current management, when considering the potential value of adding combination LABA/IGCS to the therapeutic options available to doctors treating patients with COPD.

On balance, the Delegate of the Minister found that efficacy and safety has been sufficiently demonstrated to allow registration of an extended indication for Symbicort for COPD. However, the Delegate was of the opinion that the indication should be modified (as reproduced below) to reflect that treatment is with symptomatic intent, rather than for maintenance, as it does not prevent progressive disease and inexorable decline in lung function. Based on the trial eligibility and exclusion criteria, the indication should also reflect that use be restricted to adult patients with moderate to severe COPD and $FEV_1 \leq 50\%$ of predicted, who remain symptomatic despite regular use of long-acting bronchodilators, and/or who experience recurrent exacerbations. In addition, it should be stated that Symbicort Turbuhaler or Rapihaler should not be used to initiate bronchodilator therapy in COPD patients.

*Symbicort Turbuhaler and Rapihaler are indicated for the symptomatic treatment of moderate to severe COPD ($FEV_1 \leq 50\%$ predicted normal) in adults with frequent symptoms despite long-acting bronchodilator use, and/or a history of recurrent exacerbations. Symbicort Turbuhaler and Rapihaler are not indicated for the initiation of bronchodilator therapy in COPD.*

## *Attachment 1. Product Information*

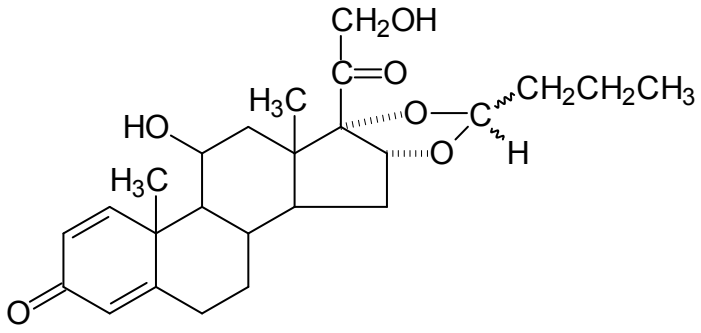
The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

# SYMBICORT® TURBUHALER® PRODUCT INFORMATION

## NAME OF THE MEDICINE

### Budesonide

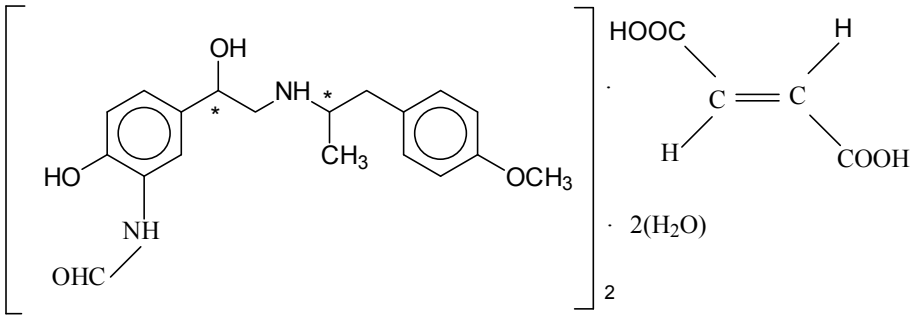
Budesonide is a non-halogenated glucocorticoid structurally related to 16α hydroxyprednisolone. The chemical name is 16α, 17α - 22 R, S-propylmethylenedioxypregna -1, 4-diene-1ß, 21-diol-3, 20-dione




CAS Number: 51333-22-3

### Eformoterol fumarate dihydrate

The chemical name is (R*R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate. The chemical structure of eformoterol fumarate dihydrate is:




CAS Number: 43229-80-7

## DESCRIPTION

Symbicort Turbuhaler contains budesonide and eformoterol fumarate dihydrate (hereafter referred to as eformoterol) as the active ingredients. Symbicort Turbuhaler also contains the inactive ingredient lactose.

## PHARMACOLOGY

Symbicort contains budesonide and eformoterol, which have different modes of action and show additive effects in terms of reduction of asthma and chronic obstructive pulmonary disease (COPD) exacerbations. The specific properties of budesonide and eformoterol allow the combination to be used both as maintenance and reliever therapy for asthma or as maintenance treatment for asthma and for symptomatic treatment of patients with moderate to severe COPD.

*Budesonide*

Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect. Budesonide has shown anti-anaphylactic and anti-inflammatory effects in provocation studies in animals and humans, manifested as decreased bronchial obstruction in the immediate as well as the late phase of an allergic reaction. Budesonide has also been shown to decrease airway reactivity to both direct (histamine, methacholine) and indirect (exercise) challenge in hyperreactive patients. Budesonide, when inhaled, has a rapid (within hours) and dose-dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer exacerbations. Inhaled budesonide has less severe adverse effects than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown.

*Eformoterol*

Eformoterol is a potent selective $\beta_2$-adrenergic agonist that when inhaled results in rapid and long acting relaxation of bronchial smooth muscles in patients with reversible airways obstruction. The bronchodilating effect is dose dependent with an onset of effect within 1-3 minutes after inhalation. The duration of effect is at least 12 hours after a single dose.

### Pharmacokinetics

Symbicort Turbuhaler and the corresponding monoproducts (budesonide Turbuhaler and eformoterol Turbuhaler as per Table 12, Presentation Section) have been shown to be bioequivalent with regard to systemic exposure of budesonide and eformoterol, respectively.

There was no evidence of pharmacokinetic interactions between budesonide and eformoterol.

Pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and eformoterol as monoproducts or as Symbicort Turbuhaler.

*Budesonide:*

After inhalation of budesonide via Turbuhaler the mean lung deposition ranged from 26 to 34% of the metered dose. The systemic bioavailability of budesonide inhaled via Turbuhaler is approximately 40% of the metered dose. Plasma protein binding is approximately 90% with a volume of distribution of approximately 3 L/kg.

Budesonide undergoes an extensive degree (approx. 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. Elimination is via metabolism mainly catalysed by the enzyme CYP3A4. The

metabolites are excreted in urine as such or in conjugated form with only negligible amounts of unchanged budesonide being detected in the urine. Budesonide has a high systemic clearance (approx. 1.2 L/min) and the plasma elimination half life after i.v. dosing averages 4 hours.

*Eformoterol:*

In studies the mean lung deposition of eformoterol after inhalation via Turbuhaler ranged from 21-37% of the metered dose. The total systemic bioavailability for the higher lung deposition is approximately 46%. Plasma protein binding is approximately 50% with a volume of distribution of approximately 4 L/kg.

Eformoterol is metabolised by conjugation to inactive glucuronides. Active O-demethylated and deformylated metabolites are formed, however plasma levels of these are low.

Elimination is via metabolism in the liver followed by renal excretion. After inhalation 6-10% of the metered dose is excreted unmetabolised in the urine. Eformoterol has a terminal elimination half-life of approximately 17 hours.

The pharmacokinetics of budesonide or eformoterol in elderly and patients with renal failure is unknown. The systemic availability of budesonide and eformoterol may be increased in patients with liver disease.

## CLINICAL TRIALS

Symbicort 100/6 and 200/6 refers to the metered dose of the corresponding monoproducts (budesonide/eformoterol) ie 100μg of budesonide and 6μg eformoterol and 200μg of budesonide and 6μg eformoterol respectively. Similarly, Symbicort 400/12 refers to the metered dose of the corresponding monoproducts ie 400μg of budesonide and 12μg eformoterol.

