

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 19, 2011
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	21-747
Supplement#	
Applicant	Boehringer Ingelheim
Date of Submission	April 8, 2011
PDUFA Goal Date	October 7, 2011
Proprietary Name / Established (USAN) names	Combivent Respimat Inhalation Spray/ipratropium bromide and albuterol sulfate
Dosage forms / Strength	Inhalation Spray/ Ipratropium bromide (monohydrate) 20 mcg and albuterol 100 mcg (equivalent to albuterol sulfate 120 mcg)
Proposed Indication(s)	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.
Recommended:	Approval

1. Introduction

This is a complete response submission by Boehringer Ingelheim Pharmaceuticals, Inc., (BI) to support the approval of Combivent Respimat Inhalation Spray (ipratropium bromide 20 mcg and albuterol 100 mcg) [Combivent Respimat 20/100] for use in patients with chronic obstructive pulmonary disease (COPD) who are on a regular aerosol bronchodilator and continue to have evidence of bronchospasm and require a second bronchodilator. The proposed dose is one inhalation four times a day. The initial submission for this 505(b)(2) new drug application was on October 8, 2008. The Division took a Complete Response action on August 7, 2009, based on the application lacking adequate long-term safety and patient use information for this new drug delivery “Respimat” platform. In this complete response submission, BI has submitted finalized 6-month safety data and preliminary 12-month safety in order to address the deficiency noted in the CR letter. This review will provide an overview of the entire application, with a focus on the newly submitted long-term clinical safety data.

2. Background

Combivent is a combination of the beta-adrenergic agonist albuterol and the anticholinergic ipratropium bromide which is indicated as a bronchodilator to relieve airflow obstruction in patients with COPD. It is one of two such combinations marketed in the United States; Combivent Inhalation Aerosol is a CFC-propelled metered dose inhaler while an albuterol and ipratropium bromide inhalation solution that is delivered via a compressed air nebulizer system is marketed by Dey. As a result of the Montreal Protocol agreements that restrict the use of ozone depleting substances such as CFCs, the CFC-containing Combivent Inhalation

Aerosol is proposed to be removed from the market in the United States by December 31, 2013. Because the Respimat delivery system does not utilize CFCs as a propellant, it is BI's intention that the proposed Combivent 20/100 Respimat Inhalation Spray product will be the replacement product for the Combivent MDI.

 (b) (4)
concentrated on the
Combivent and other BI inhaled products (Spiriva). There have been numerous interactions between BI and the Agency on the development program for Combivent Respimat.

BI submitted a protocol for Special Protocol Assessment (SPA) for a phase 3 pivotal study for a Combivent Respimat product containing 40 mcg ipratropium bromide and 200 mcg albuterol (Combivent Respimat 40/200) on November 7, 2001. This initial pivotal study using the Combivent Respimat 40/200 product was completed in 2003. However, the results of the this study did not support the efficacy of Combivent Respimat 40/200 because the study did not demonstrate the superiority of the combination product over the single ingredients as required by the regulation set forth in 21 CFR 300.50. Specifically, in that study the ipratropium single ingredient product produced a numerically superior FEV₁ response over the combination product towards the end of the dosing interval. Following multiple interactions with the Division (Type C meeting January 2006, End-of phase 2 meeting May 2006) which focused on the efficacy aspect of the application, BI revised the phase 3 program and designed a second efficacy study to address the combination rule using a lower nominal doses of ipratropium bromide (20 mcg) and albuterol (100 mcg) for the Combivent Respimat product. The Division and BI agreed with the final design of the study, including efficacy endpoints, and statistical analysis. Subsequently, another PreNDA meeting was held on February 8, 2008, with the original NDA application subsequently submitted on October 8, 2008. While this redesigned second pivotal study supported the efficacy of the Combivent Respimat 20/100 product, the Division took a Complete Response action on August 7, 2009, based on the application lacking adequate long-term safety and patient use information for the new drug delivery "Respimat" platform. In this complete response submission, BI has submitted finalized 6-month safety data and preliminary 12-month safety in order to address the deficiency noted in the CR letter.

This is a 505(b)(2) new drug application in which BI has referenced the several drug products which are no longer marketed and their respective NDAs have been withdrawn including : NDA 17559 Proventil inhalation aerosol, NDA 17853 Proventil oral tablets, NDA 19243 Proventil inhalation solution, NDA 18473 Ventolin inhalation aerosol, NDA 19112 Ventolin oral tablets, and NDA 19269 Ventolin inhalation solution. From a regulatory standpoint it should be noted that none of these products were withdrawn from the market for reasons of patient safety or efficacy, thus, the programs remain able to be referenced to support 505(b)(2) applications.

