LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Symbicort
(budesonide, formoterol fumarate dihydrate)

SE/H/229/03/DC

This module reflects the scientific discussion for the approval of Symicort. The procedure was finalised on 2016-03-03. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

AstraZeneca AB has applied for a marketing authorisation for Symbicort, 160/4.5 micrograms/actuation, pressurised inhalation, suspension. The active substances budesonide and formoterol are the same as in Symbicort, 160/4.5 micrograms/inhalation, inhalation powder, marketed by AstraZeneca AB since 2001.
The application is also a line extension, addition of a new formulation, of previously authorised Symbicort Turbuhaler, 160/4.5 micrograms/inhalation, inhalation powder.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC.

The application was discussed in the CMDh, please see section VI for further information.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substances has been adequately proven and their physico-chemical properties are sufficiently described.

The manufacture of the drug substances has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specifications include relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Budesonide
Budesonide is a potent glucocorticoid with special kinetic properties. It has a high affinity for the glucocorticoid receptor, and has displayed a wide variety of anti-allergic and anti-inflammatory effects in non-clinical pharmacological studies. Budesonide acts by inhibiting the production and release of a variety of mediators and cytokines from inflammatory cells, thus inhibiting the immediate and late allergic reaction, bronchial hyper-reactivity and cellular infiltration after allergen challenge. Budesonide is absorbed systemically from the gastrointestinal tract as well as the airways and lungs and undergoes 90% hepatic first-pass biotransformation into metabolites of low glucocorticoid potency.

No additional pharmacology data has been generated specifically using the pMDI formulation.

Formoterol
Formoterol is a potent and selective β_2-adrenoceptor agonist with a rapid onset and a long duration of action when inhaled. The primary pharmacological effect of formoterol is relaxation of airway smooth muscle. Formoterol is an almost full agonist at the β_2-adrenoceptor and demonstrates a dose-related improvement in lung function within the recommended clinical dose range. Similar to other β_2-adrenoceptor agonists, formoterol inhibits microvascular leakage and mucosal plasma exudation, and increases mucociliary transport. The clinical significance of these additional effects is still uncertain.

Budesonid and formoterol are both well-known compounds that have been in clinical use for a long time in monotherapy as well as in combination for treatment of asthma and chronic obstructive pulmonary disease (COPD). The toxicological profiles of budesonide and formoterol when administered in combination are consistent with those reported for a glucocorticoid and a potent β_2 -agonist, respectively. The lack of further non-clinical studies for Symbicort pMDI is accepted.

III.1 Ecotoxicity/environmental risk assessment

Environmental Risk Assessment (ERA)
Budesonide and formeterol are not considered as PBT compounds. The $PEC_{surfacewater}$ is below 0.01 µg/L for both compounds when the highest maximum daily dose is used in the calculation. However, budesonide should be considered as a potential endocrine disruptor and a tailored risk assessment is still required.
A ready biodegradability test according to OECD 301 B to conclude on the ready biodegradability of budesonide in the environment was required. In case that budesonide is not readily biodegradable a transformation study in aquatic sediment – systems according to OECD 308 is deemed to be necessary. The potential endocrine disruptor activity needs to be investigated in an appropriate chronic test system. This issue is to be resolved post approval and the applicant has committed to provide the requested data. The proposed testing strategy and appropriate effect endpoints is planned to be discussed with UBA in January 2016 before finalizing the testing strategy. An updated environmental risk assessment of budesonide including all necessary and final study reports will be submitted as a Type II variation.

III.2 Discussion on the non-clinical aspects

N/A

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Symbicort pMDI (inhalation aerosol) is a new formulation of two well-known active substances, budesonide and formoterol. Efficacy and safety has been extensively studied in the Phase 3 program. Thus, pharmacokinetic data mainly aim at describing the pharmacokinetic behaviour of the new formulation.