### Asthma

### Symbicort maintenance and reliever therapy

The safety and efficacy of Symbicort in the Symbicort maintenance and reliever therapy regimen have been investigated in six clinical trials using two dose strengths (100/6 and 200/6) of Symbicort Turbuhaler in patients with asthma. A total of 14219 patients (1134 elderly, 11144 adults, 1595 adolescents and 345 children) were randomised into the studies, of which 5514 were treated with Symbicort maintenance and reliever therapy. Of the overall patient population 7% were smokers. In comparison with the usual patient proportions seen in practice, smokers and the elderly were under-represented in the trials. However, the results for these subgroups were generally consistent with the results for the whole study population. Patients with chronic obstructive pulmonary disease were excluded.

The studies showed that Symbicort maintenance and reliever therapy was significantly superior compared with fixed dose combination products or higher doses of inhaled glucocorticosteroids (GCSs) with a separate short acting or long acting β-agonist used as reliever (see Tables 1 and 2). In the 5 double blind long term studies, patients

receiving Symbicort maintenance and reliever therapy used no reliever inhalations on 57% of treatment days and 0-2 reliever inhalations on 87% of treatment days.

**Table 1 Summary of primary efficacy variable**

| Treatment | Hazard Ratio | 95% Confidence interval |
|---|---|---|
| **Time to first severe asthma exacerbation** | | |
| SMILE 734 | | |
| 1. Symbicort maintenance and reliever therapy vs. Symbicort + eformoterol prn | 0.73 | 0.59, 0.90 |
| 2. Symbicort maintenance and reliever therapy vs. Symbicort + terbutaline prn | 0.55 | 0.45, 0.68 |
| 3. Symbicort + eformoterol prn vs. Symbicort + terbutaline prn | 0.76 | 0.63, 0.92 |
| COMPASS 735 | | |
| 1. Symbicort maintenance and reliever therapy vs. Symbicort + terbutaline prn | 0.74 | 0.56, 0.96 |
| 2. Symbicort maintenance and reliever therapy vs. Seretide + terbutaline prn | 0.67 | 0.52, 0.87 |
| 3. Symbicort + terbutaline prn vs. Seretide + terbutaline prn | 0.91 | 0.72, 1.16 |
| STAY 673 | | |
| 1. Symbicort maintenance and reliever therapy vs. Symbicort + terbutaline prn | 0.55 | 0.44, 0.67 |
| 2. Symbicort maintenance and reliever therapy vs. budesonide + terbutaline prn | 0.53 | 0.43, 0.65 |
| 3. Symbicort + terbutaline prn vs. budesonide + terbutaline prn | 0.97 | 0.82, 1.16 |
| STEP 668 | | |
| Symbicort maintenance and reliever therapy vs. budesonide + terbutaline prn | 0.61 | 0.50, 0.74 |
| COSMOS 691 | | |
| Symbicort maintenance and reliever therapy vs. Seretide + Ventolin prn | 0.75 | 0.61, 0.93 |
| **Morning peak flow (L/MIN)** | | |
| STEAM 667 | | |
| Symbicort maintenance and reliever therapy vs. budesonide + terbutaline prn | Mean diff= 25 L/min | 19, 31 |

**Table 2 Summary of the number of severe asthma exacerbations**

| Treatment | No. of exacerbations | No. of patients with exacerbations/ total patients (%) |
|---|---|---|
| SMILE 734 (12 months) | | |
| 1. Symbicort maintenance and reliever therapy | 194 | 143/1107 (13%) |
| 2. Symbicort + eformoterol prn | 296 | 195/1137 (17%) |
| 3. Symbicort + terbutaline prn | 377 | 245/1138 (22%) |
| COMPASS 735 (6 months) | | |
| 1. Symbicort maintenance and reliever therapy | 125 | 94/1103 (9%) |
| 2. Symbicort + terbutaline prn | 173 | 126/1099 (11%) |
| 3. Seretide + terbutaline prn | 208 | 138/1119 (12%) |
| STAY 673 (12 months) | | |
| 1. Symbicort maintenance and reliever therapy | 303 | 148/922 (16%) |
| 2. Symbicort + terbutaline prn | 553 | 248/906 (27%) |
| 3. Budesonide + terbutaline prn | 564 | 256/925 (28%) |
| STEP 668 (12 months) | | |
| 1. Symbicort maintenance and reliever therapy | 331 | 170/947 (18%) |
| 2. Budesonide + terbutaline prn | 546 | 259/943 (27%) |
| STEAM 667 (6 months) | | |
| 1. Symbicort maintenance and reliever therapy | 43 | 27/354 (8%) |
| 2. Budesonide + terbutaline prn | 94 | 54/342 (16%) |
| COSMOS 691 (12 months) | | |
| 1. Symbicort maintenance and reliever therapy | 255 | 159/1064 (15%) |
| 2. Seretide + Ventolin prn | 329 | 204/1071 (19%) |

Study 734 (SMILE), a 12 month randomised, double-blind, parallel-group, trial in 3394 adult and adolescent patients aged 12 to 89 years with moderate to severe asthma. The study comprised of the following three arms:

(1) Symbicort maintenance and reliever therapy - Symbicort Turbuhaler 200/6, 1 inhalation bd plus additional inhalations as needed
(2) Symbicort 200/6, 1 inhalation bd with eformoterol Turbuhaler as needed
(3) Symbicort Turbuhaler 200/6, 1 inhalation bd with terbutaline Turbuhaler as needed

The primary efficacy variable, time to first severe exacerbation, was significantly increased with Symbicort maintenance and reliever therapy compared with Symbicort plus eformoterol and Symbicort plus terbutaline (see Table 1).
Use of oral steroids due to exacerbations was lower in the Symbicort maintenance and reliever therapy group (1204 days total vs. 2063 and 2755 days in the Symbicort plus eformoterol and Symbicort plus terbutaline groups, respectively).

The majority of secondary variables supported the superiority of Symbicort maintenance and reliever therapy over both comparators (see Table 3). The average daily as-needed use in the Symbicort maintenance and reliever therapy group was 1.02 inhalations/day and the frequency of high as-needed use was lower for Symbicort maintenance and reliever therapy compared to both comparators.

**Table 3 Secondary efficacy variables for Study 734**

| Variable† | Symb. maintenance + reliever | Symb. + eform prn | Symb. + terb prn | Comparison (mean difference and 95% confidence interval) | |
|---|---|---|---|---|---|
| | | | | Symb maintenance + reliever v Symb + eform prn | Symb maintenance + reliever v Symb + terb prn |
| mPEF (L/min) | 15.3 | 10.6 | 7.9 | 4.8 (1.5, 8.0) | 7.5 (4.2, 10.7) |
| ePEF (L/min) | 13.8 | 8.5 | 7.5 | 5.4 (2.1, 8.6) | 6.3 (3.1, 9.5) |
| $FEV_1$ (L) | 0.060 | 0.011 | -0.016 | 0.049 (0.024, 0.075) | 0.076 (0.050, 0.101) |
| Total asthma symptom score (0-6) | -0.69 | -0.57 | -0.58 | -0.12 (-0.18, -0.06) | -0.11 (-0.17, -0.05) |
| Nocturnal awakenings due to asthma (% nights) | -16.0 | -14.0 | -13.5 | –2.0 (-3.7, -0.4) | –2.6 (-4.3, -0.9) |
| Symptom free days$^{\Delta}$ (% days) | 31.3 | 28.9 | 29.4 | 2.4 (-0.3, 5.0) | 1.9 (-0.8, 4.6) |
| Rescue medication use (inhalations/24 hours) | -0.84 | -0.67 | -0.64 | –0.17 (-0.25, -0.08) | -0.20 (-0.28, -0.11) |

*† Mean change from mean of run-in to mean of the treatment period; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; ; $^{\Delta}$ day and night with no symptoms and a night with no awakenings.*

The study specifically demonstrates that both the budesonide and the eformoterol components of Symbicort contribute to improved asthma control achieved through the as-needed dosing of Symbicort within the Symbicort maintenance and reliever therapy concept.

