HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COMBIVENT RESPIMAT safely and effectively. See full prescribing information for COMBIVENT RESPIMAT.

COMBIVENT® RESPIMAT® (ipratropium bromide and albuterol) Inhalation Spray

FOR ORAL INHALATION
Initial U.S. Approval: 1996

----------INDICATIONS AND USAGE----------
COMBIVENT RESPIMAT Inhalation Spray is a combination of an anticholinergic and beta-adrenergic indicated for:
- 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 (1)

----------DOSAGE AND ADMINISTRATION----------
For oral inhalation only
- One inhalation four times a day, not to exceed six inhalations in 24 hours (2)

----------DOSAGE FORMS AND STRENGTHS----------
- Inhalation spray: 20 mcg ipratropium bromide (monohydrate) and 100 mcg albuterol (equivalent to 120 mcg albuterol sulfate) per actuation with the COMBIVENT RESPIMAT inhaler (3)
- COMBIVENT RESPIMAT inhaler delivers 120 metered actuations (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to any of the ingredients in COMBIVENT RESPIMAT (4)
- Hypersensitivity to atropine or any of its derivatives (4)

----------WARNINGS AND PRECAUTIONS----------
- Paradoxical bronchospasm: Discontinue COMBIVENT RESPIMAT immediately and treat with alternative therapy if paradoxical bronchospasm occurs (5.1)
- Patients with cardiovascular system disorders: Use with caution because of beta-adrenergic stimulation (5.2)
- Ocular effects: Advise patients to avoid spraying into eyes and to contact a physician if blurred vision, halos, or other visual disturbances occur. Monitor patients with narrow-angle glaucoma. (5.3)
- Urinary retention: Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction (5.4)
- Hypersensitivity reactions including anaphylaxis: Discontinue COMBIVENT RESPIMAT and institute alternative therapy if immediate hypersensitivity reactions such as urticaria, angioedema, rash, bronchospasm, anaphylaxis, or oropharyngeal edema occur (5.6)
- Coexisting conditions: Use with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus (5.7)

----------ADVERSE REACTIONS----------
Most common (≥2%) adverse reactions for COMBIVENT RESPIMAT (20/100 mcg) are upper respiratory infection, nasopharyngitis, cough, bronchitis, headache, and dyspnea (6)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of COMBIVENT RESPIMAT with other anticholinergic-containing drugs (7.1)
- Beta-adrenergic agents: May increase the risk of adverse cardiovascular effects. Avoid coadministration of COMBIVENT RESPIMAT and other sympathomimetic agents (7.2)
- Beta-blockers: Inhibit the effect of albuterol. Consider alternative therapy in patients with hyperreactive airways (7.3)
- Diuretics: Electrocardiographic changes and/or hypokalemia associated with diuretics may worsen with concomitant use of beta-agonists. Consider monitoring potassium levels. (7.4)
- Monoamine oxidase inhibitors (MAOs) or tricyclic antidepressants: May potentiate effect of albuterol on the vascular system. Consider alternative therapy in patients taking MAOs or tricyclic antidepressants. (7.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Paradoxical Bronchospasm
5.2 Cardiovascular Effect
5.3 Ocular Effects
5.4 Urinary Retention
5.5 Do Not Exceed Recommended Dose
5.6 Hypersensitivity Reactions Including Anaphylaxis
5.7 Coexisting Conditions
5.8 Hypokalemia
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Post-Marketing Experience
7 DRUG INTERACTIONS
7.1 Anticholinergic Agents
7.2 Beta-adrenergic Agents
7.3 Beta-receptor Blocking Agents
7.4 Diuretics
7.5 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Ocular Effects
17.2 Urinary Retention
17.3 Frequency of Use
17.4 Preparation for Use and Priming
17.5 Concomitant Drug Use
17.6 Paradoxical Bronchospasm
17.7 Adverse Effects Associated with $Beta_2$-agonists
17.8 Pregnancy
17.9 FDA-approved Patient Labeling

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

COMBIVENT RESPIMAT is indicated 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.

2 DOSAGE AND ADMINISTRATION

The recommended dose of COMBIVENT RESPIMAT is one inhalation four times a day. Patients may take additional inhalations as required; however, the total number of inhalations should not exceed six in 24 hours.

Prior to first use, the COMBIVENT RESPIMAT cartridge is inserted into the COMBIVENT RESPIMAT inhaler and the unit is primed. When using the unit for the first time, patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then repeat the process three more times. The unit is then considered primed and ready for use. If not used for more than 3 days, patients are to actuate the inhaler once to prepare the inhaler for use. If not used for more than 21 days, patients are to actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use [*see Patient Counseling Information (17.4*)].

Safety and efficacy of additional doses of COMBIVENT RESPIMAT beyond six inhalations/24 hours have not been studied. Also, safety and efficacy of extra doses of ipratropium or albuterol in addition to the recommended doses of COMBIVENT RESPIMAT have not been studied.

3 DOSAGE FORMS AND STRENGTHS

COMBIVENT RESPIMAT consists of a COMBIVENT RESPIMAT inhaler and an aluminum cylinder (COMBIVENT RESPIMAT cartridge) containing a combination of ipratropium bromide (as the monohydrate) and albuterol sulfate. The COMBIVENT RESPIMAT cartridge is only intended for use with the COMBIVENT RESPIMAT inhaler. Each cartridge delivers 120 metered actuations after preparation for use, the equivalent of 30 days' medication when used as one inhalation four times a day.

Each actuation from the COMBIVENT RESPIMAT inhaler delivers 20 mcg ipratropium bromide (monohydrate) and 100 mcg albuterol (equivalent to 120 mcg albuterol sulfate) from the mouthpiece.

4 CONTRAINDICATIONS

COMBIVENT RESPIMAT is contraindicated in the following conditions [*see Warnings and Precautions (5.6)*]:

- Hypersensitivity to any of the ingredients in COMBIVENT RESPIMAT
- Hypersensitivity to atropine or any of its derivatives

5 WARNINGS AND PRECAUTIONS

5.1 Paradoxical Bronchospasm

COMBIVENT RESPIMAT can produce paradoxical bronchospasm that can be life-threatening. If it occurs, therapy with COMBIVENT RESPIMAT should be discontinued immediately and alternative therapy instituted.

5.2 Cardiovascular Effect

The albuterol sulfate contained in COMBIVENT RESPIMAT, like other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. If these symptoms occur, COMBIVENT RESPIMAT may need to be discontinued. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischemia associated with albuterol. In addition, beta-adrenergic agents have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Therefore, COMBIVENT RESPIMAT should be used with caution in patients with cardiovascular disorders; especially coronary insufficiency, cardiac arrhythmias, and hypertension [*see Drug Interactions (7.2)*].

5.3 Ocular Effects

Ipratropium bromide, a component of COMBIVENT RESPIMAT, is an anticholinergic and may increase intraocular pressure. This may result in precipitation or worsening of narrow-angle glaucoma. Therefore, COMBIVENT RESPIMAT should be used with caution in patients with narrow-angle glaucoma [*see Drug Interactions (7.1)*].

