

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-929

OFFICE DIRECTOR MEMO

DIVISION DIRECTOR'S MEMORANDUM

Date: July 21, 2006

To: NDA 21-929

From: Badrul A. Chowdhury, MD, PhD
 Director, Division of Pulmonary and Allergy Products, CDER, FDA

Product: Symbicort 80/4.5 (budesonide 80 mcg formoterol fumarate 4.5 mcg) Inhalation Aerosol, and Symbicort 160/4.5 (budesonide 160 mcg formoterol fumarate 4.5 mcg) Inhalation Aerosol

Applicant: AstraZeneca LP

Administrative and Introduction

AstraZeneca submitted a 505(b)(1) new drug application (NDA 21-929) on September 23, 2005 (CDER stamp date) for use of Symbicort 80/4.5 and Symbicort 160/4.5 for the maintenance treatment of asthma in patients 12 years of age and older. The PDUFA due date for this application is July 23, 2006. Symbicort is a fixed dose combination of the corticosteroid budesonide and the long-acting beta-agonist formoterol in a pressurized metered dose inhaler (MDI) using HFA 227 as the propellant. Two dose strengths are proposed, one containing 80 mcg of budesonide and 4.5 mcg of formoterol, and the other containing 160 mcg of budesonide and 4.5 mcg of formoterol. Symbicort is not a unique product. There are other single ingredient orally inhaled formulations of budesonide and formoterol approved for marketing in the US; budesonide as a dry powder inhaler (Pulmicort Turbuhaler) and as a suspension (Pulmicort Respules), and formoterol as a dry powder inhaler (Foradil Aerolizer). There is also another fixed dose combination product containing a corticosteroid and a long-acting beta agonist approved for marketing in the United States. The product is Advair, which contains the corticosteroid fluticasone and the long-acting beta-agonist salmeterol. There are two formulations of Advair approved, Advair Diskus and Advair HFA Inhalation Aerosol. Symbicort would be the second fixed dose combination product of this class. AstraZeneca submitted the necessary CMC data, pre-clinical data, and clinical data that support approval of the application.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substances budesonide and formoterol are well known compounds and are already approved as single ingredient orally inhaled products as mentioned above. The final drug product is a suspension of the two drug substances in excipients that include HFA 227 as the propellant, povidone K25 as a suspending agent, and PEG 1000 as a lubricant, contained in an aluminum canister sealed with a _____ metering value and fitted with a standard press-and-breathe actuator. This MDI will be the first one to be marketed in the United States that has HFA 227 as the propellant. Other approved MDIs have used HFA 134a as the propellant. Povidone

K25 and PEG 1000 have also not been used before as an excipient in inhalation products. There are two strengths of the drug product as mentioned above.

The drug substances budesonide is manufactured in an AstraZeneca facility in Sweden and in a facility in the Netherlands, and the drug substance formoterol is manufactured in an AstraZeneca facility in Sweden. The manufacturing sites for budesonide are the same that provide the drug substance for Pulmicort. The manufacturing site for formoterol is not related to Foradil. The final drug product is manufactured in an AstraZeneca facility in Dunkerque, France. All relevant DMFs associated with the manufacture of the drug product are adequate. The manufacturing and testing facilities associated with this drug product have acceptable EER status.

There were several CMC issues identified by the CMC review team early in the review period and were communicated to AstraZeneca in a discipline review letter. AstraZeneca resolved these issues and the CMC team recommends an approval action. I concur with this recommendation. There are three minor CMC issues worth noting. First, the drug product used in phase 3 clinical studies and the to-be-marketed product has several differences. The CMC team and the clinical team have reviewed these differences and concluded that they do not significantly impact the drug delivery characteristics. Second, the to-be-marketed product does not have a dose counter.

The current actuator has a shield component

Third, the drug product was not tested extensively for device performance and reliability in the clinical studies. Such testing is typically done in contemporary drug development programs for this class. Lack of device testing would not preclude approval because MDIs are well understood system and this device is a typical MDI. Furthermore, in the clinical studies and in laboratory testing no device performance issues were identified.

Pharmacology and Toxicology

AstraZeneca has complete nonclinical pharmacology and toxicology programs for the two monoproducts, budesonide and formoterol. In addition, AstraZeneca conducted 3-month bridging inhalation toxicology studies in rats and dogs to support the combined use of the two active ingredients. The drug product has a novel propellant HFA 227, and uses excipients, povidone K25, and PEG 1000. Although HFA 227 is not present in any marketed inhalation product, all preclinical studies with HFA 227 have been conducted under IPACT-II, for which AstraZeneca has rights of reference. The preclinical studies support use of HFA 227.