Study 735 (COMPASS), a 6 month randomised, double-blind, parallel-group trial in 3335 adult and adolescent patients aged 11 to 83 years. The study compared the following three arms:
(1) Symbicort maintenance and reliever therapy - Symbicort Turbuhaler 200/6, 1 inhalation bd plus additional inhalation as needed
(2) Seretide Inhaler 125/25, 2 inhalations bd with terbutaline Turbuhaler as needed
(3) Symbicort Turbuhaler 400/12, 1 inhalation bd with terbutaline Turbuhaler as needed

The primary efficacy variable, time to first severe exacerbation, was significantly increased with Symbicort maintenance and reliever therapy compared with both Seretide plus terbutaline and Symbicort at a higher maintenance dose plus terbutaline (see Table 1).
Use of oral steroids due to exacerbations was lower in the Symbicort maintenance and reliever therapy group compared to Seretide plus terbutaline and Symbicort plus terbutaline (619 days total use vs. 1132 and 1044 days, respectively).

Results for secondary variables, including lung function, mean use of as-needed medication and symptom variables, were not significantly different between Symbicort maintenance and reliever therapy and the other two groups. The average daily as-needed use in the Symbicort maintenance and reliever therapy group was 1.02 inhalations/day.

Since the mean daily dose in the Symbicort maintenance and reliever therapy group remained lower than in the Symbicort plus terbutaline group, the study specifically confirms the benefit of as-needed administration of part of the Symbicort dose.

Study 673 (STAY), Study 668 (STEP) and Study 667 (STEAM)
In Studies 673, 668 and 667, Symbicort maintenance and reliever therapy prolonged the time to the first exacerbation compared to Symbicort at the same maintenance dose with terbutaline as reliever and compared to a 2- to 4-fold higher maintenance dose of budesonide with terbutaline as reliever (see Table 1). Symptoms and reliever use were reduced and lung function improved compared with all other treatments (see Tables 4, 5 and 6).

**Table 4 Secondary efficacy variables for Study 673**

| Variable† | Symb. maintenance + reliever | Symb. + terb prn | Bud. + terb prn | Comparison (mean difference and 95% confidence interval) | |
|---|---|---|---|---|---|
| | | | | Symb maintenance + reliever v Symb + terb prn | Symb maintenance + reliever v Bud + terb prn |
| mPEF (L/min) | 29.9 | 22.0 | 13.0 | 7.9 (4.2, 11.7) | 16.9 (13.2, 20.7) |
| ePEF (L/min) | 26.5 | 18.3 | 9.2 | 8.3 (4.5, 12.0) | 17.4 (13.7, 21.1) |
| $FEV_1$ (L) | 0.22 | 0.15 | 0.12 | 0.075 (0.044, 0.106) | 0.102 (0.071, 0.132) |
| Total asthma symptom score (0-6) | -0.68 | -0.59 | -0.46 | –0.09 (-0.16, -0.02) | –0.21 (-0.28, -0.15) |
| Nocturnal awakenings due to asthma (% nights) | -12.7 | -8.8 | -8.4 | –3.9 (-5.4, -2.3) | –4.3 (-5.9, -2.7) |
| Symptom free days$^{\Delta}$ (% days) | 29.1 | 28.2 | 21.6 | 0.9 (-1.9, 3.8) | 7.5 (4.6, 10.3) |
| Rescue medication use (inhalations/24 hours) | -1.40 | -1.18 | -0.93 | –0.22 (-0.33, -0.11) | –0.46 (-0.57, -0.35) |

*† Mean change from mean of run-in to mean of the treatment period; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; ; $^{\Delta}$ day and night with no symptoms and a night with no awakenings.*

**Table 5 Secondary efficacy variables for Study 668**

| Variable† | Symb. maintenance + reliever | Bud. + terb prn | Comparison (mean difference and 95% confidence interval) Symb maintenance + reliever v Bud + terb prn |
|---|---|---|---|
| mPEF (L/min) | 34.2 | 13.9 | 20.3 (16.5, 24.1) |
| ePEF (L/min) | 21.8 | 7.9 | 14.0 (10.4, 17.5) |
| $FEV_1$ (L) | 0.19 | 0.09 | 0.100 (0.071, 0.130) |
| Total asthma symptom score (0-6) | -0.81 | -0.61 | –0.21 (-0.28, -0.13) |
| Nocturnal awakenings due to asthma (% nights) | -13.8 | -10.6 | –3.3 (-4.8, -1.7) |
| Symptom free days$^{\Delta}$ (% days) | 33.1 | 25.7 | 7.5 (4.5, 10.4) |
| Rescue medication use (inhalations/24 hours) | -0.99 | -0.55 | –0.44 (-0.54, -0.34) |

*† Mean change from mean of run-in to mean of the treatment period; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; ; $^{\Delta}$ day and night with no symptoms and a night with no awakenings.*

**Table 6 Secondary efficacy variables for Study 667**

| Variable† | Symb. maintenance + reliever | Bud. + terb prn | Comparison (mean difference and 95% confidence interval) Symb maintenance + reliever v Bud + terb prn |
|---|---|---|---|
| ePEF (L/min) | 25.4 | 6.6 | 18.8 (13.3, 24.3) |
| $FEV_1$ (L) | 0.21 | 0.06 | 0.148 (0.103, 0.193) |
| Total asthma symptom score (0-6) | -0.55 | -0.38 | –0.17 (-0.26, -0.07) |
| Nocturnal awakenings due to asthma (% nights) | -8.3 | -6.1 | –2.2 (-4.5, 0.01) |
| Symptom free days$^{\Delta}$ (% days) | 26.8 | 20.2 | 6.5 (2.0, 11.0) |
| Rescue medication use (inhalations/24 hours) | -0.68 | -0.34 | -0.34 (-0.51, -0.17) |

*† Mean change from mean of run-in to mean of the treatment period; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; ; $^{\Delta}$ day and night with no symptoms and a night with no awakenings.*

Study 691 (COSMOS) was a 12-month, randomised, open, parallel group trial that compared the effectiveness of Symbicort maintenance and reliever therapy with Seretide plus Ventolin in steroid-treated adult and adolescent patients (N=2143) aged 12 to 84 years with asthma. Randomised treatment started with a 4-week period during which the maintenance doses were fixed, followed by 11 months where the maintenance dose was adjusted to the lowest dose required for symptom control (see Table 7).

**Table 7 Treatments in the COSMOS (691) study**

| | Symbicort maintenance and reliever therapy | Seretide plus Ventolin |
|---|---|---|
| Fixed dose period (4 weeks) | Symbicort 200/6, 2 inhalations bd with additional inhalations as needed | Seretide 250/50, 1 inhalation bd plus Ventolin as needed |
| Dose adjustment period (11 months) | Symbicort 200/6 either<br>- 2 inhalations bd plus as needed, or<br>- 1 inhalation bd plus as needed, or<br>- 2 inhalations od plus as needed | Either<br>- Seretide 500/50, 1 inhalation bd plus Ventolin as needed<br>- Seretide 250/50, 1 inhalation bd plus Ventolin as needed, or Seretide 100/50, 1 inhalation bd plus Ventolin as needed |

This study showed that Symbicort maintenance and reliever therapy treatment is more effective than adjustable therapy with Seretide plus Ventolin in controlling asthma in adults and adolescents. Symbicort maintenance and reliever therapy increased the time to first severe asthma exacerbations, reduced the total number of severe asthma exacerbations (see Tables 1 and 2), reduced use of oral steroids for severe asthma exacerbations, and reduced use of as needed medications as compared with Seretide at a similar daily inhaled GCS dose.