Patients should avoid spraying COMBIVENT RESPIMAT into the eyes. If a patient sprays COMBIVENT RESPIMAT into their eyes they may cause acute eye pain or discomfort, temporary blurring of vision, mydriasis, visual halos, or colored images in association with red eyes from conjunctival or corneal congestion. Advise patients to consult their physician immediately if any of these symptoms develop while using COMBIVENT RESPIMAT.

5.4 Urinary Retention

Ipratropium bromide, a component of COMBIVENT RESPIMAT, is an anticholinergic and may cause urinary retention. Therefore, caution is advised when administering this medication to patients with prostatic hyperplasia or bladder-neck obstruction [*see Drug Interactions (7.1)*].

5.5 Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected [*see Drug Interactions (7.2)*].

5.6 Hypersensitivity Reactions Including Anaphylaxis

Hypersensitivity reactions including urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema may occur after administration of ipratropium bromide or albuterol sulfate. In clinical trials and post-marketing experience with ipratropium containing products, hypersensitivity reactions such as skin rash, pruritus, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported [*see Adverse Reactions (6.1, 6.2)*]. If such a reaction occurs, therapy with COMBIVENT RESPIMAT should be stopped at once and alternative treatment should be considered [*see Contraindications (4)*].

5.7 Coexisting Conditions

COMBIVENT RESPIMAT contains albuterol sulfate, a beta-adrenergic sympathomimetic amine and, therefore, should be used with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

5.8 Hypokalemia
Beta-adrenergic agents may produce significant hypokalemia in some patients (possibly through intracellular shunting) which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation [*see Drug Interactions (7.2)*].

6 ADVERSE REACTIONS
Use of albuterol, a beta-adrenergic agonist, may be associated with the following:
- Paradoxical bronchospasm [*see Warnings and Precautions (5.1)*]
- Cardiovascular effects [*see Warnings and Precautions (5.2)*]
- Hypersensitivity reactions, including anaphylaxis [*see Contraindications (4) and Warnings and Precautions (5.6)*]
- Hypokalemia [*see Warnings and Precautions (5.8)*]

Albuterol is a component of COMBIVENT RESPIMAT.

Use of ipratropium bromide, an anticholinergic, may result in the following:
- Ocular effects [*see Warnings and Precautions (5.3)*]
- Urinary retention [*see Warnings and Precautions (5.4)*]

Ipratropium bromide is a component of COMBIVENT RESPIMAT.

6.1 Clinical Trials Experience
COMBIVENT RESPIMAT 12-Week Clinical Trials
The safety data described in Table 1 below are derived from one 12-week, randomized, multi-center, double-blind, double-dummy, parallel-group trial that compared COMBIVENT RESPIMAT (20/100 mcg), CFC-propelled COMBIVENT Inhalation Aerosol (36/206 mcg), and ipratropium bromide delivered by the RESPIMAT inhaler (20 mcg) administered four times a day in 1460 adult COPD patients (955 males and 505 females) 40 years of age and older. Of these patients, 486 were treated with COMBIVENT RESPIMAT. The COMBIVENT RESPIMAT group was composed of mostly Caucasian (88.5%) patients with a mean age of 63.8 years, and a mean percent predicted FEV_1 at screening of 41.5%. Patients with narrow-angle glaucoma, symptomatic prostatic hypertrophy or bladder-neck obstruction were excluded from the trial.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 1 shows all adverse reactions that occurred with a frequency of ≥2% in the COMBIVENT RESPIMAT treatment group in the 12-week COPD trial. The frequency of the corresponding adverse reactions in the CFC-propelled COMBIVENT Inhalation Aerosol and ipratropium bromide delivered by the RESPIMAT inhaler groups is included for comparison. The rates are derived from all reported adverse reactions of that type not present at baseline, whether considered drug-related or not by the clinical investigator.

Table 1: Adverse Reactions in ≥2% of Patients in the COMBIVENT RESPIMAT Group in a 12-Week COPD Clinical Trial

Body System (Event)	**12-Week Ipratropium-Controlled Trial**		
	COMBIVENT RESPIMAT (20/100 mcg) [n=486]	CFC-propelled COMBIVENT Inhalation Aerosol (36/206 mcg) [n=491]	Ipratropium bromide by the RESPIMAT Inhaler (20 mcg) [n=483]
Patients with any adverse reaction	46	52	45
Respiratory, thoracic and mediastinal disorders			
Cough	3	2	2
Dyspnea	2	2	3
Nervous system disorders			
Headache	3	2	3
Infections and infestations			
Bronchitis	3	3	1
Nasopharyngitis	4	3	4
Upper Respiratory infection	3	4	3

Adverse reactions that occurred in <2% in the COMBIVENT RESPIMAT (20/100 mcg) group observed in this 12-week trial include: *Vascular disorders:* hypertension; *Nervous system disorders:* dizziness and tremor; *Musculoskeletal and connective tissue disorder:* muscle spasms and myalgia; *Gastrointestinal disorders:* diarrhea, nausea, dry mouth, constipation, and vomiting; *General disorders and administration site conditions:* asthenia, influenza-like illness, and chest discomfort; *Eye disorders:* eye pain; *Metabolism and nutritional disorders:* hypokalemia; *Cardiac disorders:* palpitations and tachycardia; *Skin and subcutaneous tissue disorders:* pruritus and rash; *Respiratory, thoracic and mediastinal disorders*; pharyngolaryngeal pain and wheezing.

A separate 12-week trial evaluated a higher than approved dose of COMBIVENT RESPIMAT in 1118 COPD patients. Patients were randomized to COMBIVENT RESPIMAT (40/200 mcg) (n=345), CFC-propelled COMBIVENT Inhalation Aerosol (36/206 mcg) (n=180), ipratropium delivered by the RESPIMAT (40 mcg) (n=252) or placebo (n=341). The overall incidence and nature of adverse reactions observed were similar to the adverse reactions seen with COMBIVENT RESPIMAT 20/100 mcg.

COMBIVENT RESPIMAT Long Term (48-week) Safety Trial
Long term chronic use safety data for COMBIVENT RESPIMAT were obtained from one 48-week, randomized, multi-center, open-label, parallel-group trial that compared COMBIVENT RESPIMAT (20/100 mcg), CFC-propelled COMBIVENT Inhalation Aerosol (36/206 mcg) and the free combination of ipratropium bromide (34 mcg) and albuterol (180 mcg) HFA inhalation aerosols administered 4 times a day in 465 adult COPD patients (273 males and 192 females) 40 years of age and

older. Of these patients, 157 were treated with COMBIVENT RESPIMAT. The COMBIVENT RESPIMAT group was composed of mostly Caucasian (93.5%) patients with a mean age of 62.9 years, and a mean percent predicted FEV_1 at screening of 47.0%. An evaluation of the safety data from the trial revealed that most adverse reactions were similar in type and rate between treatment groups. However, cough occurred more frequently in patients enrolled in the COMBIVENT RESPIMAT group (7.0%) compared to those in the CFC-propelled COMBIVENT Inhalation Aerosol (2.6%) or the free combination of ipratropium bromide and albuterol HFA inhalation aerosols (3.9%) groups.

