CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	October 7, 2011
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology, Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	21-747
Applicant Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission:	April 8, 2011, (original NDA submitted on October 8, 2008)
PDUFA Goal Date:	October 7, 2011
Proprietary Name:	Combivent Respimat Inhalation Spray
Established Name:	Ipratropium bromide and albuterol sulfate
Dosage form:	Inhalation Spray
Strength:	Ipratropium bromide (monohydrate) 20 mcg and albuterol 100 mcg (equivalent to albuterol sulfate 120 mcg)
Proposed Indications:	Chronic Obstructive Pulmonary Disease
Action:	Approval

1. Introduction

Boehringer Ingelheim Pharmaceuticals, Inc., (BIPI) originally submitted this 505(b)(2) new drug application on October 8, 2008, for use of Combivent Respimat Inhalation Spray (ipratropium bromide 20 mcg and albuterol 100 mcg) [referred to as Combivent Respimat 20/100 subsequently in this document] in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. The proposed dose is one inhalation four times a day. A Complete Response action for the original submission was taken on August 7, 2009, based on indequate long-term safety data and lack of patients use and handling information for this new drug delivery "Respimat" platform. BIPI submitted this resubmission to the Complete Response on April 8, 2011, with finalized 6-month safety data and preliminary 12-month safety data as agreed with the Division before. BIPI submission also included patient use and handling of Combivent Respimat Inhalation Spray. This summary review will provide an overview of the application including original data and new safety data.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-2 adrenergic agonists, anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents, combination of long-acting beta-2 adrenergic agonists and corticosteroids, and methylxanthines. Combivent is a combination of the beta-2 adrenergic agonist albuterol, and the anticholinergic ipratropium bromide. There are two fixed dose combination products containing albuterol and ipratropium bromide currently marketed in the United

States. These are Combivent Inhalation Aerosol, a CFC-propelled metered-dose inhaler (MDI), marketed by BIPI, and DuoNeb Inhalation Solution, for use in nebulizers, marketed by Dey. Combivent Inhalation Aerosol will be removed from the market in the United States effective December 31, 2013, because of the Montreal Protocol agreements that restrict the use of ozone depleting substances such as CFCs.[1] BIPI proposes to market Combivent Respimat 20/100 as a replacement product for Combivent MDI.

(b) (4)

In 2004, BIPI completed a phase 3 clinical study to support marketing of a Combivent Respimat Inhalation Spray product containing 40 mcg of ipratropium and 200 mcg of albuterol compared to 20 mcg of ipratropium and 100 mcg of albuterol in the current product. That Combivent Respimat Inhalation Spray (referred to as Combivent Respimat 40/200 subsequently in this document) failed to show superiority of the combination product over the single ingredients in the phase 3 study. Rather the ipratropium single ingredient product produced a numerically superior FEV1 response over the combination product towards the end of the dosing interval. Pharmacokinetic data showed higher drug exposure from the Respimat product compared to the CFC-propelled product. (b) (4) . Subsequently, BIPI developed a lower albuterol strength product, Combivent Respimat 20/100, which is the subject of this application.

There are no products using the Respimat device marketed in the United States. (b) (4)

More recently BIPI developed a Respimat product containing tiotropium (Spiriva Respimat) and has conducted multiple studies, including long-term studies, with that product.

3. Chemistry, Manufacturing, and Controls

The drug substances albuterol and ipratropium bromide are well known compounds that are approved as active components in other inhalation dosage forms as single ingredient products and as combination products. The product Combivent Respimat Inhalation Spray is composed of a Combivent Respimat cartridge and a Combivent Respimat inhaler. The Combivent Respimat cartridge is a 4.5 mL plastic container (crimped into an aluminum cylinder) that contains a sterile aqueous solution of albuterol sulfate and ipratropium bromide in the excipients benzalkonium chloride (b) (4) edetate disodium (b) (4) water for injection, and hydrochloric acid (b) (4) . Combivent Respimat Inhalation Spray will be supplied in a carton

[1] Use of ozone-depleting substances; Removal of essential-use designation. Final Rule published in 75 Federal Register 19213; April 14, 2010.

containing one Combivent Respimat cartridge and one Combivent Respimat inhaler. Prior to first use, the patient or care provider will place the Combivent Respimat cartridge into the Combivent Respimat inhaler and prime the unit. To actuate the product, the patient will turn the bottom of the inhaler 180°, which will cause a small volume of the formulation to be metered into a chamber and compress a spring. The patient will then press a trigger, which will release the spring to provide mechanical energy that will propel the formulation through a nozzle (b) (4) and create an aerosol cloud that will emit gently from the mouthpiece of the product. The assembled Combivent Respimat Inhalation Spray will deliver 120 metered actuations. After the 120 metered actuations are delivered, a locking mechanism will be engaged and no more actuations can be dispensed. The Combivent Inhalation Spray should be discarded after the locking mechanism is engaged or 3 months after first use, whichever comes first.