The biopharmaceutic strategy for the development of SYMBICORT pMDI had the following goals:

- Compare the relative systemic bioavailability (BA) between SYMBICORT pMDI with budesonide pMDI and formoterol TURBUHALER, which were used as active comparators in the Phase III efficacy and safety studies
- Compare plasma concentrations of budesonide and formoterol after inhalation of SYMBICORT pMDI and SYMBICORT TURBUHALER, the product upon which the Phase III dose selection justification was based
- Determine the pharmacokinetics (PK) dose proportionality across formulation strengths of SYMBICORT pMDI

To meet these goals, the exposure to budesonide and formoterol has been evaluated in eight biopharmaceutical and pharmacokinetic studies. PK-data was also evaluated in one of the Phase III studies. All phase 1 PK-studies were descriptive and not of formal bioequivalence character. One study (SD-039-0713) included administration with active charcoal to reflect pulmonary deposition. All other studies were conducted without active charcoal, thus evaluating total systemic exposure. The comparators in these studies were: budesonide pMDI inhalation aerosol, PULMICORT (budesonide) TURBUHALER inhalation powder, OXIS (formoterol) TURBUHALER inhalation powder, and SYMBICORT (budesonide+formoterol) TURBUHALER inhalation powder. Budesonide pMDI is not a marketed product but developed for use in clinical trials. It is identical to Symbicort pMDI but without formoterol.

Comparison of Symbicort pMDI and Symbicort Turbuhaler
SD-039-0730: Comparison with Symbicort Turbuhaler in healthy subjects.
Randomised, open-label, single-dose, crossover study in healthy volunteers to compare systemic BA of budesonide and formoterol after inhalation via SYMBICORT pMDI (8 x 160/4.5 μg) and SYMBICORT TURBUHALER (8 x 160/4.5 μg); and after inhalation via 2 different strengths of SYMBICORT TURBUHALER (8 x 160/4.5 μg and 4 x 320/9 μg).

Results: Budesonide AUC was comparable while Cmax was 22% lower for the pMDI formulation. Tmax was reached slightly later for the pMDI formulation (median 15 min) compared to the Turbuhaler (median 10 min). For formoterol AUC and Cmax was 22% and 39% higher for Symbicort pMDI 160/4.5 μg compared to Symbicort Turbuhaler 160/4.5 μg. Tmax was similar for both formulations. The slightly higher exposure of Symbicort pMDI is not a concern since safety has been sufficiently assured in the clinical phase 3 studies.

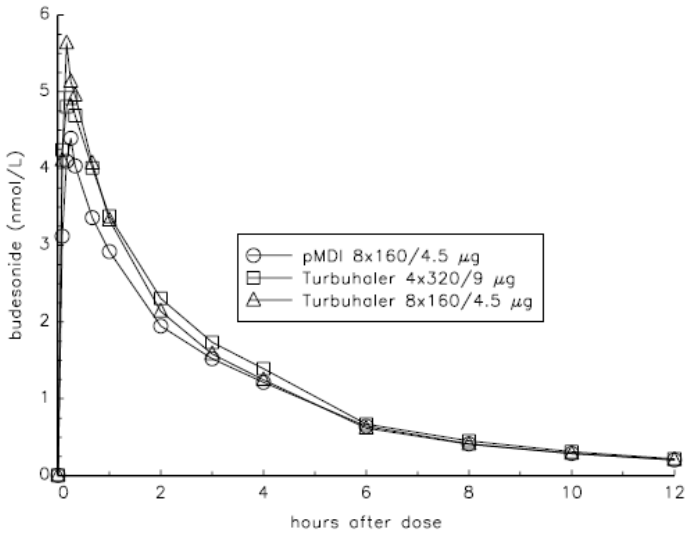

Figure 1. Mean plasma concentrations of budesonide (linear scale).

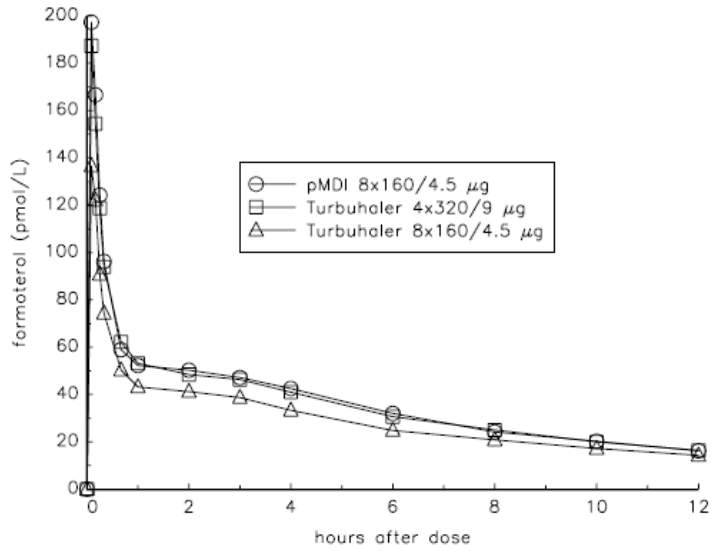

Figure 2. Mean plasma concentrations of formoterol (linear scale).

