

Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as
amended

Symbicort pMDI
budesonide, formoterol fumarate dihydrate

SE/W/0027/pdWS/001

Marketing Authorisation Holder: AstraZeneca

Rapporteur:	Sweden
Finalisation procedure (day 90):	28 March 2017

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Symbicort pMDI
INN (or common name) of the active substance(s):	budesonide and formoterol fumarate dihydrate
MAH:	AstraZeneca
Currently approved Indication(s)	Chronic Obstructive Pulmonary Disease (COPD) in adults (aged 18 and older)
Pharmaco-therapeutic group (ATC Code):	R03AK07
Pharmaceutical form(s) and strength(s):	Symbicort, 160 micrograms/4.5 micrograms/actuation pressurised inhalation, suspension

I. EXECUTIVE SUMMARY

The MAH has presented three studies where Symbicort pMDI is investigated in asthma in children. No SmPC and PL changes are proposed. Notably, the approved indication for Symbicort pMDI 160/4,5 strength is COPD.

II. RECOMMENDATION

No update of the product information is suggested or warranted.

III. INTRODUCTION

The company has submitted three studies (D5896GC0003, D589GC00002, and D5896C00027) for Symbicort pMDI in accordance with Article 46 of the Regulation No 1901/2006, as amended.

All these studies were submitted in 2016 in US where Symbicort pMDI is approved for asthma. To support approval of asthma in children 6-12 years of age, a programme of 3 studies (the “CHASE” programme) was conducted: one Phase 2 study to confirm the appropriate dose of budesonide to be carried into the combination product (Study D589GC00001, CHASE 1, not included here since the study did not include Symbicort), one Phase 2 study to determine the appropriate dose(s) of formoterol to be carried into the combination product (Studies D589GC00002, CHASE 2), and one Phase 3 study to provide a comparative assessment of the efficacy and safety of different doses of Symbicort pMDI, compared with budesonide (Study D589GC00003, CHASE 3).

The third study (D5896C00027) was conducted as the FDA required that each of the 4 marketing application holders of LABA-containing products in the US should conduct a randomized, double-blind, controlled clinical trial comparing the addition of LABAs to an ICS versus an ICS alone. Consequently 4 such studies of similar design and with an aligned protocol were initiated. The study conducted by AstraZeneca for Symbicort pMDI was study D5896C00027.

“Actuations” and “inhalations” are used interchangeably, depending on the source documentation.

IV. SCIENTIFIC DISCUSSION

IV.1 Study D589GC00002

IV.1.1 Description

A randomised, blinded, 5-period cross-over, placebo and active controlled, multicenter, dose-finding study of single doses of formoterol 2.25 µg, 4.5 µg, and 9 µg delivered via SYMBICORT pMDI and Foradil[®] Aerolizer[®] 12 µg evaluating the bronchodilating effects and safety in children, ages 6 to <12 years, with asthma who are receiving background treatment with budesonide pMDI 160 µg bid and to determine also the appropriate dose(s) of formoterol to be carried into the combination product.

IV.1.2 Methods

Objectives

The purpose of this study was to evaluate the bronchodilating effects and safety in children, ages 6 to <12 years, with asthma who are receiving background treatment with budesonide pMDI 160 µg (80 µg, 2 inhalations) bid.

Primary objective

To assess the bronchodilating effects of 3 doses of formoterol given in combination with budesonide as Symbicort pMDI in a population of asthmatic children demonstrated to be stable on a medium dose range of ICS therapy.

Assessor's comment:

The strength of Symbicort pMDI approved in EU is 160 µg/4.5 µg. In this study, lower strengths of formoterol and budesonide in free combination (80 µg/2.25 µg and 80 µg/4.5 µg) were used. The approved strength in EU was not used in this study.