The excipients, povidone K25 and PEG 1000, are present in many oral products, but these have not been used in any inhalation products. To support the use of povidone K25 and PEG 1000 AstraZeneca submitted results from a number of preclinical studies. The studies included 3-month inhalation studies in rats and dogs with the full formulation including povidone K25 and PEG 1000. In the rat study the concentration of povidone

K25 and PEG 1000 was not high enough and provided only a 2-fold increased exposure compared to human exposure. AstraZeneca also submitted results of studies where povidone K30 and PEG 600 were present; these excipients are similar to the excipients present in Symbicort. These studies included a 6-month inhalation study with rats, 6-month and 12-month inhalation studies with dogs, and a 24-month inhalation carcinogenicity study in rats. In these studies no local toxicity finding in the lung were noted.

AstraZeneca also submitted results from a 3-month inhalation toxicity study conducted in rats that received a formulation containing the excipients povidone K25 and PEG 1000. The level of the excipients in this study was higher than the other 3-month rat study mentioned above. In this study increased incidence of alveolar histiocytosis, pneumonitis, and congestion in the lung were noted that could be attributable to povidone K25 or PEG 1000 or both. This observation was concerning. The Division asked AstraZeneca to provide an explanation of the finding. In response AstraZeneca reanalyzed the slides and concluded that all tested animals (drug treated and vehicle treated) in the study had similar findings and concluded that the findings could not be attributable to the two excipients. To reconcile the difference the Division asked for an independent blinded reanalysis of the slides. On reanalysis of the slides it was again concluded that there were no histological findings that could be attributable to the two excipients. The pharmacology toxicology review team discussed the three readings with Associate Directors and accepted the final reanalysis and concluded that the preclinical concern has been resolved. The pharmacology toxicology team also took into consideration that another inhalation drug, _____, which is not yet approved for marketing but has undergone pre-clinical testing also has similar excipients, _____ in the final formulation at a level higher than what is proposed for Symbicort. Preclinical testing _____ did not show any lung or upper airway toxicity. The pharmacology toxicology team recommends approval, and I concur with this recommendation.

Clinical and Statistical

Overview of the clinical program:

The clinical program for Symbicort was large with the goal of satisfying various objectives – satisfy the combination policy; support _____ dosage strengths of Symbicort, _____ 80/4.5, and 160/4.5; support pediatric ages _____ years and older; and support _____ twice-daily dosing regimen. To satisfy the combination policy that each component makes a contribution to the claimed effect (21 CFR 300.50), the clinical studies included single ingredient products in the different studies, some of which are not approved for marketing in the United States. Particularly problematic was the single ingredient dry powder formoterol product (Oxis Turbuhaler), which is pharmaceutically different from a MDI.

The clinical program that is relevant to this application

became limited to Symbicort 80 /4.5 and 160/4.5 dosage strengths, ages 12 years and above, and twice-daily dosing regimen. The clinical studies that are pivotal to support this modified goal are one pharmacodynamic study (SD-039-0729) that compares formoterol delivered by the Turbuhaler device and MDI device, two 12-week efficacy and safety studies (SD-039-0716 and SD-039-0717), and one long term safety study (SD-039-715). Detailed review of these studies and other supporting studies can be found in Dr. Starke's clinical review and in Dr. Guo's statistical review. Dr. Starke and Dr. Guo recommend an approval action on this application and I concur with this recommendation.

The studies mentioned above are briefly commented on in the following sections. The design and conduct of these studies are briefly described, followed by efficacy and safety findings and conclusions.

Design and conduct of the pivotal efficacy and safety studies:

Pharmacodynamic study (SD-039-0729):

This study was conducted to link the clinical effects of formoterol delivered by the Symbicort and Oxis Turbuhaler devices to help resolve the pharmaceutical differences presented by the use of these two different devices in the pivotal efficacy and safety studies. This was a randomized, multi-center, open-label, single-dose, 7-treatment crossover study conducted in the United States in patients 18 years of age with asthma. The study had a screening visit, 7-14 days budesonide run-in period, and randomized treatment period. Treatment components were budesonide MDI, Symbicort, and Oxis Turbuhaler. The treatments were such that all subjects were maintained on budesonide 320 mcg twice daily as a background, and over that the subjects received either no additional formoterol, or formoterol 4.5 mcg twice daily, 9 mcg twice daily, or 18 mcg twice daily, delivered either by the Symbicort or by the Oxis Turbuhaler. The primary efficacy variable was average 12-hour FEV1 calculated on the basis of area under the curve (AUC) divided by the observation time. Safety assessment included recording of adverse events, vital signs, physical examination, ECG, and clinical laboratory measures. A total of 201 patients were randomized of whom 168 completed the study.