Comparison of Symbicort pMDI with the monocomponents

SD-039-0713: Comparison with Pulmicort Turbuhaler (budesonide) plus Oxis Turbuhaler (formoterol) in healthy volunteers.

Randomised, open-label, single-dose, crossover study in healthy volunteers to compare systemic BA of budesonide oand formoterol after inhalation of SYMBICORT pMDI (12 x 160/4.5 µg) versus PULMICORT TURBUHALER (6 x200 mcg (metered dose corresponding to 160mcg delivered dose)) + OXIS TURBUHALER (6 x 4.5 µg) given concomitantly.

Results: Comparison of Symbicort pMDI and concomitant administration of the mono-products Pulmicort Turbuhaler plus Oxis Turbuhaler in healthy volunteers resulted in a slightly lower budesonide systemic exposure (AUC 30% lower, Cmax 35% lower) and roughly comparable formoterol exposure after administration without active charcoal. After administration with active charcoal budesonide lung deposition was slightly lower (AUC 35%

lower and Cmax 32% lower) for Symbicort pMDI compared to administration of Pulmicort plus Oxis. For formoterol AUC was 24% lower for Symbicort pMDI while Cmax was very similar between formulations after administration with charcoal. The slightly lower budesonide pulmonary deposition of Symbicort pMDI compared to the mono-components might be an indication of inferior efficacy. Since efficacy of the new Symbicort pMDI formulation has been sufficiently demonstrated in the clinical phase 3 trial this is not an issue.

SD-039-0721: Comparison with budesonide pMDI plus Oxis Turbuhaler in healthy volunteers. Randomised, open-label, single-dose, crossover study in healthy volunteers to compare systemic BA of budesonide and formoterol after inhalation of SYMBICORT pMDI (8 x 160/4.5 μg) versus budesonide pMDI (8 x 160/ μg) + OXIS TURBUHALER (8 x 4.5 μg) given concurrently.

Results: In healthy volunteers, there was no marked difference in total systemic exposure of either budesonide or formoterol compared to the reference formulations.

D5899C00006: Comparison with budesonide pMDI plus Oxis Turbuhaler in COPD patients. Open-label study of the relative systemic BA of SYMBICORT pMDI to monocomponents (budesonide pMDI plus OXIS [formoterol] TURBUHALER), administered as the free combination (also, relative PK of SYMBICORT pMDI in patients with COPD versus patients with asthma).

Results: In COPD patients the total systemic exposure was slightly higher for formoterol compared to Oxis Turbuhaler. Since safety of Symbicort pMDI has been sufficiently shown in the clinical phase 3 studies this is not an issue. Exposure of budesonide was similar after administration of Symbicort pMDI compared to the reference formulation.

SD-039-0738: Comparison with budesonide pMDI plus Oxis Turbuhaler in COPD patients. Open-label, 2-way crossover study in patients with COPD of the relative BA of SYMBICORT pMDI to monocomponents (budesonide pMDI plus OXIS [formoterol] TURBUHALER), when inhaled as a single dose of 1280/36 μg from SYMBICORT pMDI compared with budesonide pMDI plus formoterol TURBUHALER (OXIS).

Results: There was a difference in formoterol AUC between the first 14 subjects and the last 16 subjects, and the Applicant suggests that the data from this study are unreliable. The study was therefore repeated (Study D5899C00006, described above). The results from both studies do however point in the same direction, with a slightly higher exposure of formoterol from Symbicort pMDI compared to Oxis Turbuhaler and similar budesonide exposure as in the reference formulation.