**Safety in the combined studies**

Symbicort maintenance and reliever therapy treatment has a safety profile that is similar to budesonide and Symbicort maintenance therapy with a decrease in asthma-related adverse events.

## Symbicort maintenance therapy

The efficacy and safety of Symbicort for maintenance therapy has been evaluated in seven randomised, double-blind, double dummy, active controlled, parallel group studies. All treatment arms in these studies used a short-acting $\beta_2$-agonist for rescue use. Six studies were conducted for 12 weeks (100/6 and 200/6 presentations) while the 400/12 presentation study was conducted for 24 weeks (12 weeks efficacy and additional 12 weeks safety). Efficacy and safety data were collected for 3340 mild to moderate/severe asthmatic patients (2411 adults, 128 adolescents, 801 children aged 4 to 11 years old); 1704 were treated with Symbicort.

*Symbicort 100/6 and 200/6*

In one study the maximum recommended maintenance dose of Symbicort 200/6 (2 inhalations twice daily) was compared to corresponding[1] doses of the free combination (budesonide Turbuhaler 200μg + eformoterol Turbuhaler 6μg, two inhalations twice daily) and budesonide Turbuhaler 200μg (2 inhalations twice daily) only in adults with moderate asthma (mean $FEV_1$ 73.8% predicted normal and reversibility 22.5%). Table 8 details the efficacy results after 12 weeks treatment.

[1] More correct way of expressing dose

**Table 8 Estimated treatment means and treatment contrasts: effects of 12 weeks treatment with twice daily Symbicort 200/6, budesonide 200μg alone and the free combination of the monoproducts**

| *Variable* | *Symb.* | *Bud.* | *Free comb.* | *Comparison p values* | |
|---|---|---|---|---|---|
| | | | | *Symb v Bud.* | *Symb v Free comb.* |
| Change[†] in mPEF[§] (L/min) | 35.7 | 0.2 | 32 | <0.0001 | ns |
| Change[†] in ePEF (L/min) | 24.8 | -3.7 | 22.3 | <0.0001 | ns |
| $FEV_1$[+] (L) | 2.47 | 2.35 | 2.50 | 0.0128 | ns |
| Total asthma symptom score[#] (0-6) | 0.75 | 1.08 | 0.84 | 0.0002 | ns |
| Nocturnal awakenings due to asthma[#] (% patients) | 8.31 | 10.94 | 11.09 | ns | ns |
| Symptom free days[Δ#] (% days) | 57.16 | 40.15 | 54.43 | <0.0001 | ns |
| Change[†] in rescue medication use (inhalations/24 hours) | -0.99 | -0.44 | -1.13 | 0.006 | ns |

*[†] Mean change from mean of baseline to mean of the 12 week treatment period; [§]Primary efficacy variable; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; [+]mean of the last value during treatment; [#]mean of the treatment average value; [Δ] day and night with no symptoms and a night with no awakenings.*

When administered twice daily, Symbicort 200/6 is a more effective treatment than budesonide, at corresponding budesonide doses.

In a study in adults with milder asthma (mean $FEV_1$ 81.7% predicted normal and reversibility 22.2%) Symbicort 100/6 (1 inhalation twice daily) was compared with budesonide Turbuhaler 200 μg (1 inhalation twice daily). Table 9 details the efficacy results after 12 weeks treatment.

**Table 9 Estimated treatment means and treatment contrasts: effects of 12 weeks treatment with twice daily Symbicort 100/6 and budesonide 200μg alone**

| *Variable* | *Symbicort* | *Budesonide* | *Comparison p values* |
|---|---|---|---|
| Change[†] in mPEF[§] (L/min) | 16.47 | 7.32 | 0.002 |
| Change[†] in ePEF (L/min) | 13.65 | 4.16 | <0.001 |
| $FEV_1$[+] (L) | 2.63 | 2.64 | ns |
| Total asthma symptom score[#] (0-6) | 0.84 | 0.94 | ns |
| Nocturnal awakenings due to asthma[#] (% patients) | 11.57 | 13.82 | ns |
| Symptom free days[Δ#] (% days) | 55.31 | 48.86 | 0.007 |
| Change[†] in rescue medication use (inhalations/24 hours) | -0.33 | -0.14 | 0.025 |

*[†] Mean change from mean of baseline to mean of the 12 week treatment period; [§]Primary efficacy variable; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; [+]mean of the last value during treatment; [#]mean of the treatment average value; [Δ] day and night with no symptoms and a night with no awakenings*

In conclusion, there was a greater improvement in lung function and asthma control with Symbicort 100/6 than with a doubled dose of budesonide.

*Symbicort 400/12*

In a study in predominantly adult patients (<3% of patients were adolescents) with moderate to severe asthma (mean $FEV_1$ 66% predicted normal and reversibility 28%) Symbicort 400/12 (2 inhalations twice daily) was compared to corresponding[2] doses of the free combination (eformoterol Turbuhaler 12μg + budesonide Turbuhaler 400μg, two inhalations twice daily) and budesonide Turbuhaler 400μg (2 inhalations twice daily) only. Table 10 details the efficacy results after 12 weeks treatment.

[2] More correct way of expressing dose

**Table 10 Mean change from baseline in efficacy variables: effects of 12 weeks treatment with twice daily Symbicort 400/12, budesonide 400µg alone and the free combination of the monoproducts**

| *Variable*[T] | *Symb.* | *Bud.* | *Free comb.* | *Comparison p values* | |
|---|---|---|---|---|---|
| | | | | *Symb v Bud.* | *Symb v Free comb.* |
| mPEF[§] (L/min) | 37.4 | 4.5 | 36.2 | <0.001 | ns |
| ePEF (L/min) | 30.7 | -0.1 | 31.3 | <0.001 | ns |
| $FEV_1$ [‡] (L) | 0.303 | 0.143 | 0.280 | <0.001 | ns |
| Total asthma symptom score (0-6) | -0.62 | -0.36 | -0.66 | 0.0051 | ns |
| • Daytime symptom score (0-3) | -0.39 | -0.19 | -0.43 | <0.001 | ns |
| • Night-time symptom score (0-3) | -0.23 | -0.18 | -0.23 | ns | ns |
| Nocturnal awakenings due to asthma (% patients) | -14.4 | -11.8 | -13.1 | ns | ns |
| Symptom free days[Δ] (% patients) | 31.2 | 15.6 | 32.2 | <0.001 | ns |
| Rescue medication use (inhalations/24 hours) | -1.08 | -0.50 | -1.20 | <0.001 | ns |

*[T]Adjusted mean change from mean of baseline to mean of the 12 week treatment period; [§]Primary efficacy variable; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; [‡]mean from visit 3 to 5; $FEV_1$ – forced expiratory volume in 1 second; [Δ] day and night with no symptoms and a night with no awakenings.*

When administered twice daily, Symbicort 400/12 is a more effective treatment for the majority of clinical endpoints than the corresponding budesonide dose.

## COPD

The efficacy and safety of Symbicort in the treatment of patients with moderate to severe COPD (pre-bronchodilator $FEV_1 \leq 50\%$ predicted normal) has been evaluated in four randomised, double-blind, placebo and active controlled, parallel-group, multi-centre clinical studies. Two 12-month studies were performed with the dry powder inhaler Symbicort Turbuhaler (studies 629 and 670), and one 12-month and one 6-month study were performed with the pressurised metered dose inhaler (pMDI) Symbicort Rapihaler (studies 001 and 002, respectively).

