CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205636Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	March 31, 2015
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	205636
Applicant Name:	Teva Pharmaceuticals
Date of Submission:	May 5, 2014
PDUFA Goal Date:	March 5, 2015
Proprietary Name:	ProAir RespiClick
Established Name:	Albuterol sulfate
Dosage form:	Multi-dose inhalation powder (dry powder inhaler)
Strength:	117 mcg of albuterol sulfate (equivalent to 97 mcg of albuterol base), and delivers 108 mcg albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece per actuation
Proposed Indications:	Treatment or prevention of bronchospasm in adults and adolescents age 12 years and older, and prevention of exercise-induced bronchospasm in adults and adolescents age 12 years and older
Action:	Tentative Approval

1. Introduction

Teva Pharmaceuticals submitted this 505(b)(2) new drug application for use of ProAir RespiClick (albuterol sulfate) inhalation powder for treatment or prevention of bronchospasm and prevention of exercise-induced bronchospasm in adults and adolescents age 12 years and older. The proposed dose for treatment or prevention of bronchospasm is 2 inhalations (216 mcg albuterol sulfate) every 4 to 6 hours, with a qualifier that in some patients 1 inhalation (108 mcg albuterol sulfate) every 4 hours may be sufficient. The proposed dose for exercise-induced bronchospasm is 2 inhalations (216 mcg albuterol sulfate) 15 to 30 minutes before exercise. Albuterol sulfate is marketed in the US from various manufacturers in various dosage forms, including solutions for inhalations and inhalation aerosols. Teva has a related product marketed in the US called ProAir HFA (albuterol sulfate) inhalation aerosol (NDA 21457, approved in October 2004). ProAir HFA inhalation aerosol delivers 108 mcg albuterol sulfate from the mouthpiece per actuation (same as the proposed ProAir RespiClick product), and has the same indication of treatment or prevention of bronchospasm and prevention of exercise induced bronchospasm, but down to a lower age of 4 years. This application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for use in patients with asthma, including long-term control medications to achieve and maintain control of persistent asthma, and quick-relief medications for short-term use. The long-term control medications include inhaled corticosteroids (ICSs), inhaled long-acting beta-adrenergic agents (LABAs), leukotriene modifying drugs, methylxanthines, and omalizumab. ICSs are considered to be the most effective long-term therapy for persistent asthma, and are commonly used as the first drug when a maintenance therapy is necessary. Quick-relief medications include short-acting beta-adrenergic agents (SABAs), and systemic corticosteroids. Albuterol is available in various dosage forms and commonly used as quick-relief medication for short-term use as a bronchodilator. There is currently no marketed inhalation powder of albuterol in the US. In other countries in the world inhalation powder of albuterol is available and commonly used.

Exercise-induced bronchospasm (EIB) is used to describe the transient increase in airway resistance after vigorous exercise that occurs in patients with or without persistent asthma. Principles of treatment of EIB involve use of bronchodilators to reverse bronchoconstriction induced by exercise, scheduled use of long-term control medications in patients who have frequent EIB, and pre-treatment before exercise to prevent EIB in susceptible patients. Drugs that are used as pre-treatment for EIB include SABA, LABA, and leukotriene antagonist. Albuterol is commonly used pre-exercise to prevent EIB.

Regulatory interaction between the Agency and Teva:

The Division and Teva had typical milestone meetings for ProAir RespiClick. The following highlights some major discussion points that occurred at some of the meetings. The development program for ProAir RespiClick was consistent with the Division recommendations and there were no major points of concerns or disagreements.

- Pre-IND meeting, March 27, 2009: Development program was discussed.
- End-of-Phase-2 meeting, October 5, 2009: The design of the phase 3 studies was discussed. It was discussed that a single EIB study showing positive results will be sufficient provided the studies for prevention and treatment of bronchospasm showed positive results.
- Pre-NDA meeting, December 16, 2013: The general content and format for the NDA was discussed. It was discussed that Teva will submit reasoning for a waiver for pediatric studies in children less than 4 years of age.