Dose proportionality and time dependency
For budesonide there was an approximately dose-proportional increase in AUC with increasing doses within the range 480-1920 μg (administered as 12 x 40/4.5 μg, 12 x 80/4.5 μg or 12 x 160/4.5 μg of Symbicort pMDI). Steady state comparisons resulted in a roughly 2-fold increase in exposure of both budesonide and formoterol following administration of Symbicort pMDI 160/4.5 μg given as 4 actuations (640/18 μg dose) bid compared to administration of 2 actuations (320/9 μg dose) bid.

Data suggests that both budesonide and formoterol accumulates to a small degree, approximately 1.3- times after repeated dose compared to single dose. This is in line with the observed half-life of 4 hours for budesonide. Accumulation was slightly larger for formoterol,

approximately 1.8-times after repeated dose compared to single dose. This is in line with the observed half-life of 7 hours for formoterol.

Overall pharmacokinetic conclusion
The pharmacokinetics of the new Symbicort pMDI formulation has been thoroughly evaluated. No major differences in exposure compared to Symbicort Turbuhaler or to the mono-products containing budesonide and formoterol were observed. There was a dose-proportional increase in exposure with increasing doses after single-dose and at steady-state.

IV.2 Pharmacodynamics

Budesonide is a potent corticosteroid and formoterol is an inhaled long-acting beta2-adrenoceptor agonist (LABA) with a rapid onset of action. Both budesonide and formoterol are widely available as inhalation monoproducts and the fixed budesonide/formoterol combination is also widely approved as a dry powder formulation, Symbicort Turbuhaler. No new data on the substances are provided with this application.

IV.3 Clinical efficacy

Five studies were presented in support of efficacy and safety of the product as summarised in Table 1.

Table 1

Phase II studies	
SD-039-0729	Randomised, multicentre, open-label, active-controlled, singledose, 5-period, incomplete block, crossover study to evaluate the relative bronchodilating effects of formoterol when administered via SYMBICORT pMDI or OXIS TURBUHALER to adults with stable asthma
D5899C00748	Randomised, double-blind, 4-period crossover study to assess the bronchodilation of single doses of SYMBICORT pMDI 160/4.5 μg, salmeterol/fluticasone 25/250 μg, salbutamol 100 μg, and placebo in patients with COPD
Phase III efficacy and safety studies	
D5899C00001	Randomised, double-blind, parallel-group, 12-month study to compare the efficacy and safety of SYMBICORT pMDI versus formoterol and placebo in adults with COPD
D5899C00002	Randomised, double-blind, parallel-group, 6-month study to compare the efficacy and safety of SYMBICORT pMDI versus formoterol, budesonide, formoterol plus budesonide as a free combination, and placebo in adults with COPD
D589CC00003	Randomised, double-blind, parallel-group, 12-month study compare the efficacy and safety of SYMBICORT pMDI versus formoterol in adults with COPD

Study SD-039-0729
This was a randomised, multicentre, open-label, active-controlled, single-dose, 5-period, incomplete block, crossover study to evaluate the relative bronchodilating effects of formoterol when administered via Symbicort pMDI or Oxis Turbuhaler to adults with stable asthma. The primary objective was to compare the bronchodilating effect of formoterol administered through the Symbicort pMDI to the bronchodilating effect of formoterol (dry powder

formulation) administered through the Oxis Turbuhaler by assessment of average 12-hour FEV1 (primary efficacy endpoint). For all formoterol doses, clinically relevant and statistically significant mean differences were noted compared with budesonide alone. The relative dose potency (Symbicort:Oxis) suggested that the 2 treatments are approximately equipotent.

Study D5899C00748
This was a randomised, placebo-controlled, double-blind, double-dummy, crossover study to assess the onset of action of two inhalations of Symbicort 160/4.5 μg, compared with two inhalations of Seretide 25/250 μg, two inhalations of Ventoline 100 μg, and placebo, delivered by pressurised metered dose inhalers, in patients with COPD. The primary objective was to study the bronchodilating effect within the first 180 minutes after two inhalations of Symbicort 160/4.5 μg compared with two inhalations of Seretide 25/250 μg, two inhalations of Ventoline 100 μg and placebo. The primary outcome variable was forced expiratory volume in one second (FEV1) 5 minutes after dose.
Male and female patients aged 40 years or older with COPD and FEV1 of 30-70% of the predicted normal value were recruited. Symbicort was superior to placebo (ratio 116%) and to Seretide (ratio 105%) for FEV1 at 5 minutes. The time to onset of effect with Symbicort was similar to that for Ventoline pMDI (ratio at 5 min 99%) although Ventoline appeared to have a higher level of effect at early time points (5 – 60 min). The FEV1 values for all three active treatments were superior to placebo after 180 minutes, but at that time point both Symbicort pMDI and Seretide pMDI appeared to maintain the effect on FEV1 better than Ventoline pMDI.