3. CMC/Device

There are no CMC issues that preclude approval as all CMC deficiencies listed in the CR letter have been satisfactorily addressed in the resubmission. Initially there was an overall recommendation of Withhold from the Office of Compliance due to significant GMP violations from the drug substance testing site (b) (4), however the issue has been resolved by changing the drug microbiology and sterility testing site to (b) (4). All DMFs have been reviewed and are acceptable.

Combivent Respimat contains albuterol and ipratropium bromide which are well known drug substances that are approved as active components in other inhalation dosage form medications. The Respimat device is a new delivery device platform for inhaled drug products. It is a cylindrical shaped plastic inhalation device with a gray colored body and a clear base into which fits an aluminum cylindrical canister covered with a tamper resistant seal on the cap (Figure 1).

The formulation is a sterile aqueous solution comprised of albuterol sulfate and ipratropium bromide as active ingredients, benzalkonium hydrochloride (b) (4), and EDTA (sodium edetate) (b) (4), water for injection, and hydrochloric acid (b) (4).



Figure 1. Combivent Respimat Device

Prior to using the product for the first time, the patient inserts the cartridge into the inhaler device at which time the seal at the top of the cartridge is pierced by the capillary tube of the Respimat device.

The Respimat drug product produces an aerosol by mechanical means; there is no propellant. The drug product must be primed before its first use, and re-primed if not used for specified intervals; this is described in the draft labeling. To use the device, the patient twists the base of the inhaler which compresses a spring and draws a metered volume (b) (4) of solution

from the cartridge into the dosing chamber of the inhaler. When the inhaler is actuated, a spring is released (b) (4)

(b) (4) to form a slow-moving aerosol cloud which is inhaled by the patient.

One actuation of Combivent Respimat delivers from the mouthpiece 20 µg ipratropium bromide monohydrate and 100 µg albuterol (equivalent to 120 µg albuterol sulfate). The delivered volume of a single actuation is 11.4 mL. A clinical dose consists of a single actuation. The drug product is labeled with 120 actuations for commercial samples and 60 actuations for physician samples. The minimum fill of the reservoir during manufacturing is (b) (4) which represents an overfill of about (b) (4). This (b) (4) overfill is not available to the patient since the device for the commercial product locks after approximately 120 actuations are dispensed. The device and cartridge container are both disposed of after device lock-out or after 3 months after the cartridge has been inserted into the device. The Respimat device contains an actuation counter.

It is physically possible to remove or switch cartridges in the Respimat device, however, since the drug product locks after the labeled number of doses, there is an absolute limit on a patient trying to reuse the device with another cartridge.

Because the steps needed to use the Respimat platform and the internal mechanisms of the product are rather complex, the Division consulted with CDRH (b) (4). While there were no issues with the quality of the Respimat product they raised concerns on performance testing with regards to human factors. The Division believes this issue has been adequately addressed by the Applicant. Patient handling was assessed in two phase 3 studies conducted for Combivent Respimat Inhalation Spray, in two phase 3 studies conducted for Spiriva Respimat, and in the Combivent Respimat one-year safety and patient usability study submitted with this complete response submission. These assessments did not suggest any significant problems with patient handling, performance, and robustness of the Respimat device.

Stability data are available through 36 months and support the proposed shelf life of 36 months.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding pharmacology/toxicology issues. The toxicology data for albuterol and ipratropium bromide alone and in combination have been previously characterized in the preclinical review for the related Combivent Inhalation Aerosol product. There was no new preclinical information about the active ingredients albuterol and ipratropium bromide. The application included inhalation toxicity studies (2 weeks in rats and 3 months in dogs) of an aqueous albuterol solution containing benzalkonium chloride (new excipient), and a 13-week inhalation toxicity study of EDTA and benzalkonium chloride in rats. These studies did not reveal any safety concerns.

5. Clinical Pharmacology/Biopharmaceutics

The general clinical pharmacology and pharmacodynamic properties for albuterol and ipratropium have been previously well characterized. For this novel Respimat delivery device program, the initial doses of albuterol and ipratropium bromide were based on clinical trials with single albuterol and ipratropium Respimat devices and a dose combination of 40 mcg of ipratropium bromide and 200 mcg of albuterol was chosen for subsequent testing in the initial Phase 3 trial (study 1012.46). However, while the efficacy results from the trial showed that the FEV1 response of Combivent Respimat 40/200 was comparable to Combivent CFC-MD 36/206 mcg, the PK evaluations revealed considerably higher (3-4 times for ipratropium and 1.5 times for albuterol) steady state systemic exposures with the Combivent Respimat inhaler in comparison to the Combivent CFC-MDI inhaler. These results prompted selection of a lower combination dose of Combivent Respimat (20 mcg of ipratropium bromide and 100 mcg of albuterol) for testing in a subsequent Phase 3 trial (study 1012.56). In that trial, the two Respimat and CFC-MDI Combivent products were comparable for all PK parameters for ipratropium bromide while for albuterol, the systemic exposure with Combivent Respimat 20/100 was less than the currently marketed Combivent CFC MDI product. These findings suggest that Combivent Respimat 20/100 should not possess any additional systemic drug burden for both drug components compared to the marketed Combivent Inhalation Aerosol product.