Study design

Single-dose treatments of inhaled formoterol 2.25 µg, 4.5 µg, and 9 µg delivered via Symbicort were compared with placebo pMDI. In addition, Foradil[™] Aerolizer[™] (12 µg, metered dose), the US-approved formoterol product for pediatric patients ≥5 years of age, was included as an active control arm. The primary efficacy variable was average forced expiratory volume in 1 second (FEV₁) over 12 hours (calculated through area under curve determination). Secondary variables included maximum FEV₁ over 12 hours, FEV₁ at 12 hours, and FEV₁ at each time point (3, 9, 15, 60, 120, 180, 240, 360, 480, 600, and 720 minutes during 12-hour serial spirometry). The study also included an evaluation of systemic exposure to formoterol.

Study population

A total of 54 patients were randomized and 50 completed the study. Four patients discontinued the study, 2 due to patient/caregiver decision and 2 due to adverse events (AEs). Of the patients randomized, 57.4% were male. The majority were either white (57.4%) or black/African American (40.7%). Mean age was 9.2 years, with 20.4% of all patients randomized between the ages of 6 to <8 years.

IV.1.3 Results

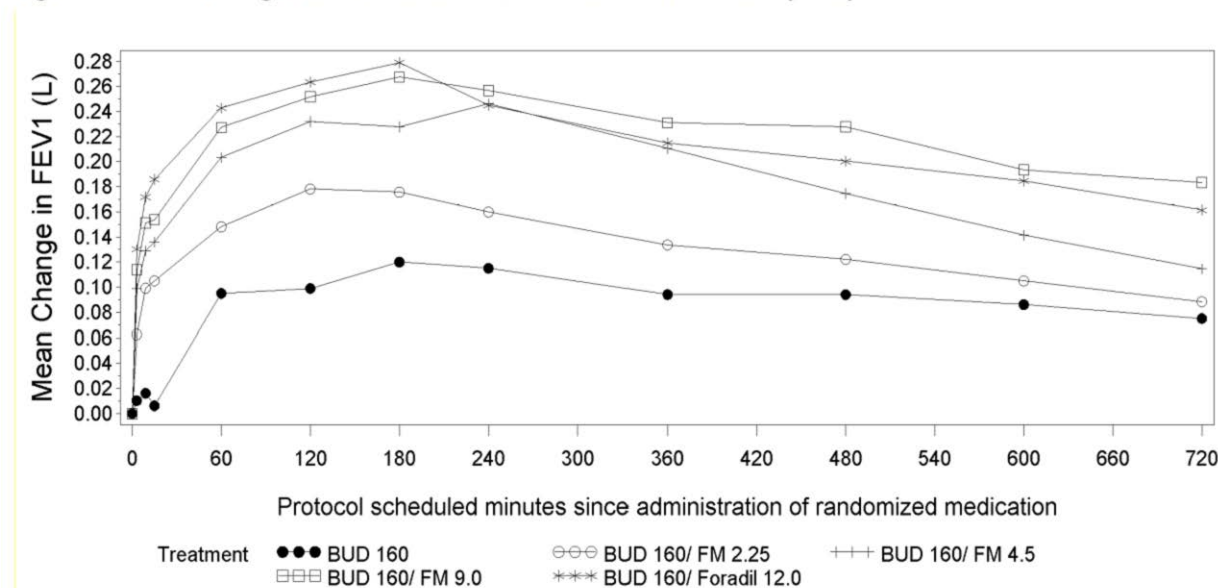
The result for the primary endpoint is found below (table 13 from the company's expert report). The mean change from baseline in FEV₁ is presented in the figure (figure 3 from the company's expert report).

Table 13 ANCOVA summary – treatment means for average 12-hour FEV₁ (L) using the LOCF imputation method – Efficacy analysis set

Treatment	From ANCOVA	
	LS Mean (SE)	95% CI
BUD 160/FM 2.25	1.546 (0.0097)	(1.527, 1.566)
BUD 160/FM 4.5	1.594 (0.0099)	(1.575, 1.614)
BUD 160/FM 9.0	1.603 (0.0099)	(1.584, 1.622)
BUD 160	1.489 (0.0101)	(1.469, 1.509)
BUD 160/Foradil 12.0	1.603 (0.0101)	(1.583, 1.623)

ANCOVA = analysis of covariance; BUD = budesonide; CI = confidence interval; FM = formoterol;
 LOCF = last observation carried forward; LS Mean = least squares mean; SE = standard error.
 Data from [Table 11.2.1.10](#).