Study No D5899C00001
This was a 12-month double-blind, double-dummy, randomized, parallel group, multicenter efficacy & safety study of Symbicort pMDI 2 x 160/4.5 μg bid and 2 x 80/4.5 μg bid compared to formoterol Turbuhaler 2 x 4.5 μg bid and placebo in patients with COPD. There were two co-primary endpoints for this study. The objectives were to show that both the two doses Symbicort pMDI (i.e. 2x160/4.5 μg bid and 2x80/4.5 μg bid) is effective in patients with COPD, when compared to placebo and formoterol 2x4.5 μg bid with regard to its effect on pre-dose FEV1 and when compared to placebo with regard to its effect on 1 hour post-dose FEV1. Based on postbronchodilator FEV1 at Visit 1, approximately 18% of the subjects had moderate COPD, 60% had severe COPD, and 22% had very severe COPD, as classified by the GOLD criteria. To be eligible for inclusion a patient should have a history of at least one COPD exacerbation requiring a course of oral steroids and/or antibiotics within 1-12 months before screening. The study population included a high prevalence of subjects with a history of comorbid conditions. Symbicort 160/4.5 demonstrated a statistically significantly greater increase from baseline in predose FEV1 compared with formoterol 4.5 ($p=0.008$) and placebo ($p<0.001$), with overall maintenance of effect over the 12-month treatment period. Additionally, Symbicort 160/4.5 demonstrated a significant increase from baseline for 1-hour postdose FEV1 compared with placebo, and also formoterol 4.5. Symbicort 80/4.5 on the other hand did not demonstrate a significant difference from formoterol 4.5 for predose FEV1. Treatment means and treatment comparisons from ANCOVA for change from baseline to the average value during the randomized treatment period (the primary analysis) are summarized for 1-hour post-dose FEV1. All three active treatments were significantly better than placebo. Symbicort 160/4.5 (but not 80/4.5) demonstrated a statistically significant increase from baseline in 1-hour post-dose FEV1 compared with formoterol 4.5.

Study No D5899C00002
This is a 6-Month Double-blind, double-dummy, randomized, parallel group, multicenter efficacy & safety study of Symbicort pMDI 2 x 160/4.5 μg & 80/4.5 μg bid compared to

formoterol Turbuhaler budesonide pMDI (& the combination) & placebo in COPD Patients. The primary objectives of the study in hierarchical order were:

- To show that Symbicort pMDI 2x160/4.5 μg bid was effective in patients with COPD, when compared to formoterol TURBUHALER 2x4.5 μg bid with regard to their effect on predose FEV1.
- To show that Symbicort pMDI 2x160/4.5 μg bid was effective in patients with COPD, when compared to budesonide HFA pMDI 2x160 μg bid with regard to their effect on 1 hour postdose FEV1.
- To show that Symbicort pMDI 2x80/4.5 μg bid was effective in patients with COPD, when compared to formoterol Turbuhaler 2x4.5 μg bid with regard to their effect on predose FEV1.
- To show that Symbicort pMDI 2x80/4.5 μg bid was effective in patients with COPD, when compared to budesonide HFA pMDI 2x160 μg bid with regard to their effect on 1 hour postdose FEV1.

Based on post-bronchodilator FEV1 at Visit 1, approximately 20% of the included subjects had moderate COPD, 58% had severe COPD, and 22% had very severe COPD, as classified by the GOLD criteria. The subjects should have had at least one COPD exacerbation (requiring a course of oral steroids and/or antibiotics) within 1-12 months before Visit 1. Of 2381 screened subjects, 1704 were subsequently randomized at 180 centres. Predose FEV1 was 90 ml lowered (change from baseline) in the Symbicort 160/45 group and somewhat less in the low dose group and the formoterol group. Only a 10 ml difference was recorded in the placebo group. Change from baseline in postdose FEV1 was approximately 200 ml for formoterol containing formulations and 30 ml for placebo.