12-week efficacy and safety studies (SD-039-0716 and SD-039-0717):

Studies SD-039-0716 and SD-039-0717 were double-blind, double-dummy, placebo-controlled, parallel group in design, conducted in the United States in patients 12 years of age and older with mild-to-moderate asthma (study SD-039-0716) or moderate-to-severe asthma (SD-039-0717). Study SD-039-0717 included 31 patients 6 to 11 years of age. These patients were not included in efficacy analyses. The studies had a 7-21 day single-blind run in period where the patients were given placebo (study SD-039-0716) or budesonide 160 mcg twice daily (study SD-039-0717), followed by 12-week double blinded treatment period. The treatment arms differed in the two studies. In study SD-039-0716 the treatment arms were Symbicort 80/4.5, budesonide MDI 80 mcg, formoterol dry powder inhaler 4.5 mcg (Oxis Turbuhaler), and placebo, all administered

as two inhalations twice daily. In study SD-039-0717 the treatment were Symbicort 160/4.5, budesonide MDI 160 mcg, formoterol dry powder inhaler 4.5 mcg (Oxis Turbuhaler), budesonide MDI 160 mcg and formoterol dry powder inhaler 4.5 mcg (Oxis Turbuhaler) given together, and placebo, all administered as two inhalations twice daily. The studies were designed to have 105 patients per treatment arms to give 95% power to detect a 0.25 L mean difference for the co-primary endpoints at two-sided alpha-level of 0.05. In study SD-039-0716 a total of 480 patients were randomized equally to the four treatment arms, and in study SD-039-0717 a total of 596 patients were randomized equally to the five treatment arms. In the two studies approximately 40% to 85% patients completed the study with notably more completers in the Symbicort and budesonide treatment arms.

The co-primary efficacy endpoints in the studies were baseline adjusted average 12-hour FEV1 (to demonstrate contribution of formoterol) at week 2, and average AM pre-dose FEV1 (to demonstrate contribution of budesonide). Originally both studies had “withdrawals due to asthma events” as a co-primary efficacy endpoint instead of pre-dose FEV1. Asthma event was defined as one of the following: (a) decrease in pre-dose FEV1 by 20% or more compared to the value at randomization or a decrease to less than 45% predicted; (b) use of 12 actuations or more of albuterol a day on 3 or more days within 7 consecutive days; (c) decrease in morning PEF by 20% or more from baseline on 3 or more days within 7 consecutive days; (d) 2 or more nights with awakening due to asthma that required rescue medication use within 7 consecutive days; (e) a clinical exacerbation requiring emergency treatment, hospitalization, or use of asthma medications not allowed in the protocol. During the course of the study the asthma event variable was demoted to a secondary efficacy variable and pre-dose FEV1 was elevated to a primary efficacy variable. AstraZeneca made the change because the investigators were not consistent in withdrawing patients from the study who met the withdrawal criteria. Some investigators continued patients who met the criteria in the study whereas the protocol actually called for these patients to be withdrawn from the study [except for criterion (d), for which withdrawal was optional]. Safety assessment in both the studies included recording of adverse events, vital signs, ECG, 24-hour Holter monitoring in a subset of patients, physical examinations, and clinical laboratory measure.

12-month safety study (SD-039-715):

Study SD-039-715 was an open-label, multi-center, parallel-group in design, conducted in France, Australia, Slovakia, South Africa, Thailand, and Philippines in patients 12 years of age and older with persistent asthma. The study had a screening visit where eligibility was determined, followed by 12 months of treatment with Symbicort MDI or Symbicort Turbuhaler in a 2:1 randomization. A total of 673 patients were enrolled in the study. Safety assessment included recording of adverse events, vital signs, physical examinations, ECG, clinical laboratory measures, and 24-hour urinary cortisol measurement in a subset of 25 patients. Periodic spirometries were done as a measure of efficacy.