3. Chemistry, Manufacturing, and Controls

The product ProAir RespiClick (albuterol sulfate) inhalation powder includes a novel multi-dose dry powder inhaler device, the RespiClick. The drug formulation contains the active ingredient albuterol sulfate (racemic), a salt of albuterol, in a blend with alpha-lactose monohydrate. The dry powder formulation is contained in the reservoir type, inspiratory flow driven, multi-dose, device-metering inhaler device called RespiClick. The albuterol and lactose blend is contained in a reservoir and the device meters each dose prior to delivery. The delivery of a dose is based on (b) (4) in the

RespiClick device that is activated by the patient inhaling through the mouthpiece of the device. The inhaler device contains 0.65 g of the formulation and is labeled for 200 doses (device will be manufactured with (b) (4) doses but is labeled as 200 doses so that patients do not inadvertently deplete their inhaler before seeking a refill). Each actuation provides a metered dose of 117 mcg of albuterol sulfate (equivalent to 97 mcg of albuterol base) with lactose from the valve (117 mcg is the metered dose, i.e., amount the device meters out when actuated before inhalation). Each metered dose delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) with lactose from the mouthpiece (108 mg is the ex-mouthpiece dose, i.e., amount targeted to leave the mouthpiece). The ProAir RespiClick has a dose counter that counts down from 200 to 0. When the counter reaches 20, the color of the number changes to red to remind the patient to get a refill. The device is not locked when the counter reaches 0. The ProAir RespiClick outwardly generally resembles a typical press-and-breathe metered dose inhaler. But, given the formulation and mechanism, RespiClick does not require priming, and should not be used with a spacer or volume holding chamber. The mouthpiece needs to be kept clean and dry, and no part of the product should be washed with water or immersed in water.

Teva has proposed (b) (4) months expiry for the packaged product and 13 months expiry for the out-of- package product based on the testing at various orientations and conditions, as well as in- and out-of-package testing. However, the FDA product quality team recommends an expiration dating period of 36 months.

The drug substance is manufactured by (b) (4) and (b) (4) The final drug product is manufactured by Teva Pharmaceutical Industries, Ltd., Israel. All manufacturing and testing facilities associated with this drug product have acceptable establishment evaluation status. All DMFs associated with this application were also found to be acceptable.

4. Nonclinical Pharmacology and Toxicology

No nonclinical pharmacology and toxicology studies were conducted or required for the proposed product. For this NDA, Teva is relying on NDAs from previously approved albuterol products, and this is acceptable.

5. Clinical Pharmacology and Biopharmaceutics

Albuterol is a well-known product and general pharmacological characteristics of albuterol are well defined. For the ProAir RespiClick product, various clinical studies compared the PK and PD characteristics of ProAir RespiClick to ProAir HFA inhalation aerosol. The PK data showed that the albuterol exposure was numerically higher for the ProAir RespiClick compared to ProAir HFA. Following cumulative doses (1440 mg in total), the ratios (ProAir RespiClick and ProAir HFA inhalation aerosol) for AUC_{0-t} and C_{max} were 1.11 (90% CI = 1.04, 1.19) and 1.34 (90% CI = 1.17, 1.53), respectively. The PD data also show effect similar in trend to the PK of ProAir RespiClick and ProAir HFA (discussed in Clinical Section 7 below).

6. Clinical Microbiology

Teva proposed acceptable microbial testing regimen involving the bulk drug product and the finished product.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision-making for this application are shown in Table 1. The development program included comparing the albuterol dry powder formulation to the approved albuterol HFA inhalation aerosol (both by Teva, and both deliver 108 mcg albuterol sulfate from the mouthpiece) by cumulative dose and dose ranging studies, and placebo controlled confirmatory studies to demonstrate efficacy and safety. Device performance was assessed in the confirmatory studies and in additional safety studies. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8.