- Studies 629 and 670 - In both studies, Symbicort Turbuhaler 200/6 was compared with placebo and the corresponding mono-products (budesonide Turbuhaler 200 µg and eformoterol Turbuhaler 6 µg), all taken as two inhalations twice daily. A total of 812 and 1022 patients with moderate to severe COPD were randomised, of which 208 and 254 were treated with Symbicort Turbuhaler. Patients in both studies had a mean age of 64 years and $FEV_1$ of 0.99 L or 36% of predicted normal at baseline.
- Studies 001 and 002 - The study plans were similar. Both studies used Symbicort Rapihaler.

  For Study 001, after a screening visit (visit 1), subjects entered a two weeks run-in period after which they were randomly assigned (visit 2) to one of the four following treatements:

  (1) Symbicort Rapihaler 200/6, fixed combination of 200 µg budesonide and 6 µg eformoterol per actuation, administered as 2 actuations twice daily;

  (2) Symbicort Rapihaler 100/6, fixed combination of 100 µg budesonide and 6 µg eformoterol per actuation, administered as 2 actuations twice daily;

  (3) eformoterol Turbuhaler, 6 µg per inhalation, administered as 2 actuations twice daily;

  (4) Placebo.

Study 002 had two additional treatment groups:

(5) budesonide pMDI 200 µg per actuation, administered as 2 actuations twice daily;

(6) free combination of budesonide pMDI 200 µg per actuation plus eformoterol Turbuhaler 6 µg per actuation, administered as 2 actuations of each twice daily.

A total of 1964 (Study 001) and 1704 (Study 002) patients with moderate to severe COPD were randomised, of which 494 and 277 were treated with Symbicort Rapihaler 200/6. The study populations had a mean age of 63 years and mean $FEV_1$ of 1.04-1.05 L or 34% of predicted normal at baseline.

*Study 629*

In Study 629, efficacy was evaluated over 12 months using the co-primary endpoints of post-dose $FEV_1$ and number of severe COPD exacerbations (defined as intake of a course of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms).

- Symbicort Turbuhaler significantly improved mean $FEV_1$ compared with placebo and budesonide by 15% ($p<0.001$) and 9% ($p<0.001$), respectively.
- Symbicort Turbuhaler significantly reduced the number of severe exacerbations compared with placebo and eformoterol by 24% ($p=0.035$) and 23% ($p=0.043$), respectively. The number needed to treat (NNT) to prevent one severe COPD exacerbation in a year for Symbicort Turbuhaler compared with eformoterol was 2.4.

*Study 670*

In Study 670, efficacy was evaluated over 12 months using the co-primary endpoints of post dose-$FEV_1$ and time to first severe COPD exacerbation (defined as intake of a course of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms).

- Symbicort Turbuhaler significantly improved mean $FEV_1$ compared with placebo, budesonide, and eformoterol by 14% ($p<0.001$), 11% ($p<0.001$), and 5% ($p=0.002$), respectively.
- Symbicort Turbuhaler significantly prolonged the time to first severe COPD exacerbation compared to all comparator treatments. The instantaneous risk of experiencing a severe COPD exacerbation compared to placebo, budesonide, and eformoterol was reduced by 29% ($p=0.006$), 23% ($p=0.033$), and 30% ($p=0.003$), respectively.

Symbicort Turbuhaler also significantly reduced the number of severe COPD exacerbations compared to placebo and eformoterol by 24% ($p=0.029$) and 26% ($p=0.015$), respectively. The NNT to prevent one COPD exacerbation in a year compared to eformoterol was 2.1.

*Study 001*

In Study 001, efficacy was evaluated over 12 months using the co-primary efficacy variables of change from baseline in average pre-dose and 1-hour post-dose $FEV_1$ over the treatment period.

Primary endpoints:

- Symbicort Rapihaler 100/6 produced a significantly greater change in postdose $FEV_1$ compared to placebo (LS mean = 0.16 L; p<0.001); however the change in predose $FEV_1$ was not significantly different to eformoterol 6 µg (LS mean = 0.02 L; p=0.161).
- Symbicort Rapihaler 200/6 significantly improved 1-hour pre-dose $FEV_1$ compared with eformoterol and placebo by 0.04 L (p=0.008) and 0.09 L (p<0.001), respectively.
- Symbicort Rapihaler 200/6 significantly improved post-dose $FEV_1$ over the treatment period compared with eformoterol and placebo by 0.03 L (p=0.023) and 0.18 L (p<0.001), respectively.

Serial $FEV_1$ measures over 12 hours were obtained in a subset of patients (N=491). The median time to onset of bronchodilation (>15% improvement in $FEV_1$) was seen within 5 minutes at the end of treatment time point in patients receiving Symbicort Rapihaler 200/6 (N=121). Maximum improvement in $FEV_1$ occurred at approximately 2 hours post-dose, and post-dose bronchodilator effect was maintained over 12 hours.

Exacerbations (secondary variable):

Symbicort Rapihaler reduced the number of severe COPD exacerbations (defined as a worsening of COPD requiring oral steroid use and/or hospitalisation) to a statistically significant degree. Overall 34.1% of subjects experienced 1159 exacerbations: Symbicort Rapihaler 200/6, 30.8%; Symbicort Rapihaler 100/6, 32.6%; placebo 37.2%. The majority of exacerbations were treated with oral glucocorticosteroids: Symbicort Rapihaler 200/6, 96.5% of exacerbations; Symbicort Rapihaler 100/6, 94.1%; placebo 97.4%. Treatment comparisons were by means of rate ratios (RR) estimates, CIs and p-values derived from a Poisson regression adjusted for treatment, country and differential treatment exposure. Symbicort Rapihaler 200/6 demonstrated a statistically significant reduction of 37% (p<0.001) and 25% (p=0.004) in the rate of exacerbations per subject-treatment year compared with placebo and eformoterol, respectively. Symbicort Rapihaler 100/6 reduced the exacerbation rate by 41% compared with placebo (p<0.001).

Symbicort Rapihaler 200/6 significantly prolonged the time to first severe COPD exacerbation compared to placebo, reducing the instantaneous risk of experiencing a severe COPD exacerbation by 26% (p=0.009). The number needed to treat (NNT) to prevent one severe COPD exacerbation in a year for Symbicort Rapihaler compared with eformoterol was 5.4.

*Study 002*

In Study 002, efficacy was evaluated over 6 months using the co-primary efficacy variables of change from baseline in average pre-dose and 1-hour post-dose $FEV_1$ over the treatment period.

- Symbicort Rapihaler 100/6: Postdose $FEV_1$ increased significantly from baseline to the average of the treatment period (LS mean (95%CI) = 0.19 (0.17, 0.22)). Symbicort Rapihaler 100/6 caused a significantly greater change from baseline compared to budesonide (LS mean = 0.16; p<0.001). Predose $FEV_1$ increased significantly from baseline to the average of the treatment period, LS mean = 0.06 (0.03, 0.08). However, the change from baseline, compared to eformoterol, for predose $FEV_1$ was not statistically significant, LS mean = 0.02 (-0.02, 0.05; p=0.335).

- Symbicort Rapihaler 200/6 significantly improved pre-dose $FEV_1$ compared with eformoterol by 0.04 L (p=0.026) and compared with placebo and budesonide by 0.08 L (p<0.001) for both comparators.
- Symbicort Rapihaler 200/6 significantly improved 1-hour post-dose $FEV_1$ compared with eformoterol by 0.04 L (p=0.039) and compared with placebo and budesonide by 0.17 L (p<0.001) for both comparators.

Study 002 was not powered for showing effect on severe COPD exacerbations.

