Air. Essential for Life.

Anticholinergics. Essential for COPD.*

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Please see Brief Summaries of Prescribing Information on accompanying pages.

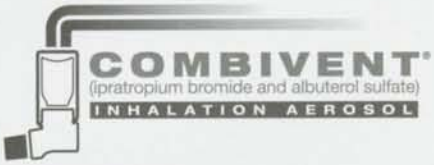
ATROVENT HFA (ipratropium bromide) INHALATION AEROSOL

COMBIVENT INHALATION AEROSOL

The COPD Essentials

*Maintenance therapy

CB-8740-3



COMBIVENT®
(ipratropium bromide and albuterol sulfate)
Inhalation Aerosol

Bronchodilator Aerosol For Oral Inhalation Only

Brief Summary of Prescribing Information

INDICATIONS AND USAGE Combivent® Inhalation Aerosol 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.

CONTRAINDICATIONS Combivent® Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to soya lecithin or related food products such as soybean and peanut. Combivent® Inhalation Aerosol is also contraindicated in patients hypersensitive to any other components of the drug product or to atropine or its derivatives.

WARNINGS 1. Paradoxical Bronchospasm: Combivent® Inhalation Aerosol can produce paradoxical bronchospasm that can be life threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

2. Cardiovascular Effect: The albuterol sulfate contained in Combivent® Inhalation Aerosol, 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. Although such effects are uncommon after administration of Combivent® Inhalation Aerosol at recommended doses, if they occur, discontinuation of the drug may be indicated. In addition, beta-adrenergic agents have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Therefore, Combivent® Inhalation Aerosol should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension.

3. 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.

4. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of ipratropium bromide or albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis and oropharyngeal edema.

5. Storage Conditions: The contents of Combivent® Inhalation Aerosol are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw the container into a fire or incinerator. Keep out of reach of children.

PRECAUTIONS General

1. Effects Seen with Anticholinergic Drugs: Combivent® Inhalation Aerosol contains ipratropium bromide and, therefore, should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

2. Effects Seen with Sympathomimetic Drugs: Preparations containing sympathomimetic amines such as albuterol sulfate should be used with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus and in patients who are unusually responsive to sympathomimetic amines. Beta-adrenergic agents may also 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.

3. Use in Hepatic or Renal Disease: Combivent® Inhalation Aerosol has not been studied in patients with hepatic or renal insufficiency. It should be used with caution in those patient populations.

Information for Patients Patients should be cautioned to avoid spraying the aerosol into their eyes and be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes from conjunctival and corneal congestion. Should any combination of these symptoms develop, consult your physician immediately.

The action of Combivent® Inhalation Aerosol should last 4-5 hours or longer. Combivent® Inhalation Aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of Combivent® Inhalation Aerosol without consulting your physician. If you find that treatment with Combivent® Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, medical attention should be sought immediately. While you are taking Combivent® Inhalation Aerosol, other inhaled drugs should be taken only as directed by your physician. If you are pregnant or nursing, contact your physician about use of Combivent® Inhalation Aerosol. Appropriate use of Combivent® Inhalation Aerosol includes an understanding of the way it should be administered (See Patient's Instructions for Use).

Drug Interactions Combivent® Inhalation Aerosol has been used concomitantly with other drugs, including sympathomimetic bronchodilators, methylxanthines and steroids, commonly used in the treatment of COPD, without adverse drug reactions. No formal drug interaction studies have been performed with Combivent® Inhalation Aerosol and these or other medications commonly used in the treatment of COPD.

Anticholinergic agents: Although ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is therefore advised in the co-administration of Combivent® Inhalation Aerosol with other anticholinergic-containing drugs.

Beta-adrenergic agents: Caution is advised in the co-administration of Combivent® Inhalation Aerosol and other sympathomimetic agents due to the increased risk of adverse cardiovascular effects.

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.

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 co-administration of beta agonist-containing drugs, such as Combivent® Inhalation Aerosol, with non-potassium sparing diuretics.

Monoamine oxidase inhibitors or tricyclic antidepressants: Combivent® Inhalation Aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or within two weeks of discontinuation of such agents because the action of albuterol on the cardiovascular system may be potentiated.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Ipratropium bromide: Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic potential at doses up to 6 mg/kg/day. This dose corresponds to approximately 360 and 180 times the maximum recommended human daily inhalation dose in rats and mice respectively, on a mg/m² basis. Results of various mutagenicity 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 3000 times the maximum recommended human daily inhalation dose on a mg/m² basis) was unaffected by ipratropium bromide administration. At doses above 90 mg/kg/day (approximately 5400 times the maximum recommended human daily inhalation dose on a mg/m² basis), increased resorption and decreased conception rates were observed.

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 two-year study in the rat at dietary doses of 2, 10 and 50 mg/kg/day (approximately 20, 100 and 500 times the maximum recommended human daily inhalation dose on a mg/m² basis). In another study this effect was blocked by the co-administration 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 2500 times the maximum recommended human daily inhalation dose on a mg/m² basis) and a 99-week study in hamsters at oral doses up to 50 mg/kg/day (approximately 375 times the maximum recommended human daily inhalation dose 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.

Pregnancy *TERATOGENIC EFFECTS Pregnancy Category C*

Ipratropium bromide: *Pregnancy Category B.* Oral reproduction studies were performed at doses of 10 mg/kg in mice, 100 mg/kg in rats and 125 mg/kg in rabbits. These doses correspond, in each species, respectively, to approximately 300, 600 and 15,000 times the maximum recommended human daily inhalation dose on a mg/m² basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg/day (approximately 90 and 210 times the maximum recommended human daily inhalation dose on a mg/m² basis). These studies have demonstrated no evidence of teratogenic effects as a result of ipratropium bromide.