6. Clinical Microbiology

The product is a sterile solution and the sterilization method is (b) (4) (b) (4)
There are no outstanding microbiology issues.

7. Clinical/Statistical- Efficacy

The efficacy of Combivent Respimat 20/100 Inhalation Spray and its non-inferiority to Combivent CFC Inhalation Aerosol, was demonstrated during the first review cycle. At that time in the original NDA submission, the Division cited 5 clinical studies that formed the basis of the review and supported the efficacy of Combivent Respimat 20/100 as a combination product bronchodilator in patients with COPD (Table 1). These studies included

- Two 12-week efficacy and safety studies, of which one is the pivotal efficacy study and the other, a supporting efficacy and safety study (with a higher nominal dose of Combivent Respimat)
- Two single-dose, dose ranging studies in COPD patients (one each with albuterol and ipratropium)
- One 6-month safety study with ipratropium delivered via the Respimat inhaler
- One 48-week safety study with Combivent 20/100 Inhalation Spray at the proposed dose to be marketed

Table 1. Combivent Respimat Inhalation Spray Clinical Studies

Study ID	Study type	Treatment groups	Treatment duration	Study design	Number (ITT)	Countries/Study Enrollment Complete
1012.56	Efficacy and safety	Combivent R 20/100 Ipratropium R 20 Combivent MDI 36/206	12 weeks	Randomized, double-blind, placebo-, active-controlled	1480*	USA, EU, Latin America, Asia/2008
1012.46	Efficacy and safety	Combivent R 40/200 Ipratropium R 40 Combivent MDI 36/206 Placebo	12 weeks	Randomized, double-blind, placebo-, active-controlled	1118	USA/2004
244.2484	Long-term safety for Ipratropium Respimat	Ipratropium R 20, 40 Atrovent MDI 36	6 months	Randomized, double-blind, placebo-, active-controlled	646	Canada/1999
244.2447	Ipratropium dose ranging	Ipratropium R 10, 20, 40, 80, 160 Atrovent MDI 18, 36 Placebo	Single dose	Crossover	116	USA/1999
243.7	Albuterol dose ranging	Albuterol R 25, 50, 100, 200 Albuterol MDI 90, 180 Placebo	Single dose	Crossover	62	USA/1997
1012.62	Long-term safety for Combivent Respimat	Combivent R 20/100 Combivent MDI 36/206 Atrovent MDI 36 + Albuterol 180	48 weeks**	Randomized, open-label	470	USA/2010

R=Respimat, MDI=Metered Dose Inhaler

*While the ITT population was 1480, for study 1012.56 the N for “PFT Full Analysis Set” was 1460 as it excluded 20 subjects from a center whose data could not be verified.

** Interim 24-week safety data and draft 48-week safety data submitted

In addition to the studies submitted during the first review cycle, as part of BIs complete response submission, 6-month safety data were supplied from study 1012.62, a long term (48-week) safety and patient acceptability study meant to address the lack of long-term safety information for the Combivent Respimat 20/100 drug product noted as a deficiency in the Division’s Complete Response Letter (Table 1).

Of the studies listed above, study 1012.56 is most relevant to this application from an efficacy standpoint as it is the single pivotal study and it demonstrated the efficacy of Combivent Respimat 20/100 Inhalation Spray and its non-inferiority to Combivent CFC Inhalation Aerosol, the marketed product which it will replace. Study 1012.46 was conducted with a higher dose of Combivent Respimat and is relevant primarily from a safety standpoint. 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) which provided patient use information for the Respimat inhalation spray delivery platform.

Following is a brief review of the design and results of study 1012.56, which forms the basis for determining the efficacy of Combivent Respimat 20/100.

Study 1012.56

This 12-week study was conducted to evaluate the bronchodilator efficacy (and safety) of Combivent Respimat 20/100 in patients with COPD. As a combination product containing ipratropium bromide and albuterol, the typical study design to satisfy the combination rule (21 CFR 300.50) would have been a full factorial design where Combivent Respimat was compared to each of its individual active ingredients and demonstrate contribution by demonstrating superiority of the combination to each of the individual components for the claimed benefit. The design of this study was different in that (a) albuterol single ingredient was not included in the study and (b) a non-inferiority design was used. With this approach, the study was designed to fulfill three efficacy objectives all of which had to be met in order to support efficacy. These efficacy objectives were selected to take into account the known duration of action of the individual ingredients albuterol (up to 4 hours), and ipratropium (up to 6 hours), and the established bronchodilator efficacy of Combivent CFC-MDI.