BIPI submitted adequate stability data to support an expiry of 36 months for the drug product that consists of the Respimat device and the unassembled cartridge containing the formulation (stored separately), and an in-use period of 3 months after the cartridge is assembled with the Respimat Inhaler.

The steps needed to use the product and the internal mechanisms of the product are rather complex. (b) (4) a consultation with CDRH was obtained because of the complexity of the product. The CDRH review did not raise any concern with the manufacturing and quality of the product, but raised concerns on performance testing with regards to human factors. BIPI has performed adequate specific patient handling studies with Respimat. In two phase 3 studies conducted for Combivent Respimat Inhalation Sprays and in two phase 3 studies conducted for Spiriva Respimat, patient handling of the device was assessed and representative devices used in clinical studies were tested for in vitro performance characteristics. These assessments did not suggest any significant problems with patient handling, performance, and robustness of the Respimat device. The only issue identified was that some older patients or patients with hand joint problems may need assistance with initial assembly of the cartridge and the Respimat Inhaler.

The device had undergone some changes during clinical studies. The phase 3 clinical studies were conducted with the A4 version of the Respimat, and the to-be-marketed product is the A5 version. (b) (4) BIPI has submitted adequate in vitro data to link the two versions of the device.

The drug substance and drug product including the Respimat device are manufactured at a Boehringer Ingelheim facility in Ingelheim am Rhein, Germany. 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 new significant pharmacology and toxicology studies were submitted with this application. BIPI submitted inhalation toxicity studies using an aqueous albuterol solution containing the excipient benzalkonium chloride for 2 weeks in rats and 3 months in dogs, and a 13-week inhalation toxicity study of EDTA and benzalkonium chloride in rats. These studies did not reveal any new safety findings of concern.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic considerations for albuterol and ipratropium have been previously characterized as single ingredient products and also as combination products. BIPI obtained blood samples from the pivotal phase 3 study to assess comparative bioavailability between Combivent Respimat 20/100 and CFC-propelled Combivent Inhalation Aerosol (36/206 mcg) at steady state. For ipratropium, the two combination products were comparable for all PK parameters. For albuterol, the systemic exposure with Combivent Respimat 20/100 was about 25% less than CFC-propelled Combivent Inhalation Aerosol. These findings suggest that Combivent Respimat 20/100 does not possess any additional systemic drug burden for both drug components compared to the marketed Combivent Inhalation Aerosol product.

6. Clinical Microbiology

The inhalation solution is manufactured using (b) (4)

(b) (4)

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The studies are shown in Table 1 in two groupings – those submitted with the original NDA, and the long-term safety study submitted with the Complete Response.

Table 1. Combivent Respimat Inhalation Spray clinical studies

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N$ (ITT)	Study Year#	Countries
Submitted with the original NDA							
1012.56	Efficacy and safety	12 weeks	≥ 40	CR 20/100 mcg CA 36/206 mg IR 20 mcg	474 482 468	2008	USA, Europe, Latin America, Asia
1012.46	Efficacy and safety	12 weeks	≥ 40	CR 40/200 mcg CA 36/206 mg IR 40 mcg	343 180 250	2004	USA

				Pbo	335		
244.2447	Dose ranging, Crossover	Single dose	≥ 40	IR 10 mcg IR 20 mcg IR 40 mcg IR 80 mcg IR 160 mcg	116	1996	USA
243.7	Dose ranging, Crossover	Single dose	≥ 40	AR 25 mcg AR 50 mcg AR 100 mcg AR 200 mcg Pbo	62	1997	USA
244.2484	Safety	6 months	≥ 40	IR 20 mcg IR 40 mcg Atr 36 mcg Pbo R Pbo Atr	180 177 172 58 59	1999	Canada
Submitted with the Complete Response							
1012.62	Long term safety	12 months	≥ 40	CR 20/100 mcg CA 36/206 mg Atr + Albuterol MDIs	157 156 157	2010	USA