Study No D589CC00003
This was a Phase IIIB, 12-month, double-blind, double-dummy, randomized, parallel-group, multicenter exacerbation study of symbicort pMDI 160/4.5 μg x 2 actuations twice-daily and 80/4.5 μg x 2 actuations twice-daily compared to formoterol Turbuhaler 4.5 μg inhalations twice-daily in COPD patients. The primary objective of this study was to compare the efficacy of Symbicort pMDI 160/4.5 μg x 2 actuations BID and 80/4.5 μg x 2 actuations BID with that of formoterol Turbuhaler 4.5 μg x 2 inhalations BID in preventing exacerbations in patients with COPD. The primary variable was the number of COPD exacerbations over the randomized treatment period. There were 1219 subjects included at 161 investigational sites. The patients had a pre-bronchodilator FEV1 ≤50% of predicted normal value at first visit, a pre-bronchodilator FEV1/forced vital capacity (FVC) <70% and a score of ≥2 on the MMRC dyspnea scale. The patients should have a history of at least one COPD exacerbation requiring a course of systemic steroids and/or antibiotics within 1 to 12 months prior to study inclusion. The number of exacerbations per patient years were 0.75 and 0.84 i the two Symbocort groups (high and low strength) and 1.14 in the formoterol group.

This new device introduces a possibility to further target treatment to the need of each patient as budesonide/formoterol has to date not been approved in a spray formulation but its usefulness is limited in the absence of conclusive information on its use with a spacer. The applicant has committed to conduct a single-dose, cross-over, pharmacokinetic study with and without charcoal in healthy volunteers. The objective of the study will be to determine the relative bioavailability of budesonide and formoterol administered with and without a spacer.

IV.4 Clinical safety

In the Phase III COPD development program, 2361 patients received study treatment. Of the included patients about 50 % were exposed for more than 50 weeks and only about 10 % for less than 14 weeks (slightly less for placebo treated patients).

The most common reason for discontinuation was the occurrence of an adverse event. The percentage of patients discontinuing for this reason was marginally lower in the Symbicort groups compared to the formoterol and placebo groups. Other reasons for discontinuation were generally similar across treatment groups, with the exception of the category of 'patient not willing to continue study'. The percentage of patients in this category was highest in the placebo group and lowest in the Symbicort pMDI 160/4.5 µg X 2 bid group. The percentage of patients discontinuing from the study was highest among patients with very severe COPD (% predicted post-bronchodilator FEV1<30%) at baseline compared to patients with less severe COPD at baseline.

The overall number of AEs and SAEs per patient treatment year for both SYMBICORT treatment groups was similar to the formoterol group and higher than the placebo group although the number of SARs was similar.

Table 17 SYMBICORT vs formoterol pool. Number (%) of patients with most common adverse events (frequency of > 3% in any treatment group) ongoing during randomised treatment in studies D5899C00001, D5899C00002 and D589CC00003, presented by preferred term (safety population)

Preferred term	SYMBICORT 160/4.5 µg X 2 bid (n=1178)	SYMBICORT 80/4.5 µg X 2 bid (n=1183)	Formoterol 4.5 µg X 2 bid (n=1182)	Total (n=3543)
Chronic obstructive pulmonary disease	187 (15.9)	203 (17.2)	228 (19.3)	618 (17.4)
Nasopharyngitis	88 (7.5)	90 (7.6)	87 (7.4)	265 (7.5)
Headache	77 (6.5)	66 (5.6)	63 (5.3)	206 (5.8)
Bronchitis	79 (6.7)	61 (5.2)	63 (5.3)	203 (5.7)
Sinusitis	47 (4.0)	49 (4.1)	45 (3.8)	141 (4.0)
Viral upper respiratory tract infection	48 (4.1)	44 (3.7)	42 (3.6)	134 (3.8)
Oral candidiasis	65 (5.5)	43 (3.6)	19 (1.6)	127 (3.6)
Back pain	42 (3.6)	31 (2.6)	43 (3.6)	116 (3.3)
Upper respiratory tract infection bacterial	36 (3.1)	43 (3.6)	32 (2.7)	111 (3.1)
Influenza	39 (3.3)	36 (3.0)	31 (2.6)	106 (3.0)
Hypertension	37 (3.1)	33 (2.8)	28 (2.4)	98 (2.8)
Muscle spasms	36 (3.1)	35 (3.0)	17 (1.4)	88 (2.5)
Oropharyngeal pain	35 (3.0)	15 (1.3)	19 (1.6)	69 (1.9)

The events are sorted by the total column.
COPD is the disease under study; the AEs related to COPD were predefined in the study protocols and reported when they were SAEs, DAEs, or new to the patient or not consistent with the patient's pre-existing COPD history.
MedDRA version 16.1.
bid twice daily; N number
Patients with multiple AEs coded to the same preferred term are counted only once for that preferred term.