Conceptually, albuterol (in the combination) would be expected to work up to 4 hours therefore, a comparison of

Combivent Respimat to Ipratropium Respimat over the last 2 hours of the dosing interval (4 -6 hours) should demonstrate non-inferiority. Using a similar rationale, the comparison of Combivent Respimat to Ipratropium Respimat over the first 4 hours (0 – 4 hours) should demonstrate superiority of Combivent Respimat to Ipratropium Respimat alone and therefore, confirm the efficacy contribution of the albuterol component to the bronchodilator efficacy of Combivent. With this rationale, the study had three co-primary efficacy variables and comparisons as follows:

The three primary efficacy variables were defined as:

- The mean FEV₁ from 0-6 hours post dose, defined as the AUC of the change from test-day baseline in FEV₁ over 0- 6 hours post-dose divided by 6 hours (FEV₁AUC_{0-6 hr})
- The mean FEV₁ from 0-4 hours post-dose defined as the AUC of the change for test-day baseline in FEV₁ over 0 -4 hours post-dose divided by 4 hours (FEV₁AUC_{0-4hr})
- The mean FEV₁ from 4-6 hours post-dose defined as the AUC of the change from test-day baseline in FEV₁ over 4-6 hours post-dose divided by 2 hours (FEV₁AUC_{4-6hr})

Test-day baseline was the FEV₁ recorded prior to inhaling the dose of randomized medication on the test day.

The three primary efficacy comparisons were:

- Non-inferiority of Combivent Respimat to Combivent CFC-MDI in FEV₁AUC_{0-6 hr} on Test Day 85

- Superiority of Combivent Respimat to Ipratropium Respimat monotherapy in $FEV_1AUC_{0-4\text{ hr}}$ on Test Day 85 (this comparison would demonstrate the contribution of albuterol in the combination product)
- Non-inferiority of Combivent Respimat to Ipratropium Respimat monotherapy in $FEV_1AUC_{4-6\text{ hr}}$ on Test Day 85 (this comparison would demonstrate the contribution of ipratropium bromide in the combination product)

BI proposed a non-inferiority margin of 50 ml to which the Division concurred. Secondary efficacy endpoints included FEV_1AUC on Days 1, 29, and 57, and FEV_1 measures to assess time to onset of bronchodilation and duration of response, PEF, as needed beta-agonists used, symptom scores, and physician's global evaluation on test Days 1, 29, 57, and 85.

Patients enrolled in the study had to have a diagnosis of COPD and had to meet spirometry criteria consistent with moderate to severe airway obstruction (i.e., $FEV_1 \leq 65\%$ predicted and $FEV_1/FVC \leq 70\%$ predicted) at screening, a smoking history of more than 10 pack years. The exclusion criteria were appropriate and included exclusion of patients with symptomatic prostatic hypertrophy or bladder neck obstruction, and patients with known narrow angle glaucoma. Following the initial screening visit for patient eligibility assessment, patients received Atrovent (ipratropium) MDI (HFA or CFC depending on what was available in the study country) 2 puffs four times a day for two weeks. Following the run-in period, patients were randomized to one of the following three study treatment administered 4 times daily:

- Combivent Respimat (20/100 mcg) 1 actuation + Placebo Combivent CFC-MDI 2 puffs
- Ipratropium bromide Respimat 20 mcg 1 actuation + Placebo Combivent CFC-MDI 2 puffs
- Combivent CFC-MDI (18/103 mcg) 2 puffs + Placebo Combivent Respimat 1 actuation

Patients were seen every 28 days and were required to bring all inhalers at each study visit. At each visit, a new set of inhalers were given. Patients who were on stable doses of inhaled steroids, theophylline preparations, mucolytic agents (not containing bronchodilators), and leukotriene receptor antagonists (prescribed for conditions other than asthma or excluded allergic conditions) for at least 6 weeks prior to screening were allowed to remain on those medications. As needed albuterol (salbutamol) was permitted as well as temporary use of oral steroids per investigator judgment to treat COPD exacerbations, and temporary increases in theophylline, and antibiotics as deemed appropriated for COPD exacerbations.

Patients recorded their study medication and any as needed albuterol/salbutamol use in an e-diary. At each visit baseline FEV_1 was measured (FEV_1 prior to inhaling study medication) and spirometry was obtained out to 6 hours following inhaling study medication. In addition to medication compliance, adverse events and concomitant therapy were evaluated at each visit. Patients were instructed to return with all inhalers (Respimat devices, cartridges, and MDIs) at each study visit. To evaluate the device acceptability, a device questionnaire was administered to patients at 37 U.S. sites. The questionnaire consisted of 10 questions that asked about patient satisfaction with using the device, following the instructions to use the device,

durability of the device, and the feeling of whether they were getting the medication into their lungs. In addition, 100 normally functioning devices were collected from patients when the dose indicator reached the 30 dose mark (7 day supply left) from the 120 doses available for each inhaler for end-of-use testing by BI.