In addition to the adverse reactions reported in the controlled clinical trial with COMBIVENT RESPIMAT, adverse reaction information concerning CFC-propelled COMBIVENT Inhalation Aerosol is derived from two 12-week controlled clinical trials (N=358 for CFC-propelled COMBIVENT Inhalation Aerosol). Adverse reactions reported in ≥2% of patients in the CFC-propelled COMBIVENT Inhalation Aerosol treatment group include: bronchitis, upper respiratory tract infection, headache, dyspnea, cough, pain, respiratory disorder, sinusitis, pharyngitis and nausea. Adverse reactions reported in < 2% of patients in the CFC-propelled COMBIVENT Inhalation Aerosol treatment group include: edema, fatigue, hypertension, dizziness, nervousness, tremor, dysphonia, insomnia, diarrhea, dry mouth, dyspepsia, vomiting, arrhythmia, palpitation, tachycardia, arthralgia, angina, increased sputum, taste perversion, urinary tract infection, dysuria, dry throat and bronchospasm.

6.2 Post-Marketing Experience

In addition to the adverse reactions reported during clinical trials, the following adverse reactions have been identified during post approval use of CFC-propelled COMBIVENT Inhalation Aerosol. Since CFC-propelled Combivent Inhalation Aerosol and Combivent Respimat contain the same active ingredients, one should take into account the fact that the adverse reactions seen with CFC-propelled Combivent Inhalation Aerosol could also occur with Combivent Respimat. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders: glaucoma, blurred vision, mydriasis, conjunctival hyperemia, halo vision, accommodation disorder ocular irritation and corneal edema
Gastrointestinal disorders: gastrointestinal motility disorder, drying of secretions, stomatitis and mouth edema
Immune system disorders: hypersensitivity; *Investigations:* intraocular pressure increased, blood pressure diastolic decreased and blood pressure systolic increased
Musculoskeletal and connective tissue disorders: muscular weakness
Psychiatric disorders: CNS stimulation, mental disorder
Respiratory, thoracic, and mediastinal disorders: throat irritation, paradoxical bronchospasm, wheezing, nasal congestion and pharyngeal edema
Skin and subcutaneous tissue disorders: angioedema, hyperhidrosis, and skin reaction
Urinary disorders: urinary retention
Cardiac disorders: myocardial ischemia

Allergic-type reactions such as skin reactions including rash, pruritus, and urticaria (including giant urticaria), angioedema including that of tongue, lips and face, laryngospasm, and anaphylactic reaction have also been reported with CFC-propelled COMBIVENT Inhalation Aerosol, with positive re-challenge in some cases [*see Warnings and Precautions (5.6)*].

In a 5-year placebo-controlled trial, hospitalizations for supraventricular tachycardia and/or atrial fibrillation occurred with an incidence rate of 0.5% in COPD patients receiving CFC-propelled Atrovent® (ipratropium bromide) Inhalation Aerosol.

Metabolic acidosis has been reported with use of albuterol-containing products.

7 DRUG INTERACTIONS

COMBIVENT RESPIMAT has been used concomitantly with other drugs, including beta-adrenergic bronchodilators, methylxanthines, and oral and inhaled steroids, commonly used in the treatment of chronic obstructive pulmonary disease. There are no formal studies fully evaluating the interaction effects of COMBIVENT RESPIMAT and these drugs with respect to safety and effectiveness.

7.1 Anticholinergic Agents

There is the potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of COMBIVENT RESPIMAT with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [*see Warnings and Precautions (5.3, 5.4)*].

7.2 Beta-adrenergic Agents

Caution is advised in the coadministration of COMBIVENT RESPIMAT and other sympathomimetic agents due to the increased risk of adverse cardiovascular effects [*see Warnings and Precautions (5.2, 5.5)*].

7.3 Beta-receptor Blocking Agents

Beta-receptor blocking agents and albuterol inhibit the effect of each other. Beta-receptor blocking agents should be used with caution in patients with hyperreactive airways.

7.4 Diuretics

The ECG changes and/or hypokalemia which may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonist-containing drugs, such as COMBIVENT RESPIMAT, with non-potassium sparing diuretics. Consider monitoring potassium levels.

7.5 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

COMBIVENT RESPIMAT should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or within 2 weeks of discontinuation of such agents because the action of albuterol on the cardiovascular system may be potentiated. Consider alternative therapy in patients taking MAOs or tricyclic antidepressants [*see Warnings and Precautions (5.2)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects*: Pregnancy Category C.*

COMBIVENT RESPIMAT Inhalation Spray
There are no adequate and well-controlled studies of COMBIVENT RESPIMAT (ipratropium bromide and albuterol sulfate) Inhalation Spray, ipratropium bromide, or albuterol sulfate, in pregnant women. Animal reproduction studies have not been conducted with COMBIVENT RESPIMAT. However, albuterol sulfate has been shown to be teratogenic in mice and rabbits. COMBIVENT RESPIMAT Inhalation Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Ipratropium bromide
Oral reproduction studies were performed in mice, rats and rabbits at doses approximately 340, 68,000 and 17,000 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mg/m^2 basis at maternal doses in each species of 10, 1000 and 125 mg/kg/day, respectively). Inhalation reproduction studies were conducted in rats and rabbits at approximately 100 and 240 times, respectively, the MRHDID in adults (on a mg/m^2 basis at maternal doses of 1.5 and 1.8 mg/kg/day, respectively). These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. Embryotoxicity was observed as increased resorption in rats at oral doses approximately 6100 times MRHDID in adults (on a mg/m^2 basis at maternal doses of 90 mg/kg/day and above). This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration.

Albuterol
Albuterol has been shown to be teratogenic in mice and rabbits. A reproduction study in CD-1 mice given albuterol subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at approximately equivalent to the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 0.25 mg/kg/day) and in 10 of 183 (9.3%) fetuses at approximately 14 times the MRHDID in adults (on a mg/m^2 basis a maternal dose of 2.5 mg/kg/day). None was observed at less than MRHDID in adults (on a mg/m^2 basis at a maternal dose of 0.025 mg/kg/day). Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg/day isoproterenol (positive control). A reproductive study with oral albuterol in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at approximately 1,100 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 50 mg/kg/day).

8.2 Labor and Delivery
Because of the potential for beta-agonist interference with uterine contractility, use of COMBIVENT RESPIMAT for the treatment of COPD during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

8.3 Nursing Mothers
It is not known whether the components of COMBIVENT RESPIMAT are excreted in human milk.

Ipratropium bromide
Because lipid-insoluble quaternary cations pass into breast milk, caution should be exercised when COMBIVENT RESPIMAT is administered to a nursing mother.