Serial $FEV_1$ measures over 12 hours were obtained in subsets of patients (n=618). The median time to onset of bronchodilation (>15% improvement in $FEV_1$) was seen within 5 minutes at the end of treatment in patients receiving Symbicort Rapihaler 200/6 (N=101). Maximal improvement in $FEV_1$ occurred at approximately 2 hours post-dose, and post-dose bronchodilator effect was generally maintained over 12 hours.

## INDICATIONS

### Asthma

Symbicort Turbuhaler is indicated for the treatment of asthma where use of a combination (inhaled corticosteroid and long acting $\beta_2$-agonist) is appropriate. This includes:

- patients who are symptomatic on inhaled corticosteroid therapy
- patients who are established on regular long acting $\beta$-agonist and inhaled corticosteroid therapy.

There are two alternative treatment regimens:

- Symbicort maintenance and reliever therapy
- Symbicort maintenance therapy

Symbicort 400/12 should only be used in patients aged 18 years and over.

The 400/12 strength should not be used for the Symbicort maintenance and reliever therapy regimen.

### Chronic obstructive pulmonary disease (COPD)

Symbicort is indicated for the symptomatic treatment of moderate to severe COPD ($FEV_1 \leq 50\%$ predicted normal) in adults with frequent symptoms despite long-acting bronchodilator use, and/or a history of recurrent exacerbations. Symbicort is not indicated for the initiation of bronchodilator therapy in COPD.

## CONTRAINDICATIONS

Hypersensitivity to budesonide, eformoterol or lactose.

## PRECAUTIONS

Treatment of asthma or COPD should be in accordance with current national treatment guidelines.

Patients with asthma should have a personal asthma action plan designed in association with their general practitioner. This plan should incorporate a stepwise treatment regime which can be instituted if the patients asthma improves or deteriorates.

Patients should be advised to have their rescue inhaler available at all times, either Symbicort (for asthma patients on Symbicort maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for other asthma patients using Symbicort as maintenance therapy only and for COPD patients).

Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids (e.g. a course of oral corticosteroids), or antibiotic treatment if a bacterial infection is present. Patients should be advised to seek medical attention if they find the treatment ineffective or they have exceeded the prescribed dose of Symbicort.

It is recommended that the dose is tapered when long-term treatment is discontinued and should not be stopped abruptly.

Symbicort therapy should not be initiated to treat a severe exacerbation.

***Oral corticosteroid usage***

Symbicort should not be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. Care should be taken when commencing Symbicort treatment, particularly if there is any reason to suspect that adrenal function is impaired from previous systemic steroid therapy.

***Potential systemic effects of inhaled corticosteroids***

Inhaled steroids are designed to direct glucocorticoid delivery to the lungs in order to reduce overall systemic glucocorticoid exposure and side effects. However, in higher than recommended doses, inhaled steroids may have adverse effects; possible systemic effects of inhaled steroids include depression of the HPA axis, reduction of bone density, cataract and glaucoma, and retardation of growth rate in children. In steroid-dependent patients, prior systemic steroid usage may be a contributing factor but such effects may occur amongst patients who use only inhaled steroids regularly.

*HPA axis suppression and adrenal insufficiency:*

Dose-dependant HPA axis suppression (as indicated by 24 hour urinary and/or plasma cortisol AUC) has been observed with inhaled budesonide, although the physiological circadian rhythms of plasma cortisol were preserved. This indicates that the HPA axis suppression represents a physiological adaption in response to inhaled budesonide, not necessarily adrenal insufficiency. The lowest dose that results in clinically relevant adrenal insufficiency has not been established. Very rare cases of clinically relevant adrenal dysfunction have been reported in patients using inhaled budesonide at recommended doses.

Clinically important disturbances of the HPA axis and/or adrenal insufficiency induced by severe stress (eg trauma, surgery, infection in particular gastroenteritis or other conditions associated with severe electrolyte loss) may be related to inhaled budesonide in specific patient populations. These are patients with prolonged treatment at the highest recommended dose of Symbicort and patients administered concomitant CYP3A4-inhibitors (see Interactions with other drugs). Monitoring for signs of adrenal dysfunction is advisable in these patient groups. For these patients additional systemic glucocorticosteroid treatment should be considered during periods of stress, a severe asthma attack or elective surgery.

*Bone density:*

Whilst corticosteroids may have an effect on bone mass at high doses, long term follow up (3 - 6 years) studies of budesonide treatment in adults at recommended doses, have not demonstrated a negative effect on bone mass compared to placebo, including one study conducted in patients with a high risk of osteoporosis. The lowest dose that does effect bone mass has not been established.

Bone mineral density measurements in children should be interpreted with caution as an increase in bone area in growing children may reflect an increase in bone volume. In three large medium to long term (12 months - 6 years) studies in children (5-16 years), no effects on bone mineral density were observed after treatment with budesonide (189 - 1322μg/day) compared to nedocromil, placebo or age matched controls. However, in a randomised 18 month paediatric study (n=176; 5-10 years), bone mineral density was significantly decreased by 0.11 g/cm$^2$ (p=0.023) in the group treated with inhaled budesonide via Turbuhaler compared with the group treated with inhaled disodium cromoglycate. The dose of budesonide was 400μg b.i.d for 1 month, 200μg bd for 5 months and 100μg b.i.d for 12 months and the dose of disodium cromoglycate 10mg t.i.d. The clinical significance of this result remains uncertain.

*Growth:*

Long term studies show that children treated with inhaled budesonide ultimately achieve adult target height. However, an initial reduction of growth velocity (approximately 1cm) has been observed and is generally within the first year of treatment. Rare individuals may be exceptionally sensitive to inhaled corticosteroids. Height measurements should be performed to identify patients with increased sensitivity. The potential growth effects of prolonged treatment should be weighed against the clinical benefit. To minimise the systemic effects of inhaled corticosteroids, each patient should be titrated to his/her lowest effective dose (see DOSAGE & ADMINISTRATION section).

***Infections / tuberculosis***

Signs of existing infection may be masked by the use of high doses of glucocorticosteroids and new infections may appear during their use. Special care is needed in patients with active or quiescent pulmonary tuberculosis or fungal, bacterial or viral infections of the respiratory system.

***Sensitivity to sympathomimetic amines***

In patients with increased susceptibility to sympathomimetic amines (e.g. inadequately controlled hyperthyroidism), eformoterol should be used with caution.

***Cardiovascular disorders***

$\beta_2$-agonists have an arrhythmogenic potential that must be considered before commencing treatment for bronchospasm.

The effects of eformoterol in acute as well as chronic toxicity studies were seen mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These are known pharmacological manifestations seen after administration of high doses of $\beta_2$-adrenoceptor agonists.

Patients with pre-existing cardiovascular conditions may be at greater risk of developing adverse cardiovascular effects following administration of $\beta_2$-adrenoreceptor agonists. Caution is advised when eformoterol is administered to patients with severe cardiovascular disorders such as ischaemic heart disease, tachyarrythmias or severe heart failure.

***Hypokalaemia***

High doses of $\beta_2$-agonists can lower serum potassium by inducing a redistribution of potassium from the extracellular to the intracellular compartment, via stimulation of $Na^+/K^+$-ATPase in muscle cells.

Potentially serious hypokalaemia may result. Particular caution is advised in acute exacerbation as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments (see PRECAUTIONS - Interactions with other drugs section). Patients receiving digoxin are particularly sensitive to hypokalaemia. Serum potassium levels should therefore be monitored in such situations.

***Diabetes***

Due to the blood-glucose increasing effects of $\beta_2$-stimulants extra blood glucose controls are initially recommended when diabetic patients are commenced on eformoterol.

***Impaired renal and hepatic function***

The effect of decreased liver and kidney function on the pharmacokinetics of eformoterol and budesonide are not known. As budesonide and eformoterol are primarily eliminated via hepatic metabolism an increased exposure can be expected in patients with severe liver disease.