Results

A total of 1480 patients 40 to 88 years (mean 64) of age were randomized in the study and of these patients, data from 1460 patients were available for the efficacy analyses. Data from 20 patients from one French site could not be verified (by the Applicant) and so data from these patients were not included in the efficacy analyses. The characteristics of the patients enrolled each study treatment group were similar. The patients had a diagnosis of COPD on average about 8.4 years and a mean FEV₁ % predicted at screening of 41.4% and FEV₁/FVC of 44.8. All patients were either current or former smokers, and the mean number of pack-years was 53.2. The mean age of patients in the study was 64 years, the majority (65%) were male, and 89% were Caucasian. Compliance was assessed by the patient recording dosing in an e-diary for each inhaler (Respimat and MDI) and approximately 66% of patients had an overall percentage compliance of 80 - < 120% which was fairly distributed across treatment groups.

In terms of efficacy, the three co-primary efficacy endpoints were met for all three primary efficacy comparisons as shown in the Table 2 below.

Table 2. Summary of Co-primary Efficacy Endpoints – Mean FEV₁ AUC Change on Test Day 85

Efficacy endpoint	Treatment comparison	N	Mean (SE) (in liters)	Treatment difference (in liters)	
				Mean (SE)	95% CI
FEV ₁ AUC ₀₋₆	Combivent Respimat 20/100	474	0.145 (0.007)	-0.003 (0.010)	-0.022, 0.015
	Combivent CFC-MDI	482	0.149 (0.007)		
FEV ₁ AUC ₀₋₄	Combivent Respimat 20/100	474	0.189 (0.007)	0.047* (0.010)	0.028, 0.066
	ipratropium Respimat 20	468	0.142 (0.007)		
FEV ₁ AUC ₄₋₆	Combivent Respimat 20/100	447	0.056 (0.008)	-0.017 (0.011)	-0.039, 0.005
	ipratropium Respimat 20	427	0.073 (0.008)		

The results demonstrate that Combivent Respimat 20/100 mcg was non-inferior to Combivent Inhalation Aerosol 36/206 in terms of mean FEV₁AUC_{0-6hr} and non-inferior to Ipratropium Respimat in terms of FEV₁AUC_{4-6hrs}. In both instances, the lower bound of the 95% CI for the point estimate for the difference from Combivent Respimat was more than -50 ml (Table 2). The demonstration of noninferiority between Combivent Respimat and Ipratropium Respimat in the FEV₁AUC_{4-6 hr} demonstrates the contribution of ipratropium in the combination product, and the demonstration of superiority of Combivent Respimat compared to Ipratropium Respimat for the FEV₁AUC_{0-4 hrs} satisfies the demonstration of the efficacy contribution of albuterol in the combination product. The efficacy results were similar across age, and gender. The majority of patients were Caucasians so an effect on race could not be ascertained.

When the primary efficacy comparisons were evaluated on test Days 1, 29, and 57, results similar to those from Day 85 were noted (Figure 2). Other secondary endpoints such as symptoms, rescue medication use, and PEFr did not show any appreciable difference among treatment groups. Onset and duration of therapeutic effect (bronchodilation) was assessed at various time points at each test day. The definition of bronchodilation used for these assessments (i.e., FEV₁ increase of 15% or greater) is acceptable. Using this definition, the

median time to onset of a therapeutic effect was 13 minutes on test Day 1 and 12 minutes on test Day 85.