* CR = Combivent Respimat Inhalation Spray; CA = Combivent Inhalation Aerosol, CFC-propelled; IR = Ipratropium Respimat Inhalation Spray; AR = Albuterol Respimat Inhalation Spray; Atr = Atrovent Inhalation Aerosol; Pbo = Placebo; Pbo R = Placebo Respimat; Pbo Atr = Placebo Atrovent
§ For study 1012.56 the N for "PFT Full Analysis Set", which excludes subjects from a center that had data not verifiable at the source. The ITT same sizes were 493, 498, and 489, for the three groups, respectively.
# Year study subject enrollment ended

Of the listed studies noted above, study 1012.56 and study 1012.62 are relevant to this application from efficacy and safety standpoints. Study 1012.46 was conducted with a higher dose of Combivent Respimat and is relevant from a safety standpoint. The other three studies submitted with the original NDA are of remote relevance and are not discussed further in this review. Of the other studies, two were single dose studies with single ingredient products to guide selection of the doses (studies 244.2447, and 243.7), and the other one was a safety study conducted with single ingredient ipratropium bromide (244.2484).

The design and conduct of study 1012.56 and study 1012.62 are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

b. Design and conduct of study 1012.56 and study 1012.62

Study 1012.56 was randomized, double-blind, double-dummy, parallel-group in design, conducted in patients with COPD. The study had a 2-week run-in period, followed by a 12-week double-blind treatment period. The objective of the study was to demonstrate the contribution of albuterol and ipratropium in the combination product. The study did not employ a typical factorial design, but rather used CFC-propelled Combivent Inhalation Aerosol as an active comparator and used a non-inferiority approach. This approach was acceptable because of prior data that exist with the single ingredient products and combination products containing these active ingredients. The Division and BIPI agreed upon design and conduct of the study and non-inferiority margin.

The primary efficacy endpoints were based on timed serial spirometry for FEV1 after 12-weeks of treatment (day 85). The mean change from baseline in FEV1 calculated as area under the curve (AUC) of the FEV1 change from the test day baseline on day 85 divided by the time period of the AUC was used as the primary efficacy endpoint for treatment comparisons. There were 3 pre-specified primary efficacy endpoint comparisons on day 85 as follows. (1) Mean FEV1 using AUC over 0 to 6 hours to determine non-inferiority of Combivent Respimat 20/100 to Combivent Inhalation Aerosol. The non-inferiority margin was 0.05 L for the 95% confidence interval, i.e., the lower bound of the 2-sided 95% confidence interval for the mean FEV1 difference, Combivent Respimat 20/100 minus Combivent Inhalation Aerosol, is above -0.05 L. The intent of this comparison was to assess comparability of the two products. (2) Mean FEV1 using AUC over 0 to 4 hours to determine superiority of Combivent Respimat 20/100 to ipratropium Respimat 20 mg. The intent of this comparison was to show contribution of the albuterol component. (3) Mean FEV1 using AUC 4 to 6 hours to determine non-inferiority of Combivent Respimat 20/100 to ipratropium Respimat 20 mcg. The non-inferiority margin was 0.05 L for the 95% confidence interval. The intent of this comparison was to show contribution of the ipratropium component. Safety assessments in the study included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, and ECG.

Study 1012.62 was a 48-week, randomized, open-label safety and patient acceptability study of Combivent Respimat 20/100 in comparison to Combivent CFC Inhalation Aerosol (36/206 mcg) and the free combination of Atrovent HFA (ipratropium bromide 34 mcg) Inhalation Aerosol and albuterol HFA Inhalation Aerosol (180 mcg) in patients with COPD. A total of 470 patients were randomized into following 3 treatment groups as shown in Table 1. The study subjects were to visit clinical centers 7 times during this 48-week study. Detailed written instructions and training for the use of the MDI and Respimat inhalers were given to the patient on enrollment. Patients who were randomized to Atrovent HFA/Ventolin HFA were instructed to use Ventolin first, then Atrovent. Patients were requested to self-administer the inhalations from the Respimat inhaler or MDI 4 times daily at approximately equally spaced intervals: upon arising, mid-day, early evening, and prior to retiring. At all subsequent visits, the investigator or qualified study personnel observed the inhalation procedure and reinforced the correct inhalation technique. The patient recorded the daily doses (number of actuations) of test medication in a patient specific diary card. At each clinic visit, oral inhalation of 2 puffs of the Combivent CFC Inhalation Aerosol, 2 puffs of Atrovent HFA and 2 puffs of albuterol HFA, or 1 actuation of the Combivent Respimat 20/100 was to be self-administered by the patient under the direct supervision of the investigating physician or qualified study personnel. Any inhaler that was reported to have malfunctioned by the patient or study staff was to be returned to BI for further investigation. Treatment compliance was checked by the number of actuations of study medications taken into the Daily Diary Card.

c. Efficacy findings and conclusions

The clinical program supports efficacy of Combivent Respimat Inhalation Spray as a bronchodilator in patients with COPD.