Figure 3 Mean change from baseline in FEV₁ over time – overall – Efficacy analysis set



BUD = budesonide; FM = formoterol.
 Figure shows mean change from baseline in FEV₁ across patients at each time point. Patients were included on only one treatment line for each week.
 Change in FEV₁ was derived at 3, 9, 15, 60, 120, 180, 240, 360, 480, 600 and 720 minutes post administration of randomized study medication.
 Data from [Figure 11.2.1.3](#).

From the ANCOVA it was concluded that formoterol 4.5 µg and 9 µg, administered as single doses via Symbicort pMDI, were superior to placebo in improving average FEV₁ over 12 hours, maximum FEV₁, and FEV₁ at 12 hours, in asthmatic children 6 to <12 years of age. Formoterol 2.25 µg, administered as a single dose via Symbicort pMDI, was also superior to placebo treatment in improving average FEV₁ over 12 hours and maximum FEV₁, while no difference could be detected at 12 hours after dose. Formoterol 4.5 µg and 9 µg, administered as single doses via Symbicort pMDI, were superior to the 2.25 µg dose as measured by improvements in average FEV₁ over 12 hours, maximum FEV₁ and FEV₁ at 12 hours.

Foradil Aerolizer 12 µg, administered as a single dose, was statistically superior to placebo and formoterol 2.25 µg in improving average FEV₁ over 12 hours, maximum FEV₁ and FEV₁ at 12 hours, while no statistically confirmed differences were recorded compared with the 4.5 µg and 9 µg formoterol doses administered via symbicort pMDI.

The amount of formoterol in urine increased with dose across the range of 2.25 µg, 4.5 µg, and 9 µg, suggesting generally dose-proportional pharmacokinetics with approximately 5% of the dose excreted unchanged. The amount of formoterol in urine after treatment with Foradil 12 µg was comparable to that after treatment with formoterol 9 µg.

Overall, the results demonstrate that the 2.25 µg formoterol dose via Symbicort pMDI does not provide optimal bronchodilation and that the bronchodilation that it provides is not maintained over a 12-hour dosing regimen. In addition, although no statistically significant differences were seen between the 4.5 µg and 9 µg doses, the numerical estimates indicate that the 9 µg dose may provide patients with additional bronchodilation above that achieved with the 4.5 µg dose.

Formoterol 2.25 µg, 4.5 µg, and 9 µg, administered as single doses via Symbicort pMDI, were safe and well-tolerated in children with asthma, 6 to <12 years of age. Overall, there was a low incidence of AEs reported in all treatment arms, and there were no serious adverse events (SAEs) reported. The AE incidences in the formoterol 2.25 µg and 4.5 µg treatments (7.4% and 7.5% respectively) were similar to the incidence reported in the pre-randomization period (7.4%) and lower than that reported in placebo (9.8%). The formoterol 9 µg treatment had a slightly higher AE incidence (13.2%). There were 2 discontinuations due to adverse event, 1 each in the formoterol 2.25 µg and formoterol 9 µg treatments. Overall, the safety profile was as expected considering previous knowledge of Symbicort.

Study D589GC00003

IV.2.1 Study design

A double-blind, randomised, parallel-group, multicenter study investigating the efficacy and safety of Symbicort pMDI 80/2.25 µg, 2 actuations twice daily, and Symbicort pMDI 80/4.5 µg, 2 actuations twice daily, compared with budesonide pMDI 80 µg, 2 actuations twice daily for 12 weeks, in children ages 6 to <12 years with asthma. The study enrolled children with a documented clinical diagnosis of asthma for at least 6 months prior to study entry and a requirement for daily medium-dose range ICS therapy or fixed combination of ICS/LABA therapy and having symptoms when treated with low-dose ICS during run-in.