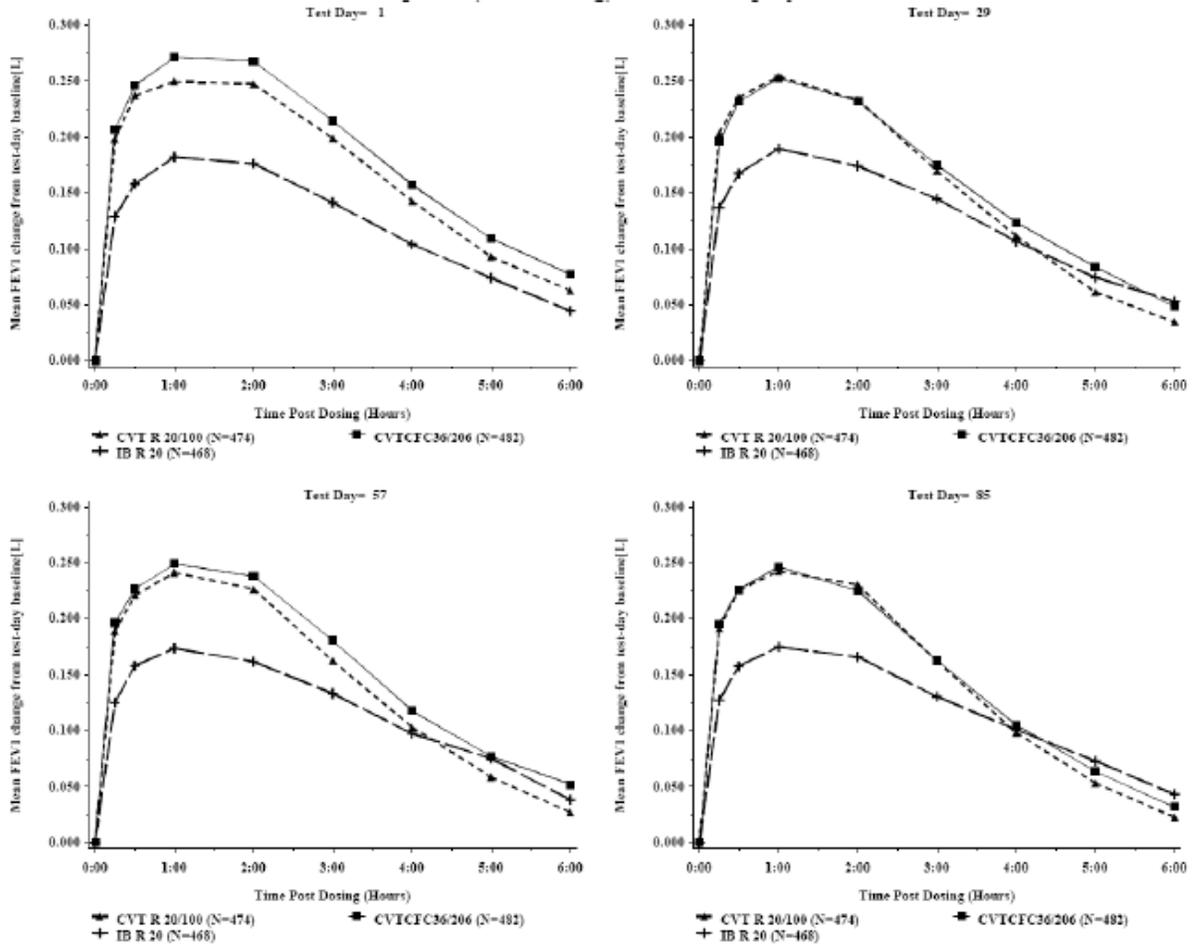


Figure 2. FEV₁ over time profile on days 1, 29, 57, and 85

Assessment of the ease of handling of the device and patient satisfaction was done with a questionnaire at the Week 12 visit. From the responses, it appears that the majority of the patients in this study did not have difficulty using the device and were satisfied that they were getting the medication into their lungs.

BI also assessed 100 normally functioning Combivent Respimat inhalers while there about 30 doses left and did end-of canister life testing, and noted that the CMC characteristics (spray plume, shape, volume, fine particle fraction of the release spray) was unchanged from the results at batch release.

8. Safety

During the first review cycle, the primary safety database for Combivent Respimat included data from the pivotal efficacy and safety 12-week treatment trial with Combivent Respimat 20/100 (study 1012.56), and data from a higher strength Combivent Respimat 40/200 12-week

treatment trial (study 1012.46). Safety data from a 6-month Ipratropium Respimat safety study was also submitted but is of limited value as it was from a different, albeit related, drug product. 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 a COPD population with serious co-morbidities. In study 1012.56, the pivotal efficacy study, the percentage of patients with serious adverse events was higher in the Combivent CFC Inhalation Aerosol treated patients (6.7%) compared to the Combivent Respimat Inhalation Spray treated patients (3.5%). The pattern of serious adverse events and other adverse events did not raise any new safety concerns. The safety profile with the higher strength product (Combivent Respimat 40/200) used in study 1012.46 also did not reveal any new safety signals.

However, during the first review cycle the overall safety database was not sufficient to support approval of Combivent Respimat 20/100 as long term safety data with the Combivent Respimat 20/100 product were lacking. This information is important because Combivent Respimat represents a new drug product and drug delivery platform and from the standpoint that this product will be the replacement product for the Combivent CFC Inhalation Aerosol MDI currently on the market. In addition, the Respimat device is new and there are no Respimat products on the market in the United States at this time so that there is no long term experience with the Respimat inhaler device. Thus, the Division felt that controlled long-term safety data to compare the Combivent 20/100 Respimat product to the current Combivent CFC MDI product would be important in order to provide information about any potential safety and/or device handling issues long term. Although Combivent CFC Inhalation Aerosol was approved with no long term (12 month safety data), the device for the Combivent CFC is the typical press and breathe MDI inhaler that has been on the market for a long time and is a very familiar device in patients' hands.