Albuterol: *Pregnancy Category C.* Albuterol has been shown to be teratogenic in mice. A reproduction study in CD-1 mice given albuterol subcutaneously (0.025, 0.25 and 2.5 mg/kg) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (equivalent to the maximum recommended human daily inhalation dose on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 10 times the maximum recommended human daily inhalation dose on a mg/m² basis). None was observed at 0.025 mg/kg (approximately one-tenth the maximum recommended human daily inhalation dose). Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study with oral albuterol in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg (approximately 1000 times the maximum recommended human daily inhalation dose on a mg/m² basis).

There are, however, no adequate and well-controlled studies of Combivent® Inhalation Aerosol, ipratropium bromide or albuterol sulfate, in pregnant women. Because animal reproduction studies are not always predictive of human response, Combivent® Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers It is not known whether the components of Combivent® Inhalation Aerosol are excreted in human milk.

Ipratropium bromide: Although lipid-insoluble quaternary bases pass into breast milk, it is unlikely that the active component, ipratropium bromide, would reach the infant to an important extent, especially when taken by aerosol. However, because many drugs are excreted in human milk, caution should be exercised when Combivent® Inhalation Aerosol 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.

Pediatric Use Safety and effectiveness of Combivent® Inhalation Aerosol in pediatric patients have not been established.

ADVERSE REACTIONS Adverse reaction information concerning Combivent® Inhalation Aerosol is derived from two 12-week controlled clinical trials (N=358 for Combivent® Inhalation Aerosol).

All Adverse Events (in percentages), from Two Large Double-Blind, Parallel, 12-Week Studies of Patients with COPD*

	Combivent® Ipratropium Bromide 36 mcg/Albuterol Sulfate 206 mcg q.i.d. N=358	Ipratropium Bromide 36 mcg q.i.d. N=362	Albuterol Sulfate 206 mcg q.i.d. N=347
Body as A Whole-			
General Disorders			
Headache	5.6	3.9	6.6
Pain	2.5	1.9	1.2
Influenza	1.4	2.2	2.9
Chest Pain	0.3	1.4	2.9
Gastrointestinal System Disorders			
Nausea	2.0	2.5	2.6
Respiratory System Disorders (Lower)			
Bronchitis	12.3	12.4	17.9
Dyspnea	4.5	3.9	4.0
Coughing	4.2	2.8	2.6
Respiratory Disorders	2.5	1.7	2.3
Pneumonia	1.4	2.5	0.6
Bronchospasm	0.3	3.9	1.7
Respiratory System Disorders (Upper)			
Upper Resp. Tract Infection	10.9	12.7	13.0
Pharyngitis	2.2	3.3	2.3
Sinusitis	2.3	1.9	0.9
Rhinitis	1.1	2.5	2.3

*All adverse events, regardless of drug relationship, reported by two percent or more patients in one or more treatment group in the 12-week controlled clinical trials.

Additional adverse reactions, reported in less than two percent of the patients in the Combivent® Inhalation Aerosol treatment group include edema, fatigue, hypertension, dizziness, nervousness, paresthesia, tremor, dysphonia, insomnia, diarrhea, dry mouth, dyspepsia, vomiting, arrhythmia, palpitation, tachycardia, arthralgia, angina, increased sputum, taste perversion, and urinary tract infection/dysuria.

Allergic-type reactions such as skin rash, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reaction have been reported, with positive rechallenge in some cases. Many of these patients had a history of allergies to other drugs and/or foods including soybean (See CONTRAINDICATIONS).

Additional information derived from the published literature and post-marketing surveillance on the use of ipratropium or albuterol inhalation aerosol singly or in combination that is not included in the lists above includes: cases of precipitation or worsening of narrow-angle glaucoma, acute eye pain, blurred vision, nasal congestion, drying of secretions, mucosal ulcers, irritation from aerosol, paradoxical bronchospasm, wheezing, exacerbation of COPD symptoms, heartburn, drowsiness, CNS stimulation, coordination difficulty, weakness, itching, flushing, alopecia, hypotension, gastrointestinal distress, constipation, and urinary difficulties.

HOW SUPPLIED Combivent® Inhalation Aerosol is supplied as a metered-dose inhaler with a white mouthpiece which has a clear, colorless sleeve and an orange protective cap. The Combivent® Inhalation Aerosol canister should be used with the Combivent® Inhalation Aerosol actuator only. The actuator should not be used with other aerosol medications. Each actuation meters 21 mcg of ipratropium bromide and 120 mcg of albuterol sulfate from the valve and delivers 18 mcg of ipratropium bromide and 103 mcg of albuterol sulfate (equivalent to 90 mcg albuterol base) from the mouthpiece. Each 14.7 gram canister provides sufficient medication for 200 inhalations (NDC 0597-0013-14).

The canister should be discarded after the labeled number of actuations have been used. The amount of medication in each actuation cannot be assured after this point.

Store between 59° F (15° C) and 86° F (30° C). Avoid excessive humidity. For optimal results, the canister should be at room temperature before use. **Shake well before using.**

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs):

> **Warning:** Contains trichloromonofluoromethane (CFC-11), dichlorodifluoromethane (CFC-12) and dichlorotetrafluoroethane (CFC-114), substances which harm public health and the environment by destroying ozone in the upper atmosphere.

A notice similar to the above **Warning** has been placed in the information for the patient of this product under the Environmental Protection Agency's (EPA's) regulations. The patient's warning states that the patient should consult his or her physician if there are any questions about alternatives.

℞ only

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