Albuterol
Because of the potential for tumorigenicity shown for albuterol in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Safety and effectiveness of COMBIVENT RESPIMAT in pediatric patients have not been established. COMBIVENT RESPIMAT is indicated for use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. This disease does not normally occur in children.

8.5 Geriatric Use
In the 12-week trial in COPD, 48% of COMBIVENT RESPIMAT clinical trial patients were 65 years of age or over. In general, there were no marked differences between the proportion of patients with adverse reactions for the COMBIVENT RESPIMAT and CFC-propelled COMBIVENT Inhalation Aerosol treated patients. Cardiac and lower respiratory disorders occurred less frequently in the patients under the age of 65 and were balanced across treatment groups.

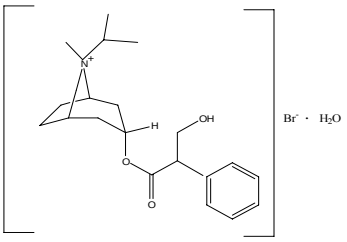
No overall differences in effectiveness were observed among treatment groups. Based on available data, no adjustment of COMBIVENT RESPIMAT dosage in geriatric patients is warranted.

10 OVERDOSAGE
The effects of overdosage are expected to be related primarily to albuterol sulfate. Acute overdosage with ipratropium bromide by inhalation is unlikely since ipratropium bromide is not well absorbed systemically after inhalation or oral administration. Manifestations of overdosage with albuterol may include anginal pain, hypertension, hypokalemia, tachycardia with rates up to 200 beats per minute, metabolic acidosis, and exaggeration of the pharmacologic effects listed in the Adverse Reactions section [*see Adverse Reactions (6)*]. As with all beta-adrenergic aerosol medications, cardiac arrest and even death may be associated with abuse. Dialysis is not appropriate treatment for overdosage of albuterol as an inhalation aerosol; the judicious use of a cardiovascular beta-receptor blocker, such as metoprolol tartrate may be indicated.

11 DESCRIPTION
COMBIVENT RESPIMAT is a combination of ipratropium bromide (as the monohydrate) and albuterol sulfate.

Ipratropium bromide is an anticholinergic bronchodilator chemically described as 8-azoniabicyclo[3.2.1] octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide monohydrate, (3-endo, 8-syn)-: a synthetic quaternary ammonium compound chemically related to atropine. Ipratropium bromide is a white to off-white crystalline substance, freely soluble in water and methanol, sparingly soluble in ethanol, and insoluble in lipophilic solvents such as ether, chloroform, and fluorocarbons.

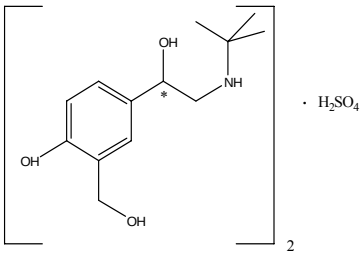
The structural formula is:



$C_{20}H_{30}BrNO_3 \bullet H_2O$ ipratropium bromide Mol. Wt. 430.4

Albuterol sulfate, chemically known as (1,3-benzenedimethanol, α'-[[(1,1dimethylethyl) amino] methyl]-4-hydroxy, sulfate (2:1)(salt), (±)- is a relatively selective beta$_2$-adrenergic bronchodilator. Albuterol is the official generic name in the United States. The World Health Organization recommended name for the drug is salbutamol. Albuterol sulfate is a white to off-white crystalline powder, freely soluble in water and slightly soluble in alcohol, chloroform, and ether.

The structural formula is:



$(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$ albuterol sulfate Mol. Wt. 576.7

The drug product, COMBIVENT RESPIMAT, is composed of a sterile, aqueous solution of ipratropium bromide and albuterol sulfate filled into a 4.5 mL plastic container crimped into an aluminum cylinder (COMBIVENT RESPIMAT cartridge) for use with the COMBIVENT RESPIMAT inhaler. Excipients include water for injection, benzalkonium chloride, edetate disodium, and hydrochloric acid. The COMBIVENT RESPIMAT cartridge is only intended for use with the COMBIVENT RESPIMAT inhaler. The COMBIVENT RESPIMAT inhaler is a hand held, pocket sized oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication from a metered volume of the drug solution. The COMBIVENT RESPIMAT inhaler has an orange-colored cap.

When used with the COMBIVENT RESPIMAT inhaler, each cartridge containing 4 grams of a sterile aqueous solution, delivers 120 metered actuations after preparation for use, the equivalent of 30 days' medication when used as one inhalation four times a day. Each actuation from the COMBIVENT RESPIMAT inhaler delivers 20 mcg ipratropium bromide (monohydrate) and 100 mcg albuterol (equivalent to 120 mcg albuterol sulfate) in 11.4 mcL of solution from the mouthpiece. As with all inhaled drugs, the actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the inhaler and inspiration through the delivery system. The duration of inspiration should be at least as long as the spray duration (1.5 seconds).

Prior to first use, the COMBIVENT RESPIMAT cartridge is inserted into the COMBIVENT RESPIMAT inhaler and the unit is primed. When using the unit for the first time, patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then repeat the process three more times. The unit is then considered primed and ready for use. If not used for more than 3 days, patients are to actuate the inhaler once to prepare the inhaler for use. If not used for more than 21 days, patients are to actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use [*see Patient Counseling Information (17.4)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COMBIVENT RESPIMAT: COMBIVENT RESPIMAT is a combination of the anticholinergic ipratropium bromide and the beta$_2$-adrenergic agonist albuterol sulfate. The mechanisms of action described below for the individual components apply to COMBIVENT RESPIMAT. The two classes of medications (an anticholinergic and a beta$_2$-adrenergic agonist) are both bronchodilators. Simultaneous administration of both an anticholinergic (ipratropium bromide) and a beta$_2$-sympathomimetic (albuterol sulfate) is designed to produce a greater bronchodilator effect than when either drug is utilized alone at its recommended dosage. The efficacy of COMBIVENT RESPIMAT is likely to be due to a local effect on the muscarinic and beta$_2$-adrenergic receptors in the lung.

Ipratropium bromide

Ipratropium bromide is an anticholinergic (parasympatholytic) agent which, based on animal studies, appears to inhibit vagally mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released at the neuromuscular junctions in the lung. Anticholinergics prevent the increases in intracellular concentration of Ca++ which is caused by interaction of acetylcholine with the muscarinic receptors on bronchial smooth muscle.

Albuterol sulfate

In vitro studies and *in vivo* pharmacology studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, recent data indicate that there is a population of beta$_2$-receptors in the human heart which comprise between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors, however, is not yet established [*see Warnings and Precautions (5.2)*].

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylyl cyclase and to an increase in the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

Albuterol has been shown in most clinical trials to have more bronchial smooth muscle relaxation effect than isoproterenol at comparable doses while producing fewer cardiovascular effects. However, all beta-adrenergic drugs, including albuterol sulfate, can produce a significant cardiovascular effect in some patients [*see Warnings and Precautions (5.2)*].