In order to address the lack of long term safety data for Combivent Respimat 20/100 which was conveyed to BI during the first review cycle, BI conducted and submitted safety data from a 48-week safety and efficacy study designed primarily to assess safety and device handling issues with Combivent Respimat 20/100 in COPD patients (study 1012.62). The study compares the safety of Combivent Respimat 20/100 to Combivent CFC Inhalation Aerosol and also to single ingredient albuterol and ipratropium products given together. In accordance with the agreement made with BI, the study 1012.62 study report contains final safety data up to the 24-week time point. Preliminary safety data from the 48-week time was subsequently submitted later during this review cycle.

Following is a summary of the design and results for study 1012.62 which support the long-term safety of Combivent 20/100 Inhalation Spray and ability of COPD patients being able to use the Respimat delivery device.

Study 1012.62

The study was a 48-week, randomized, open-label safety and patient acceptability study of Combivent Respimat 20/100 Inhalation Spray 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 1:1:1 into following 3 treatment groups:

- Combivent Respimat 20/100 Inhalation Spray, one actuation four times daily
- Combivent CFC Inhalation Aerosol, two actuations delivering 36 mcg ipratropium bromide and 206 mcg albuterol sulfate four times daily
- Atrovent HFA, two actuations delivering 34 mcg ipratropium bromide plus Ventolin (albuterol) HFA, two actuations delivering 206 mcg albuterol sulfate, four times daily

Patient inclusion criteria included ≥ 40 years of age, being a current smoker or ex-smoker with a diagnosis of COPD with a post-bronchodilator FEV1 $\leq 80\%$ of predicted normal and FEV₁/FVC $\leq 70\%$.

Pertinent exclusion criteria included significant diseases other than COPD, history of thoracotomy with pulmonary resection, history of significant alcohol or drug abuse, oxygen therapy for >1 hour per day, using beta blockers except for the treatment of non-narrow angle glaucoma, and using corticosteroids at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day.

The following medications (other than the study medications) were not allowed during the study:

- Short acting anti-cholinergic drugs including additional Atrovent Inhalation Aerosol, Atrovent Inhalation Solution, or Atrovent Nasal Spray 0.06%;
- Additional Combivent Inhalation Aerosol or combination ipratropium bromide/ albuterol solution for nebulization
- Oral beta adrenergic drugs (albuterol) or LABAs such as salmeterol and formoterol;
- Short acting beta agonist other than the provided albuterol MDI
- Long-acting anticholinergics such as tiotropium.

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 at Visit 1 and Visit 2. 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.

Safety Results

A total of 470 patients were randomized and 465 received at least one dose of study medication; 157 received Combivent Respimat 20/100, 154 received Combivent CFC 36/206, and 154 received Atrovent 34 mcg + Ventolin 180 mcg. The mean and median exposures for the safety analysis were similar for both Combivent treatment groups with patient exposure about 10% less in the free combination group.

Patient demographic information was similar between treatment groups. Overall, 59% and 41% of the treated patients were males and females, respectively and 94% of the patients were white. The average age among of the patient population was 63 years. Over 50% of the patients are in the range from 40 to 64 years old. Patients had an average smoking history of 54 pack-years, and mean duration of COPD duration of 7.6 years. The overall mean baseline FEV₁ was 1.34 liters or about 47-48% predicted. Patient compliance was assessed by patients recording the self-administered number of actuations of investigational product. Compliance was similar for the 2 Combivent products at 87% and was about 10% lower for the free combination of Ventolin (albuterol) and Atrovent (ipratropium bromide) [78%].

Three deaths were reported during the treatment phase of the study with one additional death reported during the follow-up period in a patient who was discontinued prematurely. Three of the deaths occurred in the Atrovent 34 mcg + Ventolin 180 mcg treatment group (pancreatic cancer, possible cardiac arrhythmia, and lung cancer) and one in the Combivent Respimat 20/100 group. This patient was a 49-year-old female patient with COPD who experienced respiratory failure and died at home on the Day 62 of treatment. The cause of death was listed on the death certificate as respiratory failure.

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 most frequently occurring SAEs were in the respiratory, thoracic and mediastinal disorders classification, involving a total of 22 patients (4.7%). The majority of SAEs in this category was COPD exacerbation (17 patients), which is a relatively common occurrence in older patients with severe COPD and is not viewed as a particular safety concern given the proven efficacy of the treatments received. Pneumonia, another relatively common occurring adverse event in COPD patients was reported in 2-4 % of patients.