Table 18 **SYMBICORT vs placebo pool. Number (%) of patients with most common adverse events (frequency of > 3% in any treatment group) ongoing during randomised treatment in studies D5899C00001 and D5899C00002, presented by preferred term (safety population)**

Preferred term	SYMBICORT 160/4.5 µg X 2 bid (n=771)	SYMBICORT 80/4.5 µg X 2 bid (n=775)	Placebo (n=781)	Total (n=2327)
Chronic obstructive pulmonary disease	102 (13.2)	127 (16.4)	114 (14.6)	343 (14.7)
Nasopharyngitis	57 (7.4)	55 (7.1)	39 (5.0)	151 (6.5)
Bronchitis	42 (5.4)	29 (3.7)	27 (3.5)	98 (4.2)
Oral candidiasis	46 (6.0)	28 (3.6)	16 (2.0)	90 (3.9)
Viral upper respiratory tract infection	27 (3.5)	29 (3.7)	21 (2.7)	77 (3.3)
Sinusitis	28 (3.6)	28 (3.6)	15 (1.9)	71 (3.1)
Pneumonia	18 (2.3)	21 (2.7)	26 (3.3)	65 (2.8)

The events are sorted by the total column.
MedDRA version 16.1.
COPD is the disease under study; the AEs related to COPD were pre-defined in the study protocols and reported when they were SAEs, DAEs, or new to the patient or not consistent with the patient's pre-existing COPD history.
bid twice daily; N number.
Patients with multiple AEs coded to the same preferred term are counted only once for that preferred term.

There were relatively few deaths in the Phase III studies considering the size of the patient population, the severity of COPD in the patient population, and the prevalence of several co-morbid conditions in these patients. The cases were evenly distributed between a numbers of different causes. None of the deaths reported were considered by the investigators to be related to study drug. Nonfatal SAEs were evenly distributed between the Symbicort treatment groups as compared as compared to the formoterol group (Table 21) and as compared to the placebo group. A higher proportion of patients reported a COPD SAE in each treatment group (5.1% to 7.1%) than any other SAE preferred term. No other SAE occurred in more than 1% of patients who were on Symbicort.

Relatively the formoterol group where 34 events of pneumonia (all related PTs) were recorded there was a numerically higher number of cases in the two Symbicort treated groups (49 and 44 cases respectively). This difference was not apparent in placebo-controlled data (23 and 24 for the two Symbicort groups versus 28 for placebo. The risk of pneumonia in patients with COPD taking inhaled budesonide has been evaluated elsewhere (Sin et al 2009). The analysis included pooled patient data from 7 large AstraZeneca clinical trials of inhaled budesonide (320 to 1280 µg/day), with or without formoterol, versus the control regimen (placebo or formoterol alone) in patients with stable COPD and at least 6 months of follow-up. D5899C00001, D5899C00002 and D589CC00003 were included in this analysis. The evaluation was based on data from 7042 patients, of whom 3801 were on inhaled budesonide and 3241 were on control treatment, with 5212 patient-years of exposure to treatment. They reported no significant difference between treatment groups for the occurrence of pneumonia as an AE (3% [n=122 budesonide-treated patients] vs 3% [n=103 controls]; adjusted hazard ratio 1.05, 95% CI: 0.81 to1.37) or a SAE (1% [n=53 budesonide-treated patients] vs 2% [n=50 controls]; adjusted hazard ratio 0.92, 95% CI: 0.62 to 1.35).