12.2 Pharmacodynamics

Ipratropium bromide

Cardiovascular effects

At recommended doses, ipratropium bromide does not produce clinically significant changes in pulse rate or blood pressure.

Ocular effects

In studies without a positive control, ipratropium bromide did not alter pupil size, accommodation or visual acuity.

Mucociliary clearance and respiratory secretions

Controlled clinical studies have demonstrated that ipratropium bromide does not alter either mucociliary clearance or the volume or viscosity of respiratory secretions.

Albuterol sulfate

Cardiovascular effects

Controlled clinical trials and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

12.3 Pharmacokinetics

Ipratropium bromide

Ipratropium bromide is a quaternary amine and hence, it is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract as confirmed by blood level and renal excretion studies.

The half-life of elimination is about 2 hours after inhalation or intravenous administration. Ipratropium bromide is minimally bound (0% to 9% *in vitro*) to plasma albumin and α_1-acid glycoprotein. It is partially metabolized to inactive ester hydrolysis products. Following intravenous administration, approximately one-half of the dose is excreted unchanged in the urine.

Albuterol sulfate

Albuterol is longer acting than isoproterenol in most patients because it is not a substrate for the cellular uptake processes for catecholamines, nor for metabolism by catechol-O-methyl transferase. Instead, the drug is conjugatively metabolized to albuterol 4'-O-sulfate.

Intravenous pharmacokinetics of albuterol was studied in a comparable group of 16 healthy male volunteers; the mean terminal half-life following a 30-minute infusion of 1.5 mg was 3.9 hours with a mean clearance of 439 mL/min/1.73 m^2.

COMBIVENT RESPIMAT Inhalation Spray

In a 12-week randomized, multicenter, double-blind, double-dummy parallel group trial, 108 US patients with COPD receiving either COMBIVENT RESPIMAT (20/100 mcg) or CFC-propelled COMBIVENT Inhalation Aerosol (36/206 mcg) four times daily participated in pharmacokinetic evaluations. Plasma ipratropium concentrations were low with an average peak plasma concentration of 33.5 pg/mL from COMBIVENT RESPIMAT. The majority of the study participants exhibited levels below the lower limit of quantitation (<10 pg/mL) by 4 to 6 hours following dosing. The steady state systemic exposure obtained for ipratropium bromide following COMBIVENT RESPIMAT was comparable to that of CFC-propelled COMBIVENT Inhalation Aerosol. Ipratropium plasma AUC and total amount of drug excreted unchanged in urine (Ae) ratios for COMBIVENT RESPIMAT/CFC-propelled COMBIVENT Inhalation Aerosol were 1.04 and 1.18, respectively. For albuterol the steady-state systemic exposure was less from COMBIVENT RESPIMAT compared to that of CFC-propelled COMBIVENT Inhalation Aerosol. Albuterol plasma AUC and urine Ae ratios for COMBIVENT RESPIMAT/CFC-propelled COMBIVENT Inhalation Aerosol were 0.74 and 0.86, respectively.

Pharmacokinetic drug-drug interaction between ipratropium bromide and albuterol sulfate was evaluated in a crossover study in 12 healthy male volunteers who received CFC-propelled COMBIVENT Inhalation Aerosol and the two active components separately as individual treatments. Results from this study indicated that the coadministration of these two components from a single canister did not significantly alter the systemic absorption of either component, indicating lack of any pharmacokinetic interaction between these two drugs.

Specific Populations

Age

Consistent with CFC-propelled COMBIVENT Inhalation Aerosol (36/206 mcg), patients receiving COMBIVENT RESPIMAT (20/100 mcg) aged 65 years and over had higher steady state systemic exposures than patients aged under 65 years for both ipratropium (AUC = 166 vs. 105 pg•hr/mL, C_{max} = 38.5 vs. 30.1 pg/mL) and albuterol (AUC = 5.44 vs. 3.27 ng•hr/mL, C_{max} = 1.19 vs. 0.74 ng/mL).

Gender

The AUC- and C_{max}-values for ipratropium were 131 pg.hr/mL and 35.4 pg/mL in males and 123 pg.hr/mL and 31.7 pg/mL in females, respectively. The AUC- and C_{max}-values for albuterol were 4.0 ng•hr/mL and 0.89 ng/mL in males and 4.2 ng•hr/mL and 0.93 ng/mL in females, respectively.

Hepatic and Renal Impairment

The pharmacokinetics of COMBIVENT RESPIMAT or ipratropium bromide has not been studied in patients with hepatic or renal insufficiency.

Drug-Drug Interactions

No specific pharmacokinetic studies were conducted to evaluate potential drug-drug interactions with other medications.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ipratropium bromide

Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic activity at doses up to 6 mg/kg/day (approximately 400 and 200 times the maximum recommended human daily inhalation dose of ipratropium bromide (MRHDID) in adults on a mg/m² basis, respectively).

Results of various mutagenicity/clastogenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test, and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg/day (approximately 3400 times the MRHDID in adults on a mg/m² basis) was unaffected by ipratropium bromide administration. At an oral dose of 500 mg/kg/day (approximately 34,000 times the MRHDID in adults on a mg/m² basis), ipratropium bromide produced a decrease in the conception rate.

Albuterol

Like other agents in its class, albuterol caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year study in the rat at dietary doses of 2, 10, and 50 mg/kg/day (approximately 20, 110, and 560 times the MRHDID on a mg/m² basis). In another study this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice at dietary doses up to 500 mg/kg/day (approximately 2800 times the MRHDID on a mg/m² basis) and a 99-week study in hamsters at oral doses up to 50 mg/kg/day (approximately 470 times the MRHDID on a mg/m² basis) revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis.

Reproduction studies in rats with albuterol sulfate revealed no evidence of impaired fertility.

14 CLINICAL STUDIES

The efficacy of COMBIVENT RESPIMAT (20/100 mcg) was evaluated in COPD patients in one randomized, double-blind, double-dummy parallel group trial. This was a 12-week trial in a total of 1460 adult patients (955 males and 505 females) conducted to demonstrate the efficacy and safety of COMBIVENT RESPIMAT (20/100 mcg) in COPD. All patients were required to have a clinical diagnosis of COPD, be at least 40 years of age or older, to have an FEV_1 of less than or equal to 65% predicted and an FEV_1/FVC ratio of less than or equal to 0.7 at screening, and a smoking history of greater than 10 pack-years prior to entering the trial. Patients with narrow-angle glaucoma, symptomatic prostatic hypertrophy, or bladder neck obstruction were excluded from the trial. The majority of the patients (89%) were Caucasian, had a mean age of 64 years, a mean percent predicted pre-bronchodilator FEV_1 of 41% and FEV_1/FVC ratio of 0.45. The patients were randomized to one of the following active treatments COMBIVENT RESPIMAT (20/100 mcg) (n=486), CFC-propelled COMBIVENT Inhalation Aerosol (36/206 mcg) (n=491), and ipratropium bromide delivered by the RESPIMAT (20 mcg) (n=483) administered four times a day. Data from 1424 patients were used in the efficacy analyses.