Assessor's comment:

The approved strength in EU (160 µg/4.5µg) is higher than the strength used in this study.

IV.2.2 Methods

Objectives

The purpose of this study was to evaluate the efficacy and safety of Symbicort pMDI compared with budesonide in children, ages 6 to <12 years.

Primary objective

The primary objective of the study was to demonstrate the efficacy of Symbicort pMDI 80/4.5, 2 inhalations bid and Symbicort pMDI 80/2.25, 2 inhalations bid, compared with

Budesonide pMDI 80 µg, 2 inhalations bid, in children ages 6 to <12 years with asthma.

The primary endpoint was the change from baseline to Week 12 in 1-hour post-dose FEV1.

Secondary objective

The secondary objective of the study was to compare the efficacy of Symbicort pMDI 80/4.5 µg, 2 inhalations bid with Symbicort pMDI 80/2.25 µg, 2 inhalations bid, in children ages 6 to <12 years with asthma. Secondary variables included additional clinic lung function variables, Pediatric Asthma Quality of Life Questionnaire with Standardized activities (PAQLQ(S)) scores (overall and each domain), electronic diary (eDiary) variables, time to discontinuation of investigational product, and time to occurrence of first asthma exacerbation.

Safety objective

The safety objective of the study was to compare the safety of Symbicort pMDI 80/4.5, 2 inhalations bid, Symbicort pMDI 80/2.25, 2 inhalations bid, and budesonide pMDI 80 µg, 2 inhalations bid, in children ages 6 to <12 years with asthma.

Study population

A total of 279 patients were randomized, of whom 6 (2 in each group) did not receive treatment and were not included in the efficacy or safety analysis set. In all, 249 (89.2%) patients completed treatment and 253 (90.7%) completed the study. Among the randomized patients, 40.5% were female and 59.5% male. Approximately one third were 6 to <9 years of age and two thirds were 9 to <12 years of age. The majority were White (62.4%); 27.2% were Black/African American and 0.7% were Asians. A total of 38.0% were of Hispanic or Latino ethnicity.

Patients included in the study had asthma with majority receiving a medium-dose inhaled ICS or an inhaled ICS/LABA prior to study entry. After consent, all had to demonstrate asthma symptoms and/or need of reliever medication during a single-blind run-in phase on low-dose ICS.

IV.2.3 Results

Efficacy results

A statistically significant improvement was observed with Symbicort 80/4.5 compared with budesonide 80 µg for the primary endpoint, change in 1-hour post-dose FEV1 from baseline to Week 12, with an estimated difference of 0.12 L (95% CI: 0.03, 0.20, p=0.006). The difference between Symbicort 80/2.25 and budesonide 80 µg for the primary endpoint was not statistically significant (estimated difference: 0.08 L; 95% CI: 0.00, 0.16, p=0.063). Furthermore, the difference observed between Symbicort 80/4.5 and Symbicort 80/2.25 for the primary endpoint was not statistically significant (estimated difference 0.04 L; 95% CI -0.05, 0.12; p=0.373); it should be noted that the study was not powered to detect a difference between these groups.

Safety results

No deaths were reported. There were 2 serious AEs (acute lymphocytic leukemia and asthma exacerbation), both in the budesonide group. There were 5 patients who discontinued treatment due to AEs, 1 in each Symbicort group and 3 in the budesonide group. Most common AEs (frequency $\geq 3\%$) were evenly distributed across groups. However, the following were reported more frequently in the Symbicort groups than the budesonide group: upper respiratory tract infection, pharyngitis, headache, and vomiting. There were few patients with potentially ICS-related AEs: 2 (dysgeusia and candida infection) in the Symbicort 80/2.25 group and 2 (oral candidiasis and upper limb fracture) in the budesonide 80 µg group. The only potentially β_2 -agonist-related adverse event reported was headache (4 patients in each Symbicort group and none in the budesonide group). Laboratory, vital signs, ECG, and physical examination findings did not raise any safety concerns.