In the pivotal efficacy study the 3 pre-specified primary efficacy endpoints were met (Table 2). Combivent Respimat 20/100 was non-inferior to Combivent Inhalation Aerosol at 0 to 6 hours, superior to ipratropium Respimat at 0 to 4 hours showing the contribution of albuterol and non-inferior to ipratropium Respimat at 4 to 6 hours showing the contribution of ipratropium. The effect was consistent at other treatment days during the study (Figure 1). The secondary efficacy variables were also supportive (data not shown in this review).

A single study using the non-inferiority approach in this specific program is adequate to conclude efficacy of Combivent Respimat 20/100 as a bronchodilator and to establish contribution of albuterol and ipratropium in the combination product. The reasons are established efficacy of both albuterol and ipratropium as bronchodilators in COPD patients, and the established efficacy of Combivent Inhalation Aerosol, a combination product with the same active ingredients that was also used as an active comparator in this study. Furthermore, this study was built on top of study 1012.46 that used Combivent Respimat 40/200, which showed efficacy, however, there were issues including adequate albuterol efficacy. In study 1012.46, the single ingredient ipratropium produced a numerically higher in FEV1 response than Combivent Respimat 40/200 towards the end of the dosing interval. For Combivent Respimat 20/100, the combination product was non-inferior to ipratropium on pre-specified margin for the whole dosing interval (0 to 6 hours) and for the last two hours of the dosing interval (4 to 6 hours). The non-inferiority margin was set by taking into consideration the results of 1012.46.

Table 2. Summary of primary efficacy endpoints, mean FEV1 AUC in Liters (L) on test day 85

		n	Mean in L	Treatment difference in L	
				Mean	95% CI
FEV1 AUC 0-6 hr	Combivent Respimat 20/100	474	0.145	-0.003	-0.022, 0.015
	Combivent Inhalation Aerosol	482	0.149		
FEV1 AUC 0-4 hr	Combivent Respimat 20/100	474	0.189	0.047	0.028, 0.066
	Ipratropium Respimat 20	468	0.142		
FEV1 AUC 4-6 hr	Combivent Respimat 20/100	447	0.056	-0.017	-0.039, 0.005
	Ipratropium Respimat 20	427	0.073		