There were three primary efficacy variables: (i) Mean FEV_1 over 0 to 6 hours post-dose defined as the AUC of the change from test-day baseline in FEV_1 over 0 to 6 hours post-dose divided by 6 hours (FEV_1 $AUC_{0\text{-}6h}$); (ii) Mean FEV_1 over 0 to 4 hours post-dose defined as the AUC of the change from test-day baseline in FEV_1 over 0 to 4 hours post-dose divided by 4 hours (FEV_1 $AUC_{0\text{-}4h}$), and (iii) Mean FEV_1 over 4 to 6 hours post-dose defined as the AUC of the change from test-day baseline in FEV_1 over 4 to 6 hours post-dose divided by 2 hours (FEV_1 $AUC_{4\text{-}6h}$). Test-day baseline was the FEV_1 recorded prior to inhaling the dose of randomized treatment on test day.

The three primary efficacy comparisons were: (i) Non-inferiority of COMBIVENT RESPIMAT (20/100 mcg) to CFC-propelled COMBIVENT Inhalation Aerosol (36/206 mcg) for the FEV_1 $AUC_{0\text{-}6h}$ on Test Day 85; (ii) Superiority of COMBIVENT RESPIMAT (20/100 mcg) to ipratropium RESPIMAT (20 mcg) for the FEV_1 $AUC_{0\text{-}4h}$ on Test Day 85, to demonstrate the contribution of albuterol in the combination product, and (iii) Non-inferiority of COMBIVENT RESPIMAT (20/100 mcg) in comparison to ipratropium RESPIMAT (20 mcg) for FEV_1 $AUC_{4\text{-}6h}$ on Test Day 85, to demonstrate the contribution of ipratropium in the combination product. Non-inferiority was declared if the lower bound of the 95% confidence interval for the point estimate for the difference of COMBIVENT RESPIMAT minus the comparator was more than -50 mL.

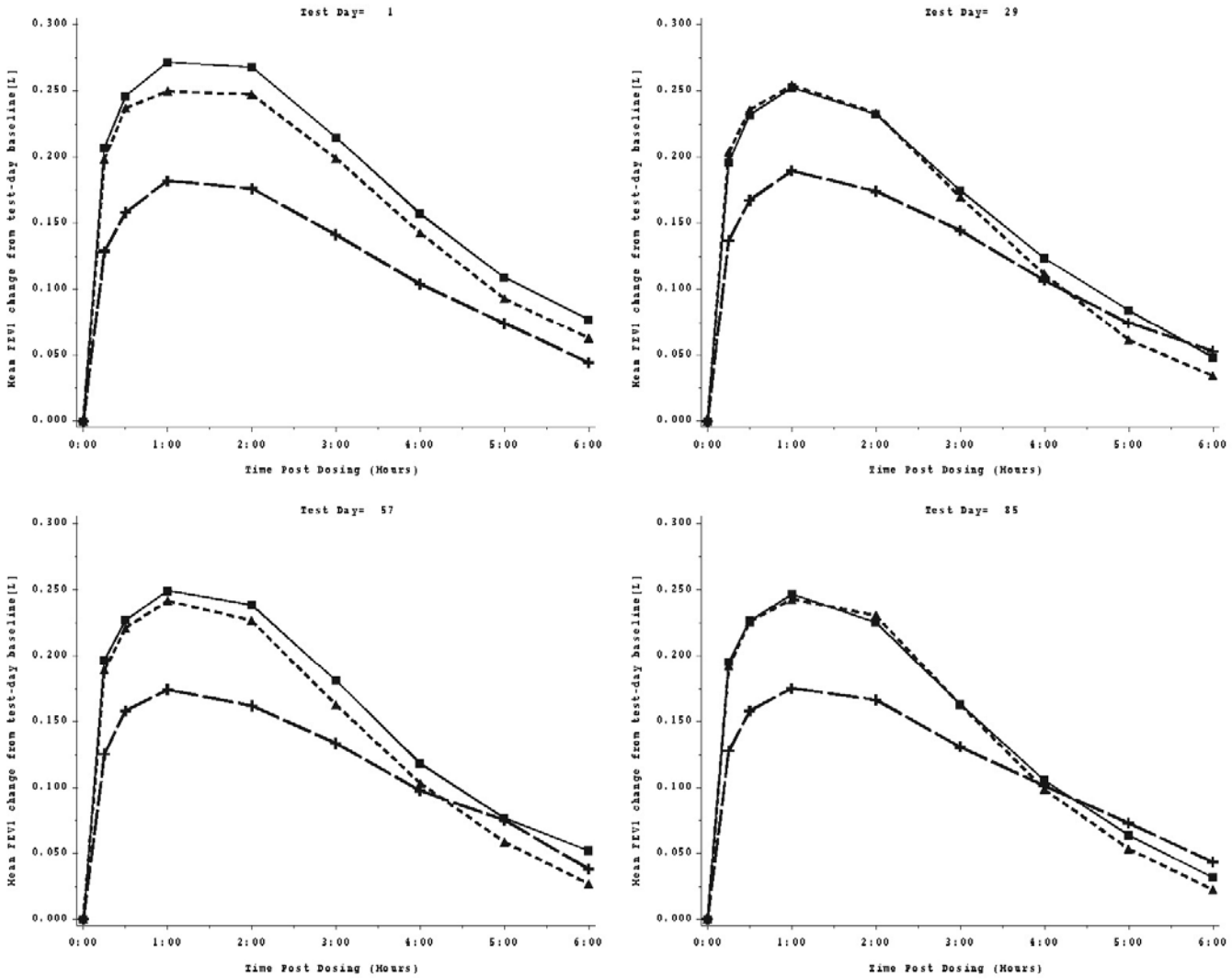
COMBIVENT RESPIMAT (20/100 mcg) was shown to be non-inferior to CFC-propelled COMBIVENT Inhalation Aerosol (36/206 mcg) in terms of mean FEV_1 $AUC_{0\text{-}6h}$. The LS mean (mL) (95% CI) of the treatment difference was -3 (-22, 15). The FEV_1 $AUC_{0\text{-}4h}$ for COMBIVENT RESPIMAT (20/100 mcg), was superior to that of ipratropium bromide [LS mean (mL) (95% CI) of the treatment difference was 47 mL (28, 66)] and the mean FEV_1 $AUC_{4\text{-}6h}$ for COMBIVENT RESPIMAT (20/100 mcg) was non-inferior to that of ipratropium bromide [LS mean (mL) (95% CI) of the treatment difference was -17 (-39, 5)]. The FEV_1 results on Test Days 1, 29, 57, and 85 are shown in Figure 1.

In this trial, COMBIVENT RESPIMAT (20/100 mcg) was shown to be clinically comparable (statistically non-inferior) to CFC-propelled COMBIVENT Inhalation Aerosol (36/206 mcg).

Additionally, in this trial, no differences in these efficacy comparisons were identified in males and females or in patients over 65 years of age versus those under 65 years of age. There were too few African-American subjects to adequately assess differences in effects in that population.