IV.3 Study D5896C00027

IV.3.1 Study design

Study D5896C00027 was a randomized, double-blind, parallel-group, 26-week study which recruited patients ≥ 12 years old who were either currently being treated with an ICS/LABA combination, or who had asthma that was not adequately controlled on a long-term asthma control medication, or whose disease severity warranted initiation of treatment with ICS/LABA. Depending on prior treatment and asthma control at baseline (as assessed by the Asthma Control Questionnaire 6 [ACQ6]), patients received 2 actuations twice daily (bid) of either Symbicort pMDI 80/4.5 µg or Symbicort pMDI 160/4.5 µg, or the corresponding dose of budesonide pMDI.

The study was supervised by several committees, including the Joint Adjudication Committee which adjudicated all potential primary safety endpoints (deaths, intubations, and hospitalizations) and assessed whether they were asthma-related.

IV.3.2 Methods

Objectives

The purpose of this study was to evaluating the risk of serious asthma-related events during treatment with SYMBICORT over 26-week.

Primary objective

The primary objective of this study was to evaluate the risk of serious asthma-related events during treatment with Symbicort pMDI or budesonide pMDI alone over a 26-week treatment period in adult and adolescent patients with asthma.

The primary outcome variable is a composite safety endpoint of serious asthma events:

- Asthma-related deaths
- Asthma-related intubations
- Asthma-related hospitalizations

Other safety assessments were serious adverse events (SAEs) and discontinuation of treatment with investigational product due to adverse event (DAEs) or discontinuations due to asthma exacerbations.

Secondary objective

The secondary objective of this study was to evaluate the efficacy of Symbicort pMDI compared to budesonide pMDI alone over a 26-week treatment period in adult and adolescent patients with asthma. The variables for this objective included:

Primary efficacy endpoint:

- Asthma exacerbations, defined as a deterioration of asthma requiring systemic corticosteroids (tablets, suspension, or injection) for at least 3 days, or an inpatient hospitalization, or an emergency room (ER) visit due to asthma that required systemic corticosteroids.

Secondary efficacy endpoints:

- Healthcare utilization for asthma: telephone contact with study doctor, telephone contact with other physician or healthcare provider, unscheduled or unplanned visit to study doctor (including home visits), unscheduled or unplanned visit to other physician or healthcare provider (including home visits), emergency department or hospital (<24 hours), hospital admission or emergency department (≥ 24 hours). Hospitalizations were collected with the SAE reports
- Days (a part of a day was counted as a full day) of school or work missed due to asthma
- Rescue medication use
- Asthma symptoms
- Asthma symptoms leading to activity limitations
- Nights with awakening(s) due to asthma
- Assessment of current asthma control by the Asthma Control Questionnaire (ACQ) 6

Study population

A total of 11693 patients were randomly assigned to treatment. The median age was 45 years (range 12 to 89 years). There were 1268 (10.8%) patients aged 12 to 17 years, meeting the protocol target of 10% to 12% adolescents.

IV.3.3 Results

Efficacy results

The efficacy of SYMBICORT was superior to that of budesonide, as assessed by time to first asthma exacerbation (16% lower risk of an exacerbation; hazard ratio 0.835, 95% CI 0.745, 0.937, $p=0.002$). These results were supported by analysis of the total number of exacerbations. A total of 539 (9.2%) patients reported 637 exacerbations in the Symbicort group and 633 (10.8%) patients reported 762 exacerbations in the budesonide group. The majority of events were classed as exacerbations based on use of systemic steroids due to asthma for at least 3 days.