***Other***

Symbicort Turbuhaler contains lactose (<1 mg/inhalation) which may contain milk protein residue. This amount does not normally cause problems in lactose intolerant people.

**Carcinogenicity**

The carcinogenic potential of the budesonide/eformoterol combination has not been investigated in animal studies.

In eformoterol carcinogenicity studies performed by AstraZeneca, there was a dose dependent increase in the incidence of uterine leiomyomas in mice dosed orally at 0.1,

0.5 and 2.5 mg/kg/day for two years, and a mesovarian leiomyoma was observed in a female rat dosed by inhalation at 0.13 mg/kg/day for two years. The effects observed are expected findings with high dose exposure to ß$_2$-agonists.

Eformoterol carcinogenicity studies performed by other companies used systemic exposure levels 800 to 4800-fold higher than those expected upon clinical use of eformoterol (based on an 18μg daily dose).

Some carcinogenicity activity was observed in rats and mice. However, in view of the dose levels at which these effects were observed and the fact that eformoterol is not mutagenic (except for very weak activity at high concentrations in one test system), it is concluded that the cancer risk in patients treated with eformoterol fumarate is no greater than for other beta-adrenoceptor agonists.

The carcinogenic potential of budesonide has been evaluated in the mouse and rat at oral doses up to 200 and 50 μg/kg/day, respectively. In male rats dosed with 10, 25 and 50 μg budesonide/kg/day, those receiving 25 and 50 μg/kg/day showed an increased incidence of primary hepatocellular tumours. In a repeat study this effect was observed in a number of steroid groups (budesonide, prednisolone, triamcinolone acetonide) thus indicating a class effect of corticosteroids.

**Genotoxicity**

Individually, budesonide and eformoterol were not genotoxic in a series of assays for gene mutations (except for a slight increase in reverse mutation frequency in *Salmonella typhimurium* at high concentrations of eformoterol fumarate), chromosomal damage and DNA repair. The combination of budesonide and eformoterol has not been tested in genotoxicity assays.

***Effects on fertility***

There are no animal studies on the effect of the budesonide/eformoterol combination on fertility.

Long-term treatment of female mice and rats with eformoterol fumarate causes ovarian stimulation, the development of ovarian cysts and hyperplasia of granulosa/theca cells as a result of the β-agonist properties of the compound. A study by another company showed no effect on fertility of female rats dosed orally with eformoterol fumarate at 60 mg/kg/day for two weeks. This finding was repeated in an AstraZeneca study where no effect was seen on the fertility of female rats dosed orally with eformoterol fumarate at 15 mg/kg/day for two weeks.

Testicular atrophy was observed in mice given eformoterol fumarate in the diet at 0.2 to 50 mg/kg/day for two years, but no effect on male fertility was observed in rats dosed orally at 60 mg/kg/day for nine weeks, in studies undertaken by another company.

**Use in pregnancy (Category B3)**

For Symbicort Turbuhaler or the concomitant treatment with budesonide and eformoterol, no clinical data on exposed pregnancies are available. Animal studies with respect to the reproductive toxicity of the combination have not been performed.

Symbicort Turbuhaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Only after special consideration should Symbicort Turbuhaler be used during the first 3 months and shortly before delivery.

Because beta-agonists, including eformoterol, may potentially interfere with uterine contractility, due to a relaxant effect on uterine smooth muscle, Symbicort Turbuhaler should be used during labour only if the potential benefit justifies the potential risk.

*Budesonide:* Results from a large prospective epidemiological study and from worldwide post marketing experience indicate no adverse effects of inhaled budesonide during pregnancy on the health of the fetus or newborn child.

If treatment with glucocorticosteroids during pregnancy is unavoidable, inhaled corticosteroids such as budesonide should be considered due to their lower systemic effect. The lowest effective dose of budesonide to maintain asthma control should be used.

*Eformoterol:* No teratogenic effects were observed in rats receiving eformoterol fumarate at doses up to 60 mg/kg/day orally or 1.2 mg/kg/day by inhalation. Fetal cardiovascular malformations were observed in one study in which pregnant rabbits were dosed orally at 125 or 500 mg/kg/day during the period of organogenesis, but similar results were not obtained in another study at the same dose range. In a third study, an increased incidence of subcapsular hepatic cysts was observed in fetuses from rabbits dosed orally at 60 mg/kg/day. Decreased birth weight and increased perinatal/postnatal mortality were observed when eformoterol fumarate was given to rats at oral doses of 0.2 mg/kg/day or greater during late gestation.

**Use in lactation**

Budesonide is excreted in breast milk. However, due to the relatively low doses used via the inhalational route the amount of drug present in the breast milk, if any, is likely to be low.

It is not known whether eformoterol is excreted in human milk. In reproductive studies in rats eformoterol was excreted into breast milk. There are no well-controlled human studies of the use of Symbicort Turbuhaler in nursing mothers. Administration of Symbicort to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

**Use In children**

Symbicort is not recommended for children below 12 years of age.

**Effect on ability to drive and use or operate machines**

Driving or using machinery should be undertaken with caution until the effect of Symbicort Turbuhaler on the individual is established. Symbicort Turbuhaler does not generally affect the ability to drive or use machinery.

## Interactions with other Drugs

*Pharmacokinetic interactions*

The metabolism of budesonide is primarily mediated by the enzyme CYP3A4. Inhibitors of this enzyme, e.g. ketoconazole, may therefore increase systemic exposure to budesonide. This is of limited clinical importance for short-term (1-2 weeks) treatment with ketoconazole, but should be taken into consideration during long-term treatment with ketoconazole or other potent CYP3A4 inhibitors.

*Pharmacodynamic interactions*

Neither budesonide nor eformoterol have been observed to interact with any other drug used in the treatment of asthma or COPD.

*β-receptor blocking agents:*
β-receptor blocking agents, especially those that are non-selective, may partially or totally inhibit the effect of $\beta_2$-agonists. These drugs may also increase airway resistance, therefore the use of these drugs in asthma patients is not recommended.

*Other sympathomimetic agents:*

Other β-adrenergic stimulants or sympathomimetic amines such as ephedrine should not be given concomitantly with eformoterol, since the effects will be cumulative. Patients who have already received large doses of sympathomimetic amines should not be given eformoterol.

*Xanthine derivatives, mineralocorticosteroids and diuretics:*

Hypokalaemia may result from $\beta_2$-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, mineralocorticosteroids, and diuretics (see “Precautions - Hypokalaemia” section).

*Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines:*

The adverse cardiovascular effects of eformoterol may be exacerbated by concurrent administration of drugs associated with QT interval prolongation and increased risk of ventricular arrhythmia. For this reason caution is advised when eformoterol is administered to patients already taking monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines or antihistamines associated with QT interval prolongation (e.g. terfenadine, astemizole).

## ADVERSE REACTIONS

Since Symbicort Turbuhaler contains both budesonide and eformoterol, the same adverse effects as reported for these substances may be expected. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side-effects of $\beta_2$-agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of commencing treatment.

If oropharyngeal candidiasis develops, it may be treated with appropriate anti-fungal therapy whilst still continuing with Symbicort therapy. The incidence of candidiasis can generally be held to a minimum by having patients rinse their mouth out with water after inhaling their maintenance dose.

Adverse reactions, which have been associated with budesonide, eformoterol and Symbicort, are given in Table 11 below.