Three versions of ProAir RespiClick were used in clinical studies during development. The first version was not used in any study that supports this application or reviewed in this document. The changes from the second version to the third version were relatively minor and did not change the drug flow path. The final version of the device, the to-be-marketed version, was used in the pivotal phase 3 studies.

Table 1. Relevant clinical studies in patients with asthma

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy variable ¶**	**Regions and Countries**
Cumulative dose safety and efficacy study					
101 [2010]	- 18 to 45 yrs - Stable ICS, FEV_1 50-80% - Cumulative dose q 30 min - XO, DB, DD	Alb DPI 90 mcg Alb MDI 90 mcg	47	1^o: ΔFEV_1 30 min after each dose 2^o: ΔFEV_1 $AUC_{0\text{-}6hr}$	US
Single-dose dose-ranging efficacy and safety study					
201 [2010]	- ≥ 12 yr, mean 43 yrs - Stable ICS, FEV_1 50-80% - XO, DB, DD - Single dose	Alb DPI 90 mcg Alb DPI 180 mcg Alb MDI 90 mcg Alb MDI 180 mcg Placebo	71	1^o: ΔFEV_1 $AUC_{0\text{-}6hr}$ 2^o: ΔFEV_1 $AUC_{0\text{-}6hr}$ % predicted	US
Confirmatory efficacy and safety Phase 3 studies					
301 [2012-2013]	- ≥ 12 yr, mean 39 yrs - Stable ICS, FEV_1 50-85% - Parallel arm, DB - 12 weeks	Alb DPI 180 mcg QID Placebo	79 79	1^o: ΔFEV_1 $AUC_{0\text{-}6hr}$ over 12 weeks 2^o: ΔFEV_1 $AUC_{0\text{-}6hr}$ baseline to week 12	US
304 [2012-2013]	- ≥ 12 yr, mean 38 yrs - Stable ICS, FEV_1 50-85% - Parallel arm, DB	Alb DPI 180 mcg QID Placebo	75 85	1^o: ΔFEV_1 $AUC_{0\text{-}6hr}$ over 12 weeks 12 2^o: ΔFEV_1 $AUC_{0\text{-}6hr}$	US

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy variable ¶**	**Regions and Countries**
	- 12 weeks			baseline to week 12	
Exercise-induced bronchospasm study					
302 [2013]	- 12 to 50 yrs - EIB, Stable ICS - XO, DB - 24 weeks	Alb DPI 180 mcg Placebo	38	1^{o}: Maximum post-exercise fall in FEV_1	US
Long-term safety studies					
307 [2012-2013]	- ≥ 12 yr, mean 37 yrs - Stable ICS, FEV_1 50-85% - BD followed by OL - 12 wk DB + 40 wk OL	Alb DPI 180 mcg	337		US
308 [2013]	- ≥ 4 yr, mean 51 yrs - Asthma - Device and counter check - 8 wk, OK	Alb DPI 180 mcg	317		US

* Study ID shown as Teva's study number, and [year study started-completed]
† XO = cross over; DB = double blind; DD = double dummy; OL = open label
‡ Alb DPI = ProAir RespiClick; Alb MDI = ProAir HFA inhalation aerosol;
§ Intent to treat (ITT)
¶ Analysis varied by study

b. Design and conduct of the studies

Cumulative dose study (study 101):

The study was conducted in patients with persistent asthma controlled on ICS. Eligible patients entered a run-in period of 7-14 days, followed by two random cross-over treatment sequences separated by 3-14 days washout. There were two treatment arms (shown in Table 1) of a cumulative dose of 1440 mcg albuterol administered either by dry powder inhaler or HFA inhalation aerosol of 90 mcg per inhalation administered as 1+1+2+4+8 inhalation (cumulative inhalations of 1, 2, 4, 8, 16, or cumulating dose of 90, 180, 360, 720, and 1440 mcg). The primary efficacy variable was based on timed FEV_1 measurement done at 30 minute pre-dose, and hourly for 6 hours post-dose. Safety assessments included plasma potassium, plasma glucose, heart rate, and ECG.