The SYMBICORT pMDI clinical programme included regular assessments of cardiac safety (ECGs, Holter monitoring) to monitor for the occurrence of cardiac events that potentially could be associated with β2-agonists (eg, cardiac arrhythmias, tachycardia, prolongation in QTc intervals). Mean changes in QRS and PR intervals from baseline were small, and not clinically meaningful. There were no clinically relevant differences relatively placebo in change from baseline. Although the data provided did not indicate any specific concerns, the warning in the SmPC section 4.4 for Symbicort Turbuhaler on QTc-prolongation was introduced also for the pMDI formulation.

Symbicort pMDI was first approved for the treatment of asthma in Switzerland on 27 July 2005 and in the United States on 21 July 2006. As of July 2014 it is approved in more than 25 countries for asthma and in approximately 20 countries for the treatment of COPD. As of 31 March 2014, the number of treatment days for Symbicort pMDI has been estimated to 1185 million. The overall pattern of adverse events in post-marketing surveillance reports does not deviate from the experience from clinical studies using Symbicort pMDI. The most frequently reported AEs from post-marketing surveillance are well-known class-effects of β2-agonists and ICS and expected events for this patient population, clinical manifestations of the underlying disease and its progression. The AE pattern in the post-marketing surveillance reports does not deviate from the extensive experience with Symbicort Turbuhaler or the monoproducts Pulmicort (budesonide) and Oxis (formoterol).

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Symbicort.

Summary of safety concerns for SYMBICORT inhalation products

Important identified risks	Cardiac disorders Hypersensitivity Paradoxical bronchospasm
Important off-label use	SYMBICORT PMDI is prescribed for the treatment of asthma, in children, adolescents, or adults, for which it is not approved. SYMBICORT PMDI is prescribed as SYMBICORT maintenance and reliever therapy, for which it is not approved.
Missing information	No missing information that is considered to be an important safety concern has been identified.

There are no pharmacovigilance studies/activities proposed to further investigate the above safety concerns besides routine pharmacovigilance processes.

The RMP is approvable.

V. USER CONSULTATION

The package leaflet has been evaluated via a bridging report making reference to Symbicort Turbohaler (SE/H/229/01-02/II/35; SE/H/230/01/II/27) and a user consultation study (focus test) in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The bridging report submitted by the applicant together with the results of the focus test shows that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Following a discussion in the CMDh:
The applicant committed to conduct an *in vitro* re-priming study data generated throughout canister life in line with the guideline. In addition the specification for fine particle dose was updated.

Benefits
The development of a pMDI formulation for Symbicort allows the use of this combination therapy in patients for whom an aerosol formulation is the preferred method of delivery.

The application is supported by data from three pivotal clinical studies. A clinically relevant effect on FEV1 post dosing is shown as least square mean for the difference vs placebo or budesonide was 160-180 ml for the high dose (160/4.5 μg). The effect on pre-dose FEV_1 documented in studies was minor, only 40 ml for the higher dose and an effect of this size is likely not meaningful in "moderately" affected patients. There was a recorded effect on the number of exacerbations as compared to formoterol in an adequately designed study but the magnitude of effect was not appealing with a reduction of in average only approximately 3 days under exacerbation each treatment year for the high dose group compared to formoterol.

Risk
The pattern of adverse reaction resembles what it previously known for budesonide/formoterol combinations such as Symbicort and no major new concerns were identified.

The benefit/risk balance is positive and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

Post approval commitments

Description	Due date
An updated environmental risk assessment of budesonide including all necessary and final study reports will be submitted as a Type II variation. The proposed testing strategy and appropriate effect endpoints is planned to be discussed with UBA in January 2016 before finalizing the testing strategy.	Since the testing strategy has not been defined, specific timelines cannot be provided.
In order to support a named spacer in the SmPC and PL, AstraZeneca will conduct a single-dose, cross-over, pharmacokinetic study with and without charcoal in healthy volunteers. The objective of the study will be to determine the relative bioavailability of budesonide and formoterol administered with and without a spacer.	The study protocol will be discussed with the RMS in early 2016. The study will be started during 2016. Submission of a type II variation is planned Q2 2017.
Generate re-priming delivered dose data for different storage	

orientations (valve down, valve up and horizontal) through canister life, to be submitted as a Type IB variation, variation code B.II.f.z Stability. Other variation.	End of 2016

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Symbicort, 160/4.5 micrograms/actuation, pressurised inhalation, suspension was positively finalised on 2016-03-03.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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