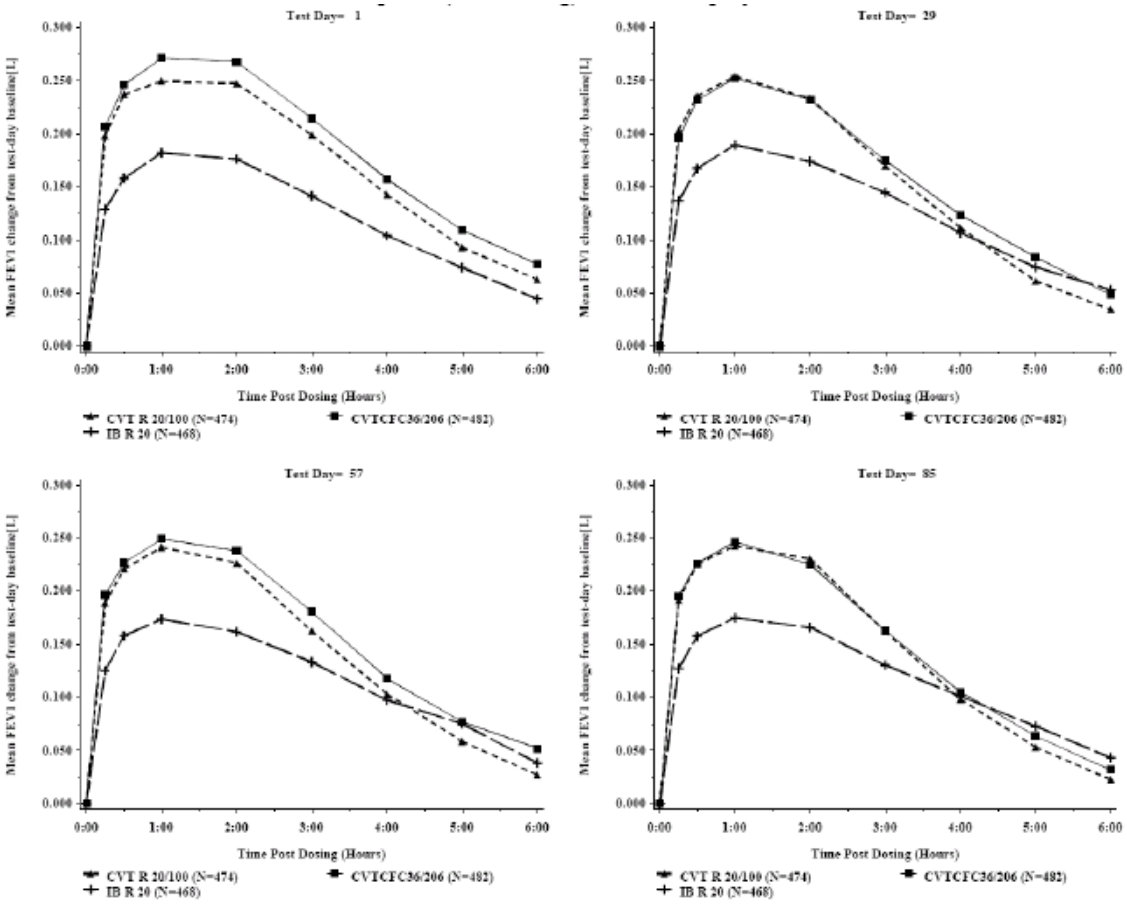

Figure 1. FEV1 time profile change on days 1, 29, 57, and 85

8. Safety

a. Safety database

The safety assessment of Combivent Respimat for COPD patients is based on studies shown in Table 1. The safety database with the addition of the safety study submitted with this Complete Response is adequate.

b. Safety findings and conclusion

During the review of the original NDA, the safety database for Combivent Respimat included data from the pivotal efficacy and safety studies 12-week in duration (Table 1). There were no long-term safety and patients use information data with Combivent Respimat.

In the original NDA, there were a total of 11 deaths in the clinical studies. The number of deaths was generally similar across treatment groups and from causes expected in this study population. The percentages of patients with serious adverse events were higher in the Combivent Inhalation Aerosol treated patients (6.7%) compared to the Combivent Respimat Inhalation Spray treated patients (2.9%). The pattern of serious adverse events and other adverse events did not raise any new safety concerns.

The main safety concern identified during review of the original NDA was the lack of long-term safety data and patient use information with Combivent Respimat Inhalation Spray. Although Combivent Inhalation Aerosol was approved with no long-term study (no 6-month of 12-month study), the device for Combivent Inhalation Aerosol is the typical press and breathe metered dose inhaler that has been in the market for a long time and is a familiar device for patients. This was not the case with Combivent Respimat. There are no products using the Respimat device marketed in the United States. (b) (4)

(b) (4)

(b) (4)

BIPI later developed a Respimat product containing tiotropium (Spiriva Respimat) and conducted multiple studies, including long-term studies, with that product, but Spiriva Respimat is not a marketed product in the United States.

During review of the original NDA, the lack of long-term safety with Combivent Respimat Inhalation Spray as an approvability concern was discussed with BIPI. BIPI proposed to conduct a 12-month safety and efficacy study designed primarily to assess safety and device handling issues with Combivent Respimat 20/100 in COPD patients. The study was designed to compare Combivent Respimat 20/100 to Combivent Inhalation Aerosol and also to two single ingredient albuterol and ipratropium products given together. The study was designed to provide long-term safety data with Combivent Respimat 20/100 in COPD patients, and also to provide data to support Combivent Respimat 20/100 as a replacement product for Combivent Inhalation Aerosol. The study protocol was reviewed during the original NDA application review period and comments were transmitted to BIPI.

BIPI has submitted the results of the new safety study 1012.62 with this Complete Response (Table 1). As agreed before, BIPI submitted finalized 6-month safety data and preliminary 12-month safety data. The data from this new study is assuring of safety, patient acceptance and usability of the Respimat device as described below.

In the safety study 1012.62 there were 3 deaths during treatment period and another death during the follow-up period. Three of the deaths occurred in the free combination of Atrovent and albuterol MDIs and one in Combivent Respimat. The causes of deaths were expected for this patient population. Serious adverse events (SAEs) occurred in a total of 54 patients (11.6%) across all treatment groups. The frequency of SAEs across treatment groups was similar for the three groups. The pattern of serious adverse events and other adverse events did not raise any new safety concerns.