**Table 11 Tabulation of adverse reactions**

| | | |
|---|---|---|
| **Common** 1 to 10% | *Cardiac disorders* | Palpitations |
| | *Infections and infestations* | Candida infections in the oropharynx |
| | *Nervous system disorders* | Headache, tremor |
| | *Respiratory:, thoracic and mediastinal disorders* | Mild irritation in the throat, coughing, hoarseness |
| **Uncommon** 0.1 to 1% | *Cardiac disorders* | Tachycardia |
| | *Gastrointestinal disorders* | Nausea, diarrhoea |
| | *Metabolism and nutrition disorders* | Weight gain |
| | *Musculoskeletal and connective tissue disorders* | Muscle cramps |
| | *Nervous system disorders* | Dizziness, bad taste, thirst, tiredness |
| | *Psychiatric disorders* | Agitation, restlessness, nervousness, sleep disturbances |
| **Rare** 0.01 to 0.1% | *Immune system disorders* | Immediate and delayed hypersensitivity reactions including dermatitis, exanthema, urticaria, pruritis, angioedema and anaphylactic reaction |
| | *Cardiac disorders* | Cardiac arrhythmias e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles |
| | *Respiratory, thoracic and mediastinal disorders* | Bronchospasm |
| | *Skin and subcutaneous tissue disorders* | Skin bruising |
| | *Metabolism and nutrition disorders* | Hypokalaemia |
| **Very Rare** < 0.01% | *Cardiac disorders* | Angina pectoris |
| | *Endocrine disorders* | Signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunction of the adrenal gland |
| | *Metabolism and nutrition disorders* | Hyperglycaemia |
| | *Psychiatric disorders* | Depression, behavioural disturbances |
| | *Vascular disorders* | Variations in blood pressure |

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases.

Treatment with β-sympathomimetics may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

## DOSAGE AND ADMINISTRATION

### Asthma

There are two alternative dosage regimens for the treatment of asthma with Symbicort:

- Symbicort maintenance and reliever therapy
- Symbicort maintenance therapy

**Symbicort maintenance and reliever therapy for Asthma**

Symbicort taken as both regular maintenance treatment and as needed in response to symptoms. The as-needed inhalations provide both rapid relief and improved asthma control. Patients should be advised to have Symbicort available for rescue use at all times. A separate inhaler for rescue use is not necessary.

***The 400/12 strength should not be used for Symbicort maintenance and reliever therapy regimen.***

**Adults and adolescents (12 years and older):**

The recommended maintenance dose is Symbicort 100/6 or Symbicort 200/6 two inhalations per day, given as either one inhalation in the morning and evening or as two inhalations in either the morning or evening. For some patients, a maintenance dose of Symbicort 200/6 two inhalations twice daily may be appropriate. The maintenance dose should be titrated to the lowest dose at which effective control of asthma is maintained.

Patients may take an additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, another inhalation should be taken. No more than 6 inhalations should be taken on any single occasion.

If the patient experiences a three day period of deteriorating symptoms after taking the appropriate maintenance therapy and additional as needed inhalations, the patient should be reassessed for alternative explanations of persisting symptoms. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily.

**Symbicort maintenance therapy for Asthma**

Symbicort taken as regular maintenance treatment, with a separate rapid-acting bronchodilator as rescue. Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants reassessment of the asthma therapy. The dosage of Symbicort should be individualised according to disease severity. When control of asthma has been achieved, the dose should be titrated to the lowest dose at which effective asthma control is maintained.

**Adults and adolescents (12 years and older):**

*Symbicort 100/6*

1 - 2 inhalations of Symbicort 100/6 twice daily. The maximum recommended daily maintenance dose is 4 inhalations (2 inhalations twice daily corresponding to 400μg budesonide / 24μg eformoterol).

*Symbicort 200/6*

1 - 2 inhalations of Symbicort 200/6 twice daily. The maximum recommended daily maintenance dose is 4 inhalations (2 inhalations twice daily corresponding to 800μg budesonide / 24μg eformoterol).

*Symbicort 400/12*

Adults (*18 years and over) who require* a higher daily maintenance dose (1600/48):

2 inhalations of Symbicort 400/12 twice daily. The maximum recommended daily maintenance dose is 4 inhalations (corresponding to 1600μg budesonide / 48μg eformoterol). When control of asthma has been achieved, the dose can be decreased to 1 inhalation twice daily.

**COPD**

**Adults:**

*Symbicort 200/6*

2 inhalations of Symbicort 200/6 twice daily. The maximum recommended daily dose is 4 inhalations (corresponding to 800μg budesonide / 24μg eformoterol).

*Symbicort 400/12*

1 inhalation of Symbicort 400/12 twice daily. The maximum recommended daily dose is 2 inhalations (corresponding to 800μg budesonide / 24μg eformoterol).

**General Information:**

For optimal benefit the patient should be instructed to take the maintenance dose of Symbicort Turbuhaler even when asymptomatic.

**Elderly*:***

There are no special dosing requirements for elderly patients.

**Hepatic/renal impairment**

There are no data available for use of Symbicort Turbuhaler in patients with hepatic or renal impairment. As budesonide and eformoterol are primarily eliminated via hepatic metabolism an increased systemic availability can be expected in patients with severe liver disease.

### Instruction for correct use of Turbuhaler

Turbuhaler is inspiratory flow-driven which means that, when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

***NOTE:*** *It is important to instruct the patient to:*

- Carefully read the instructions for use in the patient information leaflet that are provided with each pack of Symbicort
- Breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs
- Never to breathe out through the mouthpiece
- Replace the cover of Symbicort Turbuhaler after use
- Rinse their mouth out with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush.

The patient may not taste or feel any medication when using Turbuhaler due to the small amount of drug delivered.

## OVERDOSAGE

An overdose of eformoterol may lead to effects that are typical for $\beta_2$-adrenergic agonists: tremor, headache, palpitations, and tachycardia. Monitoring of serum potassium concentrations may be warranted. Hypotension, metabolic acidosis, hypokalaemia and hyperglycaemia may also occur. Supportive and symptomatic treatment may be indicated. β-blockers should be used with care because of the possibility of inducing bronchospasm in sensitive individuals. A metered dose of 120μg administered during three hours in patients with acute bronchial obstruction raised no safety concerns.

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. However, the plasma cortisol level will decrease and number and percentage of circulating neutrophils will increase. The number and percentage of lymphocytes and eosinophils will decrease concurrently. When used chronically in excessive doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may appear.

Withdrawing Symbicort or decreasing the dose of budesonide will abolish these effects, although the normalisation of the HPA-axis may be a slow process.

## PRESENTATION

Symbicort is available in a multidose inspiratory flow driven, metered dose dry powder inhaler (Turbuhaler). To avoid confusion Symbicort Turbuhaler is labelled as the metered dose of the corresponding monoproducts (Pulmicort (budesonide)/Oxis (eformoterol)). Pulmicort and Oxis Turbuhaler are also labelled as metered doses. The following table gives the corresponding dose delivered to the patient.

**Table 12**

| Symbicort | Metered dose* (μg) | Corresponding dose delivered to patient (μg)** |
|---|---|---|

| | Pulmicort (budesonide) | Oxis (eformoterol) | Budesonide | Eformoterol |
|---|---|---|---|---|
| **100 / 6** | 100 | 6 | 80 | 4.5 |
| **200 / 6** | 200 | 6 | 160 | 4.5 |
| **400/12** | 400 | 12 | 320 | 9 |

** not possible to measure metered dose for Symbicort*
*** doses referred to in Symbicort publications*

Symbicort 100/6 and 200/6 are available as a 60 or 120 dose Turbuhaler. Symbicort 400/12 is available as a 60 dose double Turbuhaler pack.

### Storage conditions

Do not store above 30°C. Replace cap firmly after use.

## POISON SCHEDULE OF THE DRUG

Prescription only medicine (Schedule 4).

## NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
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