Single-dose dose-ranging study (study 201):

The study was conducted in patients with persistent asthma controlled on ICS. Eligible patients entered a run in period of 14 days, followed by 5-treatment cross-over treatment sequence separated by 7 days washout. The treatment arms and efficacy variables are shown in Table 1. At each treatment visit, FEV_1 data was collected at 30 minutes and 5 minutes pre-dose, and 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, and hourly for 6 hours post-dose. Safety assessments included plasma potassium, plasma glucose, heart rate, and ECG.

Confirmatory efficacy and safety studies (301, and 304):

These studies were conducted in patients with persistent asthma controlled on ICS. Eligible patients entered a run in period of 14 days, followed by randomized treatment for 12 weeks. The treatment arms and efficacy variables are shown in Table 1. Safety assessments included plasma potassium, plasma glucose, heart rate, and ECG.

Exercise-induced bronchospasm (EIB) study (study 302):

The study was conducted in patients with history of EIB. Eligible patients entered a run-in period of 1-14 days, followed by two random cross-over treatment sequence separated by 2-7 days washout. The treatment arms and efficacy variables are shown in Table 1. At each treatment visit, FEV_1 data was collected 30 minutes and 5 minutes prior to treatment, 30 minutes after treatment, and 5 minutes prior to exercise challenge, and 5, 10, 15, 30, 60 minutes after exercise challenge. Safety assessments included plasma potassium, plasma glucose, heart rate, and ECG.

Long-term safety studies (307, 308):

Study 307 consisted of two parts; first part was a 12-week double blind treatment when patients were randomized to receive two inhalations QID of either albuterol dry powder inhaler or placebo; and second part was a 40-week open-label treatment period when patients received open-label albuterol dry powder inhaler as needed. The objective of the study was to assess the safety of albuterol dry powder inhaler over 52 weeks, with special attention to assess device performance. A total of 337 subjects were randomized to either placebo (n=169) or albuterol dry powder inhaler (n=168) in the first part of the study.

Study 308 enrolled a broad spectrum of patients, including patients with COPD. The primary objective of the study was to assess performance of the dose counter in the albuterol dry powder inhaler.

c. Efficacy findings and conclusions

The clinical program is adequate to support efficacy of ProAir RespiClick for use as a bronchodilator and for EIB. The proposed dose and dosing regimen is supported by the data from the ProAir RespiClick program, and known efficacy profile of albuterol.

The PK and PD comparative data between ProAir RespiClick and ProAir HFA shows numerically higher FEV_1 response with cumulative doses of ProAir RespiClick compared to ProAir HFA (Table 2). Some other parameters, such as heart rate, blood pressure, serum glucose, and serum potassium were also suggestive of a higher numerical response, more pronounced at around 2 to 3 hours after dosing (Figure 1). On single-dose, dose-response study, there was also a numerical higher response with ProAir RespiClick compared to ProAir HFA (Table 3, Figure 2). The higher PD responses with ProAir RespiClick compared to ProAir HFA, more pronounced at around 2 to 3 hours after dosing, are consistent with the higher albuterol exposure with ProAir RespiClick compared to ProAir HFA, particularly at the Cmax (see section 5 above). The

differences in the PK and PD parameters between the two products are small and unlikely to be of clinical consequence. Further confirmatory studies show efficacy and safety of ProAir RespiClick at the proposed dose (described below).