The median time to onset of bronchodilation, defined as an FEV_1 increase of 15% or greater from test-day baseline, for the COMBIVENT RESPIMAT (20/100 mcg) group occurred at 13 minutes post-dose on Day 1.

Figure 1 Time Profile of FEV_1 at Days 1, 29, 57, and 85



COMBIVENT RESPIMAT (20/100 mcg), 1 inhalation (N=474)
CFC-propelled COMBIVENT Inhalation Aerosol (18/103 mcg), 2 inhalations (N=482)
Ipratropium bromide delivered by the RESPIMAT (20 mcg), 1 inhalation (N=468)

The means are adjusted for treatment baseline and investigator site. A separate ANCOVA was fitted for each time point.
The imputation method for data missing because the patient withdrew from the trial was Last Visit Carried Forward.
The imputation method for data missing at the end of test days depends on why the data were missing.

A second study was conducted in 1118 COPD patients using a higher than approved dose of COMBIVENT RESPIMAT. Patients were randomized to COMBIVENT RESPIMAT (40/200 mcg) (n=345), CFC-propelled COMBIVENT Inhalation Aerosol (36/206 mcg) (n=180), ipratropium delivered by the RESPIMAT (40 mcg) (n=252) or placebo (n= 341). The study was supportive, particularly for safety [*see Adverse Reactions (6.1)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

COMBIVENT RESPIMAT Inhalation Spray is supplied in a carton containing one COMBIVENT RESPIMAT cartridge and one COMBIVENT RESPIMAT inhaler (NDC 0597-0024-02).

The COMBIVENT RESPIMAT cartridge is provided as an aluminum cylinder with a tamper protection seal on the cap. The COMBIVENT RESPIMAT cartridge is only intended for use with the COMBIVENT RESPIMAT inhaler.

The COMBIVENT RESPIMAT inhaler is a cylindrical shaped plastic inhalation device with a gray colored body and a clear base. The clear base is removed to insert the cartridge. The inhaler contains a dose indicator. The orange colored cap and the written information on the label of the grey inhaler body indicate that it is labeled for use with the COMBIVENT RESPIMAT cartridge.

The COMBIVENT RESPIMAT cartridge has a net fill weight of 4 grams and when used with the COMBIVENT RESPIMAT inhaler, is designed to deliver 120 metered actuations after preparation for use; the equivalent of 30 days' medication when used as one inhalation four times a day. Each actuation from the

COMBIVENT RESPIMAT inhaler delivers 20 mcg ipratropium bromide (monohydrate) and 100 mcg albuterol (equivalent to 120 mcg albuterol sulfate) from the mouthpiece.

When the labeled number of metered actuations (120) has been dispensed from the inhaler, the RESPIMAT locking mechanism will be engaged and no more actuations can be dispensed.

After assembly, the COMBIVENT RESPIMAT inhaler should be discarded at the latest 3 months after first use or when the locking mechanism is engaged (120 actuations), whichever comes first.

Keep out of reach of children. Do not spray into eyes.

Storage
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Avoid freezing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling

17.1 Ocular Effects
Caution patients to avoid spraying the aerosol into their eyes and be advised that this may result in precipitation or worsening of narrow-angle glaucoma, mydriasis, increased intraocular pressure, acute eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes from conjunctival and corneal congestion. Patients should also be advised that should any combination of these symptoms develop, they should consult their physician immediately.

Since dizziness, accommodation disorder, mydriasis, and blurred vision may occur with use of COMBIVENT RESPIMAT, patients should be cautioned about engaging in activities requiring balance and visual acuity such as driving a car or operating appliances or machinery.

17.2 Urinary Retention
Inform patients that COMBIVENT RESPIMAT may cause urinary retention and should be advised to consult their physician if they experience difficulty with urination.

17.3 Frequency of Use
The action of COMBIVENT RESPIMAT should last 4 to 5 hours or longer. COMBIVENT RESPIMAT should not be used more frequently than recommended. Safety and efficacy of additional doses of COMBIVENT RESPIMAT beyond six inhalations in 24 hours have not been studied. Patients should be told not to increase the dose or frequency of COMBIVENT RESPIMAT without consulting a physician. Patients should be instructed that if they find that treatment with COMBIVENT RESPIMAT becomes less effective for symptomatic relief, their symptoms become worse, and/or they need to use the product more frequently than usual, medical attention should be sought immediately.

17.4 Preparation for Use and Priming
Instruct patients that priming COMBIVENT RESPIMAT is essential to ensure appropriate content of the medication in each actuation.

When using the unit for the first time, the COMBIVENT RESPIMAT cartridge is inserted into the COMBIVENT RESPIMAT inhaler and the unit is primed. COMBIVENT RESPIMAT patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then repeat the process three more times. The unit is then considered primed and ready for use. If not used for more than 3 days, patients are to actuate the inhaler once to prepare the inhaler for use. If not used for more than 21 days, patients are to actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use. [*See FDA-approved Patient Labeling (17.9)*].

17.5 Concomitant Drug Use
Remind patients that while taking COMBIVENT RESPIMAT, other inhaled drugs should be taken only as directed by a physician.

17.6 Paradoxical Bronchospasm
Inform patients that COMBIVENT RESPIMAT can produce paradoxical bronchospasm that can be life-threatening. If paradoxical bronchospasm occurs, patients should discontinue using COMBIVENT RESPIMAT.

17.7 Adverse Effects Associated with Beta$_2$-agonists
Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

17.8 Pregnancy
Patients who are pregnant or nursing should contact their physician about the use of COMBIVENT RESPIMAT.

17.9 FDA-approved Patient Labeling
Instructions for Use is supplied as a tear-off following the full prescribing information.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Address medical inquiries to: (800) 542-6257 or 800 459-9906 TTY.

COMBIVENT® and RESPIMAT® are registered trademarks and used under license from Boehringer Ingelheim International GmbH

Copyright 2012 Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

OT24008DI052012
301041-03

IT5581B
301198-04

Instructions for Use

COMBIVENT® RESPIMAT® (COM beh vent - RES peh mat)
(ipratropium bromide and albuterol)
Inhalation Spray

For Oral Inhalation Only
Do not spray COMBIVENT RESPIMAT into your eyes

Read this Instructions for Use before you start using COMBIVENT RESPIMAT and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

Use COMBIVENT RESPIMAT exactly as prescribed by your doctor. Do not change your dose or how often you use COMBIVENT RESPIMAT without talking with your doctor.

Tell your doctor about all of the medicines you take. COMBIVENT RESPIMAT may affect the way some medicines work and some other medicines may affect the way COMBIVENT RESPIMAT works. Do not use other inhaled medicines with COMBIVENT RESPIMAT without talking to your doctor.

The COMBIVENT RESPIMAT inhaler has a slow moving mist that helps you inhale the medicine.