Common adverse events included, as would be expected in a COPD population, those related to the respiratory system and AEs as a result of infection. Again, the single most common AE was COPD exacerbation. Overall, 15.9% of patients had an exacerbation of COPD, followed by 7.1 % of patients with upper respiratory tract infections, and 5.2% of patients reporting bronchitis. There was essentially no difference in frequency of these AEs across treatment groups. Cough was noted to be reported in 6.4% of patients treated with Combivent Respimat 20/100, a slightly higher frequency than patients in the other 2 groups (about 3%). In contrast, dyspnea was reported in fewer patients treated with Combivent 20/100 Inhalation Spray compared to the other treatment groups, 2% compared to 5-6%, respectively.

Patient Use Assessment

In addition to the reporting of adverse events, another analysis was the comparison of patient acceptability between the Combivent Respimat 20/100 mcg Inhalation Spray to the 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. They were less likely willing to continue treatment with the individual products.

In addition to the 24-week data from study 1012.62, as per an agreement with the Division, BI submitted preliminary safety 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.

Inhalation complaints and malfunctioning inhalers

All device malfunctions and complaints were recorded and reviewed. At the time of data lock for the 24-week interim report, a total of 4 device complaints were recorded. There were 3 complaints for the Combivent Respimat (incorrect dose counting, device base detached, no medication released). When evaluated by BI, one complaint for the Combivent Respimat (device base detached) was confirmed. There was also one complaint for the Ventolin MDI (device sticking). These data suggest the Respimat drug delivery system is robust enough to withstand daily chronic use by patients.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. The product is a fixed dose combination of two well known drug substances – albuterol sulfate and ipratropium bromide and the proposed indication is the same as the indication for the currently approved CFC version of the product.

10. Pediatrics

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this COPD-specific drug product. This application was discussed with PeRC and they agreed that a full waiver should be granted because the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

DSI Audits

In the previous review cycle, DSI audits were conducted at three study sites which enrolled the largest number of patients in the pivotal phase 3 study (1012.56). Audits of the sites did not show any major irregularities that would raise a concern and all studies were conducted in accordance with accepted ethical standards. For the current submission of the long-term safety study, as the efficacy of the Combivent Respimat 20/100 Inhalation Aerosol had already been established in the first review cycle and review of the data from the study did not reveal any specific irregularities that would raise concerns regarding data integrity, no DSI audits were requested during this review cycle.

Financial Disclosure

During the first review cycle seven investigators were noted to have significant financial interest in BI, however, the number of subjects that those investigators enrolled was not large enough to alter the outcome of any study. For study 1012.62, the safety study submitted with BI's complete response this review cycle, no investigators had financial interests requiring disclosure.

CDRH Consult

Because the steps needed to use the Respimat platform and the internal mechanisms of the product are rather complex, the Division originally consulted with CDRH [REDACTED] (b) (4). While there were no issues with the quality of the Respimat product they raised concerns regarding the need for a human factors study. The Division pointed out that, while no specific human factors study had been performed, BI had adequately addressed human factors issues during the phase 3 program during which both patient handling and device robustness were assessed in two phase 3 studies conducted for Combivent Respimat Inhalation Spray, two phase 3 studies conducted for Spiriva Respimat, and in the Combivent Respimat one-year safety and patient usability study submitted with this complete response submission. These assessments did not suggest any significant problems with patient handling, performance, and robustness of the Respimat device.

12. Labeling

The proprietary name will essentially remain the same (Combivent) with the exception of adding the new dosing format ("Combivent Respimat Inhalation Spray" as opposed to Combivent Inhalation Aerosol"). This change was reviewed by OSE/DMEPA and was found to be acceptable.

During the review of the original NDA application, the physician labeling was reviewed by all the disciplines and by the Division of Drug Marketing Advertising and Communication (DDMAC). The label was extensively revised to be consistent with the new Physician Labeling Rule and for consistency with other labels in PLR format. The Complete Response letter to the Applicant contained the revised proposed physician label with the exception of the inclusion of the 6-month safety data from the Combivent Respimat long term safety study.

At the time of this review, final label discussions are continuing.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is for Approval. The efficacy of Combivent Respimat 20/100 Inhalation Spray was demonstrated in study 1012.56 during the first review cycle while the long-term safety of Combivent Respimat 20/100 is supported by the 6-month and preliminary 12-month data from study 1012.62. In addition, the robustness and acceptability of the Respimat inhaler by patients were supported by the clinical program.

- Risk Benefit Assessment

The submitted data 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. Combivent Respimat 20/100 Inhalation Spray demonstrated efficacy and safety in the single pivotal 12-week study and its long-term safety and device handling and patient acceptability are supported by the final 6-month and preliminary 12-month data from the long-term safety study 1012.62.

- Recommendation for Postmarketing Risk Management Activities

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

- Recommendation for other Postmarketing Study Commitments

There are no recommendations for post-marketing commitments.

- Recommended Comments to Applicant

There are no additional comments which need to be conveyed to the Applicant.

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/s/

ANTHONY G DURMOWICZ
09/19/2011