Table 2. ΔFEV_1 after cumulative dosing with ProAir RespiClick dry powder inhaler and ProAir HFA inhalation aerosol (Study 101)

	ΔFEV_1 in mL		Treatment Difference (90% CI)
Cumulative Dose	**RespiClick**	**HFA**	**RespiClick - HFA**
90 mcg	426	383	43 (-25, 110)
180 mcg	505	439	66 (-02, 133)
360 mcg	573	528	45 (-22, 112)
720 mcg	611	563	48 (-19, 115)
1440 mcg	649	613	36 (-31, 103)

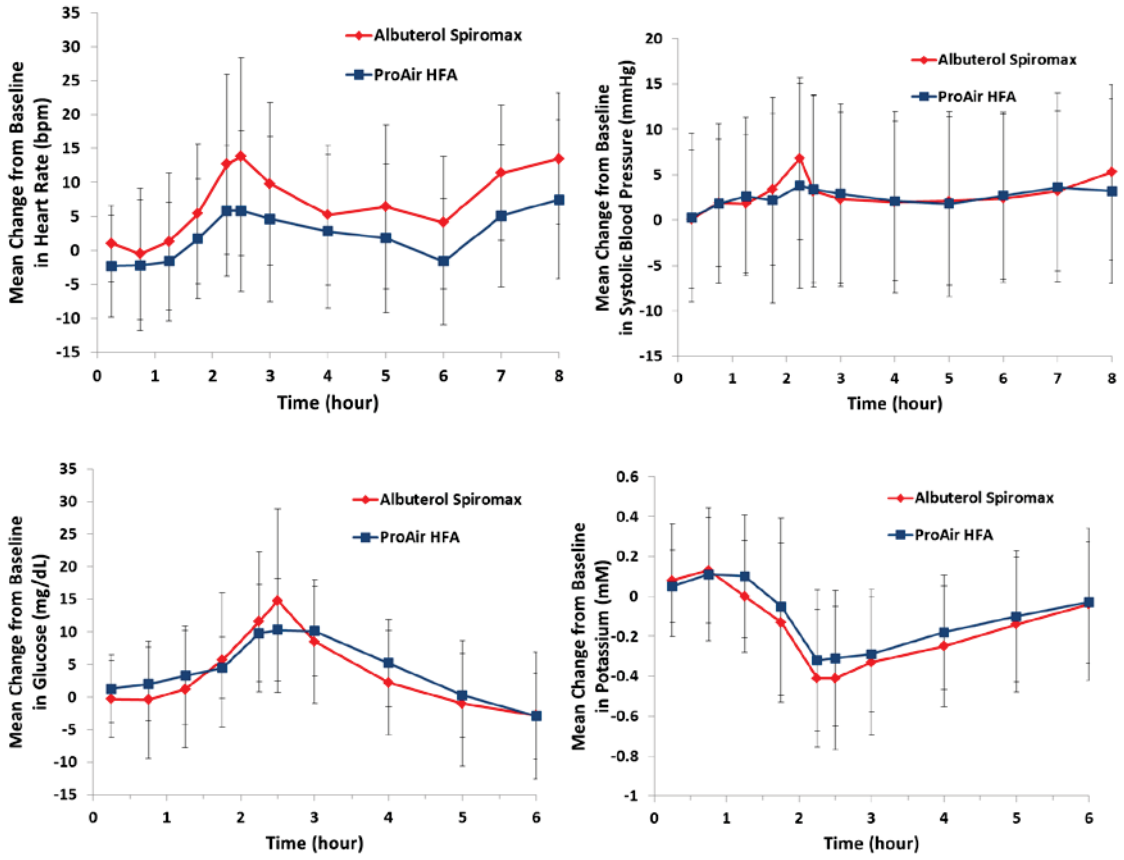

Figure 1. Arithmetic mean change from baseline in heart rate (top left panel), systolic blood pressure (top right panel), plasma glucose concentration (bottom left panel) and plasma potassium concentration (bottom right panel) following inhalation of 1440 mcg cumulative dose of albuterol via either ProAir RespiClick (same as (b) (4)) or ProAir HFA. Error bars represent standard deviation (Study 101).