In study 1012.62, patient acceptability was assessed between the Combivent Respimat 20/100 mcg Inhalation Spray and other treatment groups using the Patient Satisfaction and Preference Questionnaire (PASAPQ) at 24 weeks. The answers were measured using a 7-point scale for questions 1 to 14 (1 means very dissatisfied and 7 means very satisfied) and a 100-point scale for question 15. Secondary analyses included dropout rate, Clinical COPD questionnaire (CCQ), Physician's Global Evaluation, COPD exacerbation, rescue medication use, and pulmonary function. The 24-week data showed that the scores of performance and patient satisfaction in the Combivent Respimat 20/100 Inhalation Spray group, as measured by the Patient Satisfaction and Preference Questionnaire (PASAPQ) performance domain, were higher than that in the Combivent CFC Inhalation Aerosol and the free combination of Atrovent HFA (ipratropium bromide) Inhalation Aerosol and albuterol HFA inhalation aerosol groups suggesting that patients did not have major issues using and accepting the new inhaled drug delivery device. In addition, there were no differences in overall patient satisfaction between Combivent Respimat 20/100 and the Combivent CFC or Atrovent and Ventolin free combination groups. Patients were also similarly willing to continue on the treatment when receiving the Combivent Respimat 20/100 product compared to the Combivent CFC product. In addition to the 24-week data, as per an agreement with the Division, BIPI submitted preliminary data for the remaining 6 months of the study in June 2011. Review of the data showed that the safety findings were consistent with the interim 24-week data with no unexpected safety signals or issues of patient use or satisfaction for Combivent Respimat (20/100 mcg) Inhalation Spray. Also, review of post-marketing experience reports covering the 6-year period between 2004 and 2010 for two Respimat product marketed in Europe (Berodual Respimat and Spiriva Respimat) did not reveal any new safety signals or patient acceptability/acceptance issues for the 2 Respimat products.

c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended for Combivent Respimat. Other products containing albuterol or ipratropium or combination of both do not have REMS and RiskMAP, and no new safety findings were seen for Combivent Respimat 20/100 that will require REMS or RiskMAP.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Albuterol and ipratropium are well studies molecules, and there are other fixed dose combination product containing these two active ingredients approved and marketed in the US with similar indication. The efficacy and safety findings seen in the clinical program were fairly obvious. There were no issues that warrant discussion at an advisory committee meeting.

10. Pediatric

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD. This application was discussed with PeRC and it

was decided that a full waiver should be granted because studies would be impossible or highly impracticable because the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited four sites recommended by the review team. These sites enrolled the largest number of patients in the pivotal phase 3 study. Audit of these sites did not show any major irregularities. 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. A total of 7 investigators had significant financial interest in BIPI. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that these financial interests could have influenced or biased the results of these studies.

c. Other

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

12. Labeling

a. Proprietary Name

There are no issues with the proprietary name as the root name Combivent is already in the market for a similar product, which will be removed from the market in favor of this product. The qualifiers for the device name Respimat, and dosage form of Inhalation Spray are also acceptable.

b. Physician Labeling

BIPI submitted a label in the Physician's Labeling Rule format that generally contains information consistent with other similar products. The label was reviewed by various disciplines of this Division, OSE, and DDMAC. Various changes to different sections of the label were recommended to reflect the data accurately and better communicate the findings to health care providers. The Division and BIPI have agreed on the final labeling 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

The Patient Counseling Information was reviewed and found to be acceptable. The product does not need a Medication Guide.

13. Action and Risk Benefit Assessment

a. Regulatory Action

BIPI has submitted adequate data to support approval of Combivent Respimat Inhalation Spray (ipratropium bromide 20 mcg and albuterol 100 mcg) for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. The regulatory action for this application will be Approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment supports approval of Combivent Inhalation Spray for use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who requires a second bronchodilator. The major safety concern with this product is device usability and reliability, which BIPI have adequately addressed. The overall safety data for this product do not show any findings that are unique or new to this product. From an efficacy standpoint, the clinical program showed efficacy of the product and contribution of albuterol and ipratropium. The submitted data also support an acceptable risk-benefit assessment for the Combivent Respimat 20/100 Inhalation Spray as a replacement product for the currently marketed Combivent Inhalation Aerosol CFC-containing MDI.

c. Post-marketing Risk Management Activities

There are no recommendations for any additional post-marketing risk management activities beyond standard pharmacovigilance.

d. Post-marketing Study Commitments

There are no recommendations for post-marketing commitments.

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BADRUL A CHOWDHURY
10/07/2011