There was a clinically relevant improvement in asthma control in both treatment arms, as defined by a decrease in mean ACQ6 total score of at least 0.5 from baseline to the average for the randomized treatment period, with a greater mean change from baseline in the SYMBICORT group than the budesonide group ($p<0.001$). The proportion of patients with well-controlled asthma ($ACQ6 \leq 0.75$) at the end of treatment was 4.41% higher in the SYMBICORT group than the budesonide group ($p<0.001$). Patient-reported outcomes such as rescue medication use, symptom-free days, and night-time awakenings due to asthma were consistently better with SYMBICORT than budesonide, with the exception of asthma symptoms leading to activity limitation, for which there was no statistically significant difference between treatment groups.

Results for efficacy comparisons within the low and high-dose treatment strata were consistent with results for the population as a whole.

Safety result

A total of 43 (0.7%) patients in the Symbicort arm and 40 (0.7%) patients in the budesonide arm experienced a serious asthma-related event, the majority of whom experienced an asthma-related hospitalization (42 [0.7%] patients in the Symbicort arm and 40 [0.7%] patients in the budesonide arm). There were 2 asthma-related deaths (both in the Symbicort arm) and 1 asthma-related intubation (in 1 of the patients who died).

The risk of serious asthma-related events was comparable for Symbicort pMDI and budesonide pMDI as assessed by the composite endpoint of asthma-related deaths, asthma-related intubations, and asthma-related hospitalizations (hazard ratio 1.073, 95% CI 0.698, 1.650). Statistical non-inferiority was demonstrated based on the upper limit of the 95% CI for the hazard ratio being <2.

There were 125 (2.1%) patients with SAEs in the Symbicort arm and 123 (2.1%) in the budesonide arm. The most common SAEs in both treatment arms were asthma and pneumonia.

There was a numerically lower proportion of patients who discontinued treatment with investigational product due to an adverse event in the Symbicort arm (93 [1.6%] patients) than in the budesonide arm (132 [2.3%] patients). The most common reason for discontinuation due to an adverse event was asthma. There was a numerically lower rate of discontinuations of investigational product due to asthma exacerbations in the SYMBICORT arm (53 [0.9%] patients) compared with the budesonide arm (71 [1.2%] patients) (hazard ratio 0.739; 95% CI 0.518 to 1.055; $p=0.095$).

The number of deaths of any cause was similar in the Symbicort arm (6 [0.1%] patients) and in the budesonide arm (8 [0.1%] patients).

Results for safety comparisons within low and high dose treatment strata were consistent with results for the total treatment arms.

The study fulfilled its primary objective by showing non-inferiority of SYMBICORT pMDI compared with budesonide pMDI, indicating that within the pre-defined and agreed assumptions, there is no evidence for an increase in risk of serious asthma-related events. The study also fulfilled its secondary objective of confirming the efficacy of Symbicort pMDI compared with budesonide pMDI, and thus supports the continued positive balance of benefit to risk for Symbicort pMDI.

Assessor's comment:

Data in the adolescents are not presented separately. However, this is acceptable considering the well-established use of budesonide/formoterol in adolescents. This study is also discussed in the PSUSA PSUSA/00000450/201608 where it was concluded that no further action was warranted based on these data.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

V.1 Overall conclusion

The two first studies are included in study programs to be used to extend the marketing authorisation for Symbicort pMDI in US to include asthma in children 6-12 years of age. From the first study it was concluded that the formoterol dose 4.5 µg was the lowest that gave adequate effect and from the second study Symbicort 80/4.5 µg, 2 inhalations (160/9 µg) bid, was found superior to budesonide 80 µg, 2 inhalations (160 µg) bid for the primary endpoint. There were no notable safety differences among treatments. The products used in these studies had lower budesonide content than the strength approved in EU.

The third study included adolescents as a part of a safety study conducted to address concerns raised by FDA. The study fulfilled its objective to show non-inferiority between Symbicort and budesonide as mono-component on the rate of serious asthma-related events

V.2 Recommendation

No further action required.