Table 3. ΔFEV_1 $AUC_{0\text{-}6\ hr}$ after single dose with ProAir RespiClick dry powder inhaler (Study 201)

Treatment Arm	ΔFEV_1 $AUC_{0\text{-}6\ hr}$ L*hr	Treatment Difference (p-value) RespiClick - Placebo
ProAir RespiClick 90 mcg	1.21	0.97 (<0.001)
ProAir RespiClick 180 mcg	1.39	1.15 (<0.001)
ProAir HFA 90 mcg	1.12	0.88 (<0.001)
ProAir HFA 180 mcg	1.33	1.08 (<0.001)
Placebo	0.24	-

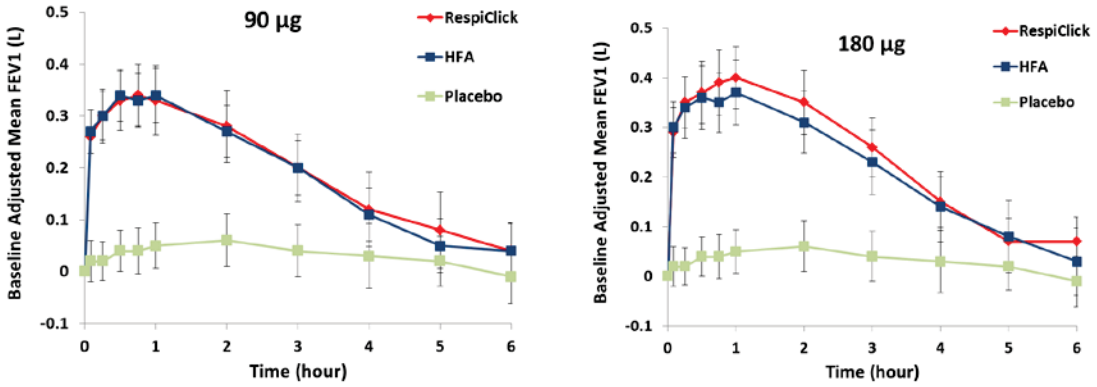

Figure 2. Arithmetic baseline-adjusted mean FEV1 following single dose with ProAir RespiClick dry powder inhaler. Error bars represent 95% CI. (Study 201)

The two confirmatory studies with ProAir RespiClick show consistent bronchodilator efficacy over placebo. The difference between ProAir RespiClick and placebo were statistically significant for the primary analysis over 12 weeks, and also at specific time points (Table 4). There was a slight blunting of FEV_1 response at day 85 compared to day 1, which is consistent with known tachyphylaxis of bronchodilator beta-agonists. These two studies are consistent with and supportive of the efficacy findings from the cumulative dose and single-dose dose-response findings described above.

Table 4. ΔFEV_1 $AUC_{0\text{-}6\ hr}$ after treatment with ProAir RespiClick dry powder inhaler at a dose of 216 mcg QID (Study 301 and 304)

	ΔFEV_1 $AUC_{0\text{-}6\ hr}$ L*hr		Treatment Difference (95% CI)
	ProAir RespiClick	Placebo	RespiClick - Placebo
Study 301, over 12 week	1.11	0.28	0.83 (0.57, 1.08) [<0.0001]
Study 301, on day 1	1.58	0.52	1.07 (0.68, 1.46) [p <0.001]
Study 301, on day 85	0.75	0.06	0.68 (0.38, 0.99) [p <0.001]
Study 304, over 12 week	1.30	0.38	0.92 (0.59, 1.24) [p<0.001]
Study 304, on day 1	1.63	0.58	1.05 (0.56, 1.55) [p <0.001]
Study 304, on day 85	1.12	0.20	0.93 (0.57, 1.28) [p <0.001]

Results of the EIB study are shown in Table 5. There was consistent protection by ProAir RespiClick of exercise-induced fall in FEV_1 for the primary analysis of maximum exercise-induced percent decrease in fall in FEV_1 (first row in Table 5), and also for patients with exercise-induced fall in FEV_1 at specific cut-off (second and third row in Table 5). The 20% cut-off is perhaps more relevant because the 20% cut-off is commonly used to define presence or absence of EIB.