Your COMBIVENT RESPIMAT cartridge contains 120 puffs (equal to 120 doses of medicine) after you prepare your inhaler for the first use. There is enough medicine for 30 days when it is used as 1 puff 4 times a day. Before your COMBIVENT RESPIMAT inhaler is used for the first time, the COMBIVENT RESPIMAT cartridge must be inserted into the COMBIVENT RESPIMAT inhaler and then primed. The instructions below show you how to prepare and prime the inhaler for first time use and how to use the inhaler for daily dosing.

Do not turn the clear base before inserting the cartridge.

The COMBIVENT RESPIMAT inhaler

Prepare For First Time Use

Figure 1

Step 1. With the orange cap closed, press the safety catch while pulling off the clear base. See Figure 1.

Be careful not to touch the piercing element located inside the bottom of the clear base.

Figure 2

Step 2. Write the **discard by** date on the label of the COMBIVENT RESPIMAT inhaler. The **discard by** date is 3 months from the date the cartridge is inserted into the inhaler. See Figure 2.

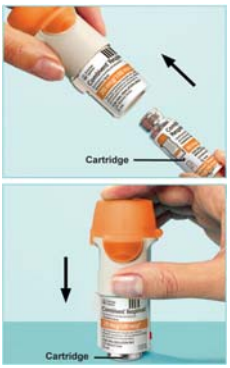


Figure 3

Step 3. Take the COMBIVENT RESPIMAT cartridge out of the box.

Push the **narrow** end of the cartridge into the inhaler. The base of the cartridge will not sit flush with the inhaler. **About 1/8 of an inch will remain visible** when the cartridge is correctly inserted. See Figure 3.

The cartridge can be pushed against a firm surface to ensure that it is correctly inserted. See Figure 3.

Do not remove the cartridge once it has been inserted into the inhaler.

Figure 4

Step 4. Put the clear base back into place. See Figure 4.

Do not remove the clear base again.

Your COMBIVENT RESPIMAT inhaler should not be taken apart after you have inserted the cartridge and put the clear base back.

Prime For First Time Use

The following steps are needed to fill the dosing system the first time you use it and will not affect the number of doses available. After preparation and initial priming, your COMBIVENT RESPIMAT inhaler will be able to deliver 120 doses.

Proper priming of the inhaler is important to make sure the correct amount of medicine is delivered.

Figure 5

Step 5. Hold the COMBIVENT RESPIMAT inhaler upright, with the orange cap closed, to avoid accidental release of the dose.
Turn the clear base in the direction of the white arrows on the label until it clicks (half a turn). See Figure 5.

Figure 6

Step 6. Flip the orange cap until it snaps fully open. See Figure 6.

Figure 7

Step 7. Point the COMBIVENT RESPIMAT inhaler toward the ground (away from your face).

Press the dose release button. See Figure 7. Close the orange cap.

Repeat Steps 5, 6, and 7 until a spray is visible.

Once the spray is visible, you must repeat Steps 5, 6, and 7 three more times to make sure the inhaler is prepared for use.

Your COMBIVENT RESPIMAT inhaler is now ready to use.

These steps will not affect the number of doses available. After preparation and initial priming, your COMBIVENT RESPIMAT inhaler will be able to deliver 120 doses.

Daily Dosing

Figure A

Step A. Hold the COMBIVENT RESPIMAT inhaler upright with the orange cap closed, so you do not accidentally release a dose of medicine.

Turn the clear base in the direction of the white arrows on the label until it clicks (half a turn). See Figure A.

Figure B

Step B. Flip the orange cap until it snaps fully open.

Breathe out slowly and fully, and then close your lips around the end of the mouthpiece without covering the air vents. See Figure B.

Point your COMBIVENT RESPIMAT inhaler to the back of your throat.

While taking in a slow, deep breath through your mouth, press the dose release button and continue to breathe in slowly for as long as you can.

Hold your breath for 10 seconds or for as long as comfortable.
Close the orange cap until you use your COMBIVENT RESPIMAT inhaler again.

If your COMBIVENT RESPIMAT inhaler has not been used for more than 3 days, spray 1 puff toward the ground to prepare the inhaler for use.

If your COMBIVENT RESPIMAT inhaler has not been used for more than 21 days, repeat Steps 5, 6, and 7 until a spray is visible. Then repeat Steps 5, 6, and 7 three more times to prepare the inhaler for use.

For more information or a video demonstration on how to use COMBIVENT RESPIMAT, go to www.combivent.com. You may also call 1-800-542-6257 or (TTY) 1-800-459-9906 for further information about COMBIVENT RESPIMAT.

When should I get a new COMBIVENT RESPIMAT inhaler?

The COMBIVENT RESPIMAT inhaler contains 120 puffs, equal to 120 doses. The dose indicator shows approximately how much medicine is left. When the pointer enters the red area of the scale, there is enough medicine for 7 days. This is when you need to refill your prescription or ask your doctor if you need another prescription for COMBIVENT RESPIMAT Inhalation Spray.

Once the dose indicator has reached the end of the scale, all 120 puffs have been used and the COMBIVENT RESPIMAT inhaler locks automatically. At this point, the base cannot be turned any further.

Throw away the COMBIVENT RESPIMAT inhaler 3 months after insertion of cartridge into inhaler, even if all the medicine has not been used, or when the inhaler is locked (after 120 puffs), whichever comes first.

Questions and Answers about your COMBIVENT RESPIMAT inhaler

What if...	Reason	What to do
I can not turn the base easily?	The COMBIVENT RESPIMAT inhaler is already prepared and ready to use. The COMBIVENT RESPIMAT inhaler is locked after 120 puffs.	The COMBIVENT RESPIMAT inhaler can be used as it is. Prepare and use a new COMBIVENT RESPIMAT inhaler.
I can not press the dose release button?	The clear base has not been turned.	Turn the clear base until it clicks (half a turn).
The clear base springs back after I have turned it and a small amount of moisture is released?	The clear base was not turned far enough.	Prepare the COMBIVENT RESPIMAT inhaler for use by turning the clear base until it clicks (half a turn).
I can turn the clear base past the point where it clicks?	Either the dose release button has been pressed, or the clear base has been turned too far.	With the orange cap closed, turn the clear base until it clicks (half a turn).

How should I care for my COMBIVENT RESPIMAT inhaler?
Clean the mouthpiece, including the metal part inside the mouthpiece, with a damp cloth or tissue only, at least 1 time a week. Any minor discoloration in the mouthpiece does not affect your COMBIVENT RESPIMAT inhaler.

If the outside of your COMBIVENT RESPIMAT inhaler gets dirty, wipe it with a damp cloth.

How Should I store my COMBIVENT RESPIMAT inhaler?

- Store COMBIVENT RESPIMAT at Room Temperature between 59°F to 86°F (15°C to 30°C).
- Do not freeze your COMBIVENT RESPIMAT cartridge and inhaler.

Keep your COMBIVENT RESPIMAT cartridge and inhaler out of the reach of children.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

COMBIVENT® and RESPIMAT® are registered trademarks and are used under license from Boehringer Ingelheim International GmbH

Copyright 2012 Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: August 2012

OT24008DI052012
301041-03

IT5581B
301198-04