Efficacy findings and conclusion:

A concern with the Symbicort pivotal efficacy studies was the use of different formulations of the single ingredient comparator products, which raises the possibility that the difference between Symbicort and a single ingredient product could be due to pharmaceutical differences. In the two 12-week efficacy studies budesonide was delivered by a MDI device not marketed in the United States or elsewhere, and formoterol was delivered by a dry powder inhaler device (Oxis Turbuhaler) also not marketed in the United States. The pharmacodynamic study SD-039-0729, inclusion of placebo arms in the two 12-week efficacy studies, and inclusion of the free combination of monoproducts in study SD-039-0717 resolved this concern.

The pharmacodynamic study SD-039-0729 demonstrated that formoterol delivered either by Symbicort or by Oxis Turbuhaler at the same dose provided comparable bronchodilating effect. In this study all formoterol treatments resulted in greater bronchodilation compared to budesonide alone, and with increasing doses of formoterol there were greater bronchodilation with the differences between treatment with either Symbicort or Oxis Turbuhaler for the same dose being very small (Table 1). Timed FEV1 curve over 12 hours showed consistent dose ordering with very close approximation of the curves for the same doses delivered with the two devices (not shown). This link forms the basis of comparing the formoterol effect across these two devices used in the pivotal efficacy and safety studies.

Table 1. SD-039-0729, Treatment LS means for FEV1 (L)

Formoterol Treatment Device	Formoterol dose	n	Pre-dose FEV1 (L)	Treatment 12-hr FEV1(L)
None	0	125	2.42	2.51
Symbicort	4.5	127	2.35	2.69
Symbicort	9	130	2.40	2.74
Symbicort	18	133	2.41	2.81
Oxis Turbuhaler	4.5	132	2.35	2.71
Oxis Turbuhaler	9	148	2.34	2.74
Oxis Turbuhaler	18	126	2.38	2.78

The two 12-week replicate studies (SD-039-0716 and SD-039-0717) support efficacy of Symbicort 80/4.5 and Symbicort 160/4.5 in patients 12 years of age and older with differing asthma severity. Table 2 shows the differences between treatment groups, and Tables 3 and 4 show the results of the two efficacy endpoints. In both the studies Symbicort was superior to each of the single ingredients in the relevant primary endpoints. Symbicort was superior to budesonide for 12-hour FEV1 showing contribution of formoterol, and Symbicort was superior to formoterol for pre-dose FEV1 showing contribution of budesonide (Table 2). In both the studies the single ingredients were superior to placebo establishing that they were active and therefore valid comparators (Table 2).

Table 2. Difference between treatment groups, expressed as baseline adjusted LS mean (95% CI)

	12-hour FEV1 (L) at week 2		Pre-dose FEV1 (L)	
	Study 716	Study 717	Study 716	Study 717
Symbicort vs placebo	0.35 (0.26, 0.44)	0.37 (0.29, 0.45)	0.31 (0.21, 0.40)	0.37 (0.28, 0.45)
Symbicort vs budesonide	0.18 (0.09, 0.27)	0.20 (0.11, 0.28)	0.14 (0.04, 0.23)	0.12 (0.04, 0.21)
Symbicort vs formoterol	0.07 (-0.02, 0.16)	0.15 (0.07, 0.23)	0.16 (0.06, 0.26)	0.26 (0.17, 0.35)
Symbicort vs bud + for		0.01 (-0.07, 0.09)		0.04 (-0.05, 0.12)
Budesonide vs placebo	0.17 (0.08, 0.25)	0.17 (0.09, 0.25)	0.17 (0.08, 0.27)	0.25 (0.16, 0.33)
Formoterol vs placebo	0.28 (0.19, 0.37)	0.22 (0.14, 0.30)	0.15 (0.05, 0.25)	0.11 (0.02, 0.19)

Table 3. Average 12-hour FEV1 (L) at week 2

Treatment Groups	Study	n	Baseline FEV1	LS Mean change in FEV1 (95% CI)
Symbicort				
160/9 mcg BID	716	123	2.40	0.45 (0.38, 0.52)
320/9 mcg BID	717	124	2.24	0.32 (0.26, 0.38)
Budesonide				
160 mcg BID	716	121	2.33	0.26 (0.19, 0.34)
320 mcg BID	717	109	2.30	0.13 (0.06, 0.19)
Formoterol				
9 mcg BID	716	114	2.38	0.38 (0.31, 0.45)
9 mcg BID	717	123	2.18	0.17 (0.11, 0.23)
Bud + Formoterol				
320 mcg + 9 mcg BID	717	115	2.24	0.31 (0.24, 0.37)
Placebo				
	716	122	2.39	0.10 (0.03, 0.17)
	717	125	2.28	-0.05 (-0.11, 0.02)