Table 5. Exercise-induced FEV_1 decrease after single dose of ProAir RespiClick dry powder inhaler (Study 302)

	ΔFEV_1 $AUC_{0\text{-}6\ hr}$ L*hr		**Treatment Difference (95% CI)**
	ProAir RespiClick	**Placebo**	**RespiClick - Placebo**
Maximum percent decrease	6	22	-16 (-20, -12) [p<0.0001]
Percentage of patients with <10% decrease	84	16	68 (53, 84) [p <0.001]
Percentage of patients with <20% decrease	97	42	55 (47, 63) [p <0.001]

8. Safety

a. Safety database

The safety assessment of ProAir RespiClick is based on studies shown in Table 1. The safety database for ProAir RespiClick was adequate.

b. Safety findings and conclusion

The submitted data support the safety of ProAir RespiClick at the proposed doses based on findings from the submitted studies (Table 1), and known safety profile of inhaled albuterol. The PK and PD comparative studies (studies 101 and 201) link ProAir RespiClick to ProAir HFA, the confirmatory studies (studies 301 and 304) show safety of ProAir RespiClick, and the long-term safety studies (studies 307 and 308) further show safety of the product and reliability of the delivery device and dose counter. Overall, the safety of ProAir RespiClick as assessed in this submission, is consistent with the known profile of inhaled albuterol with no new safety signals identified. The device and dose counter performance were robust and consistent in the clinical program.

Teva conducted a comprehensive safety analysis of the available data. Safety analysis included evaluation of deaths, serious adverse events (SAEs[1]), common adverse events (AEs), assessment of adverse events of interest related to albuterol, and device performance.

[1] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Deaths, SAEs, Discontinuations due to Adverse Events:

There were no deaths in the program. A total of 15 patients reported SAEs in the program, 13 from the ProAir RespiClick treatment arm, and 2 from the placebo treatment arm. The frequencies of SAEs were comparable between treatment groups during the controlled period of studies (2 SAEs from ProAir RespiClick treatment arm, and 1 SAE from placebo treatment arm). Review of specific SAE events did not raise any safety concerns for albuterol. Discontinuations of adverse events were balanced across treatment arms and also did not raise any safety concerns for albuterol.

Common adverse events:

Common adverse events reported in the program included back pain, pain in general, gastroenteritis, sinus headache, and UTI. These are common adverse events seen in clinical studies with asthma and do not raise any safety concerns with ProAir RespiClick.

Adverse events of interest:

Adverse events of interest were identified based on the albuterol formulation, known pharmacologic actions of albuterol, and the delivery device.

Anaphylaxis and hypersensitivity were events of interest because of the presence of lactose in the formulation, and rare reports of hypersensitivity with albuterol. In the ProAir RespiClick program, one case of anaphylaxis was reported in the placebo treatment arm, which was attributed to lactose. There were four cases of hypersensitivity reactions (2 cases of urticaria, 1 case of face swelling, and 1 case of pruritus), all from patients in the ProAir RespiClick treatment arms.

Cardiovascular events were of interest because of beta-adrenergic effect of albuterol. In the overall ProAir RespiClick clinical program there were no cardiovascular or related safety findings of concern. In the cumulative dose study there was expected increase in heart rate, blood pressure, along with changes in glucose and potassium (Figure 1).