Table 4. Average pre-dose FEV1 (L)

Treatment Groups	Study	n	Baseline FEV1	LS Mean change in FEV1 (95% CI)
Symbicort				
160/9 mcg BID	716	123	2.40	0.32 (0.24, 0.40)
320/9 mcg BID	717	117	2.23	0.17 (0.10, 0.23)
Budesonide				
160 mcg BID	716	116	2.32	0.18 (0.11, 0.26)
320 mcg BID	717	108	2.30	0.05 (-0.02, 0.12)
Formoterol				
9 mcg BID	716	105	2.41	0.16 (0.08, 0.24)
9 mcg BID	717	114	2.19	-0.09 (-0.16, -0.03)
Bud + Formoterol				
320 mcg + 9 mcg BID	717	111	2.23	0.13 (0.07, 0.20)
Placebo				
	716	111	2.43	0.01 (-0.07, 0.09)
	717	116	2.29	-0.20 (-0.26, -0.13)

Secondary endpoints generally favored Symbicort over placebo and also over the single ingredient components depending on the endpoint. Withdrawals due to asthma events were an important secondary endpoint, which was originally defined as the co-primary efficacy endpoint for evaluation of the budesonide component. Results of this endpoint for the two studies are shown in Table 5. For this variable Symbicort was superior to

formoterol, supporting the contribution of budesonide. It is interesting to note that the added benefit of Symbicort over budesonide alone was not remarkable for patients with mild-to-moderate asthma (Study 716). Another secondary endpoint of note was AQLQ. In both the studies AQLQ score for Symbicort increased from baseline to end of treatment. The increase over placebo crossed the 0.5 MID threshold and was statistically significant. The mean increase for Symbicort over placebo in study SD-039-0716 was 0.84 (95% CI 0.58, 1.09) and in study SD-039-0717 was 0.70 (95% CI 0.47, 0.93).

Table 5. Number (percentage) of subjects meeting pre-defined asthma event withdrawal criteria

	Symb	Bud	For	Bud + For	Placebo
Study 716	n=123	n=121	n=114		n=122
Total	23 (18.7)	26 (21.5)	48 (42.1)		69 (56.6)
- Decrease in FEV1	3 (2.4)	3 (2.5)	11 (9.6)		9 (7.4)
- Rescue medication	1 (0.8)	3 (2.5)	1 (0.9)		3 (2.5)
- Decrease in PEF	3 (2.4)	1 (0.8)	8 (7.0)		14 (11.5)
- Nighttime awakening	17 (13.8)	20 (16.5)	31 (27.2)		52 (42.6)
- Exacerbation	1 (0.8)	3 (2.5)	5 (4.4)		20 (16.4)
Study 717	n=124	n=109	n=123	n=115	n=115
Total	37 (29.8)	48 (44.0)	68 (55.3)	24 (20.9)	84 (67.2)
- Decrease in FEV1	4 (3.2)	7 (6.4)	15 (12.2)	8 (7.0)	14 (11.2)
- Rescue medication	2 (1.6)	3 (2.8)	3 (2.4)	0 (0.0)	7 (5.6)
- Decrease in PEF	2 (1.6)	5 (4.6)	17 (13.8)	5 (4.3)	15 (12.0)
- Nighttime awakening	24 (19.4)	29 (26.6)	32 (26.0)	11 (9.6)	49 (39.2)
- Exacerbation	7 (5.6)	5 (4.6)	17 (13.8)	6 (5.2)	16 (12.8)

Safety findings and conclusion:

The review of the submitted data and other sources did not reveal any new or unusual trends. Both active ingredients in this combination product are marketed in the United States for use in patients with asthma and their safety characteristics are well understood. Inhaled corticosteroids, including budesonide, have been marketed for a long-time period, and long-acting beta-agonist has been in the market since 1994. There have been concerns about adrenal axis effects with inhaled corticosteroids, and concerns with worsening asthma including asthma related death with chronic use of long-acting beta-agonists. The clinical program for Symbicort did not reveal any adverse events related to adrenal axis effects. There was one death in the whole program. The death was due to asthma attack and occurred 7 weeks after completion of the one-year open label safety study. The adverse events profile reported by patients was typical for this class of drug. Common adverse events reported were nasopharyngitis, headache, upper respiratory tract infection, sinusitis, etc. There were more reports of pharyngolaryngeal pain, oropharyngeal candidiasis, and hoarseness on Symbicort or budesonide treated patients compared to formoterol or placebo treated patients. These events are typically seen with orally inhaled corticosteroids due to local effects.