Device and dose counter reliability were assessed adequately in the clinical program, and support robustness of the device and reliability of the dose counter. Device reliability was assessed in all pivotal studies, and there was a dedicated study (study 308) that assessed dose counter reliability. From the long-term safety study (study 307), 1319 devices were collected from the 12-week double-blind treatment period (647 devices with albuterol, and 672 devices with placebo), and 1252 devices were collected from the open-label treatment period (all with albuterol). There were 14 reported cases of device malfunction and 7 broken inhalers. Testing of these devices did not reveal any overt functional or mechanical problem with the device. There were two patients who reported inadequate dose delivery, but in vitro testing of these devices did not corroborate the findings. On dose counter assessment (study 308), the counter was assessed to function as designed with very low frequency of over-count or under-count.

c. REMS/RiskMAP

(b) (4)

A REMS is not necessary for ProAir RespiClick as inhaled albuterol products have a well-established safety profile and there were no unique safety signals identified for ProAir RespiClick that would require a REMS.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discus this application as the safety and efficacy for an inhaled albuterol as a bronchodilator is well understood. There were no unique findings in the ProAir RespiClick program that would warrant a discussion at an Advisory Committee meeting.

10. Pediatric

Overall, review of the application did not show and differences in the efficacy and safety in children 12 to 18 years of age with asthma who were treated with ProAir RespiClick compared with the findings in adults. The EIB study submitted with this application enrolled only 2 patients younger than 18 years of age. Therefore, extrapolation was used to establish efficacy for the EIB indication in children 12 to 18 years of age. Studies in patients with EIB beyond what has been conducted would not be necessary as prevention of EIB response can be extrapolated down to younger age as long as the general bronchodilator response and safety for the age group has been demonstrated. This is based on the relatedness of bronchodilator response and prevention of EIB response of a drug product, prior knowledge with other inhaled albuterol products, and lack of any age-specific safety findings in patients 12 to 18 years of age with asthma who were enrolled in the ProAir RespiClick clinical program.

Teva requested a deferral for studies to assess bronchodilation in patients 4 to 11 years of age and a waiver for patients below 4 years of age. The deferred studies in patients 4 to 11 years of age are ongoing. Waiver of studies below 4 years of age is reasonable because the preferred mode of delivery of albuterol in this age group is with a nebulizer and studies with a dry powder inhaler, such as ProAir RespiClick, would be impractical. Additionally, because of the nature of the dry powder delivery device, the product cannot be used with a spacer or holding chamber. Teva's proposal for deferral and waiver was discussed at PeRC meeting on January 7, 2015, and PeRC found Teva's proposal acceptable.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit was not necessary and not conducted for this application. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Five investigators had significant financial interest in Teva. The number of subjects enrolled at these investigator sites was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that financial interest could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

Teva submitted ProAir RespiClick as the proposed proprietary name, which was accepted by DMEPA. The originally proposed proprietary name (b) (4) was not found to be acceptable by DMEPA.

b. Physician Labeling

Teva submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Division of Medical Policy Programs (DMPP), DMEPA, and OPDP. Various changes to different sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers. The Division and Teva have agreed on the final label language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

ProAir RespiClick will have a patient labeling. There will not be a Medication Guide for ProAir RespiClick.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Teva has submitted adequate data to support approval of ProAir RespiClick (albuterol sulfate) inhalation powder at a dose of 2 inhalations (108 mcg albuterol sulfate per inhalation) for use as a bronchodilator in patients 12 years of age and older, and prevention of EIB in patients 12 years of age and older. The submitted data also support the dosing recommendation that for some patients 1 inhalation may be sufficient.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of ProAir RespiClick for prevention of bronchospasm and prevention of EIB in patents 12 years of age and older. The risk of ProAir RespiClick is consistent with other inhalation albuterol products. The

benefit demonstrated was consistent across the submitted studies. The benefit of ProAir RespiClick outweighs the potential risk. ProAir RespiClick will provide a choice of dry powder albuterol inhaler to patients. Currently there is no dry powder formulation of albuterol marketed in the US.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

None, other than PREA required pediatric studies.

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/s/

BADRUL A CHOWDHURY
03/31/2015