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Clinical Pharmacology and Biopharmaceutics

The pharmacokinetic properties of the two active components budesonide and formoterol are well known. AstraZeneca performed a limited program to ensure that the pharmacokinetic properties of the two active ingredients are not changed in this combination product. The two main studies were SD-093-0723 and SD-039-0717. In study SD-093-0723 the pharmacokinetic dose proportionality across the different dose strengths of Symbicort was shown. In study SD-039-0717, which was one of the two pivotal efficacy studies, pharmacokinetic assessment showed that the systemic exposure from the combination product was comparable to that from the single ingredient products. These studies and other studies are reviewed in detail in the Office of Clinical Pharmacology (OCP) review of Dr. Al Habet. The OCP team has determined that the submitted clinical pharmacology program is adequate and recommends an approval action. I concur with that recommendation.

Data Quality, Integrity, and Financial Disclosure

A DSI audit was request of five specific sites that covered the pharmacodynamic study (SD-039-0729) and the two 12-week efficacy and safety studies (SD-039-0716 and SD-039-0717). Specific sites were recommended by the clinical review team based on large number of subjects enrolled at these sites or trends in efficacy finding differing from the overall group or disclosed financial conflict. The results of the DSI audit showed that in general the sties adhered to the applicable regulations and good clinical practices governing conduct of clinical investigations. During review of the submission no irregularities that would raise concerns regarding data integrity were found. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements. There was one investigator who had significant financial interest in AstraZeneca. Review of the efficacy and safety data of that particular investigators' site did not show any suspicious trends. That particular site was also one of the sites audited by DSI.

Pediatric Considerations

AstraZeneca is seeking approval for ages 12 years and above and requested deferral of pediatric studies for patients 6 to 12 years of age and waiver of pediatric studies for patients below 6 years of age. The deferral and waiver was granted on filing the application. AstraZeneca has already conducted studies in patients 6 to 12 years of age,

age group. Waiver of studies below 6 years of age is reasonable because this fixed dose product is not suitable for very young patients as it does not allow easy titration of the corticosteroid dose. Single ingredient inhaled budesonide products available in the market is better suited for this young age group.

AstraZeneca proposed to add pediatric growth data from a published study conducted with Pulmicort Turbuhaler 200 mcg twice daily and placebo (N Eng J Med 2000; 343:1054-63). The study was conducted by a well reputed group with NIH funding and

shows an inhibitory effect on growth that is consistent with this class of drug. Although the primary data was not submitted by AstraZeneca and therefore not reviewed by the Agency, the results in the publication are convincing enough that merits inclusion in the label. The label will mention the 1-year growth results with on-treatment results out to 4 years, with some qualifications as to the interpretability on the data.

Product Name

The trade name Symbicort was reviewed by the DMETS of Office of Surveillance and Epidemiology (OSE) and found to be acceptable. The various review team of this Division also finds the trade name acceptable.

Labeling

AstraZeneca submitted a label that generally conforms with labeling of other products of this class, specifically with the labeling of Advair (fluticasone/salmeterol). The notable difference was that the warning, including boxed warning, and medication guide related to the risk of asthma death with the use of long-acting beta-agonist was not present. When this NDA was submitted boxed warning was not present on the Foradil Aerolizer (formoterol fumarate inhalation powder) label, but it was included within the review period of this NDA. Review of the label was done by various disciplines of the Division, and on consult by OSE and DDMAC. Various changes to different sections of the label were done to better reflect the data and better communicate the finding to health care providers. Warning statements, including boxed warning and medication guide were added. The language of the warning was consistent with that of the Foradil label. The Division and AstraZeneca have agreed to the final version of the label.

Action

AstraZeneca has submitted adequate data to support approval of Symbicort 80/4.5 (budesonide 80 mcg formoterol fumarate 4.5 mcg inhalation aerosol) and Symbicort 160/4.5 (budesonide 160 mcg formoterol fumarate 4.5 mcg inhalation aerosol) for the long-term maintenance treatment of asthma in patients 12 years of age and older. The action on this application will be APPROVAL.

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Badrul Chowdhury
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