

# MATERIAL SAFETY DATA SHEET

Boehringer Ingelheim Pharmaceuticals, Inc.

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**Combivent®**

DATE ISSUED: 2/3/03

EMERGENCY TELEPHONE NUMBER  
CHEMTREC - 24 hours  
1-800-424-9300

## 1. SUBSTANCE IDENTIFICATION

**CHEMICAL NAME:**

**Atrovent®:** 8-Azoniabicyclo (3.2.1)-octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-,bromide, monohydrate (endo,syn)-,(±).and,  
**Albuterol sulfate:** (1,3-benzenedimethanol,  $\alpha'$ -[[[(1,1-dimethyl-ethyl)amino] methyl]-4-hydroxy, sulfate (2:1)(salt),(±)

CAS TYPE: 1

GENERIC NAME: Ipratropium bromide & Albuterol sulfate

MOLECULAR FORMULA:  $C_{20}H_{30}BrNO_3 \cdot H_2O$  &  $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$

TRADEMARK: **Combivent® Inhalation Aerosol**

MOLECULAR WEIGHT: 430.4 (Atrovent®)  
576.7 (Albuterol Sulfate)

CHEMICAL FAMILY: Bronchodilator

CAS NUMBER: 66985-17-9 (Atrovent®)  
51022-70-9 (Albuterol Sulfate)

SYNONYMS: Atrovent®-Sch 1000, Ipratropium bromide (German), Itrop, Ventolin®-Albuterol sulfate, salbutamol

## 2. COMPONENTS PER UNIT DOSE

**MATERIAL**

**Active Ingredient:**

Ipratropium Bromide

Albuterol Sulfate

**Excipients:**

Dichlorodifluoromethane (Freon 12)

Dichlorotetrafluoroethane (Freon 114)

Trichloromonofluoromethane (Freon 11)

Soya Lecithin

**EXPOSURE LIMITS**

15  $\mu\text{g}/\text{m}^3$  BIEL\*\*

N/E

1000 ppm\*

1000 ppm\*

1000 ppm ceiling\*

No TLV established\*

\*As per 2002 ACGIH

\*\*BIEL is the BI Exposure Control Level. When lower governmentally imposed occupational exposure limits exist, such limits should take precedence.

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### 3. HAZARD IDENTIFICATION

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#### EMERGENCY OVERVIEW

**Milky white liquid.**

**Warning: May cause sensitization  
May cause eye, skin or respiratory irritation**

**Will not burn. If involved in a fire, material emits toxic fumes. Use extinguishing media suitable for the material that is burning.**

**Pressurized containers may explode when heated.**

ROUTES OF ENTRY: Inhalation, Ingestion, Skin and Eye contact.

TARGET ORGANS: Liver, GI tract, adrenals, male reproductive organs and eyes.

CONTRAINDICATIONS: Although rare, this product can cause immediate hypersensitivity in patients. Therefore, **Combivent® Inhalation Aerosol** should not be used by patients who have had a previous allergic reaction to soya lecithin or related food products such as soybean and peanuts. This product should also not be taken by individuals who have a history of sensitivity to atropine, its derivatives, or any of the product's components.

ADVERSE REACTIONS TO PRODUCT: Upper respiratory tract infections, bronchitis, headache, palpitations, nervousness, dizziness coughing, nausea, vomiting, tremor, dry mouth, dyspnea (difficult or rapid breathing), edema, fatigue, chest pain, urinary tract infections, increased sputum and taste perversion.

#### **WARNING:**

**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.

Do not spray in eyes. Direct eye contact with product may cause temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma or eye pain. If these symptoms occur, contact your physician.

Immediate hypersensitivity (allergic) reactions may occur after use such as urticaria (hives), angioedema (giant hives), bronchospasm (spasms of the lung's bronchial tubes), oropharyngeal edema (swelling of the lips, tongue and throat) and rash.

Paradoxical Bronchospasm: **Combivent® Inhalation Aerosol** can produce paradoxical bronchospasm that can be life-threatening. If this occurs, the preparation should be discontinued immediately and alternative therapy instituted. Patients should be aware that this reaction frequently occurs with the first use of a new canister.

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.

ACUTE EXPOSURE: Eye, skin and/or respiratory irritation.

**WARNING:** At levels above the TLV, the CFC's (freon components) of this product can cause central nervous system effects (tremor), cardiac dysrhythmias (irregular heartbeats) and death.

SIGNS AND SYMPTOMS OF EXPOSURE: Eye contact may cause temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma or eye pain. Possible allergic reaction if inhaled, dry mouth, cough, nervousness, dizziness, headache, nausea, gastrointestinal distress, palpitations, dilation of pupils.

CHRONIC EXPOSURE: Possible hypersensitization (development of abnormal sensitivity).

MEDICAL CONDITIONS POTENTIALLY AGGRAVATED BY EXPOSURE: Dust allergies, pre-existing hypersensitivity (allergic reaction) to any of the product's components, narrow angle glaucoma, prostatic hypertrophy, bladder neck obstruction, convulsive disorders, hyperthyroidism, or diabetes mellitus.

CARCINOGENICITY: Not listed as carcinogen/potential carcinogen by NTP/IARC Monographs or OSHA.

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#### 4. EMERGENCY FIRST AID PROCEDURES

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**Persons developing anaphylactic (life-threatening) reactions, such as difficulty in breathing or unconsciousness, must receive immediate medical attention.** NOTE TO PHYSICIAN: Treat symptomatically.

**INGESTION:** Rinse mouth out with large amounts of water. Do not induce vomiting or give anything by mouth to an unconscious or convulsing person. Seek medical attention.

**INHALATION:** Remove affected person to a well ventilated area and get immediate medical attention. If breathing becomes difficult, give oxygen. If breathing stops, start artificial respiration.

**SKIN CONTACT:** Remove contaminated clothing. Flush affected area with copious amounts of water. If irritation or rash develops, get medical attention.

**EYE CONTACT:** Flush eyes with large amounts of running water for at least 15 minutes. Get immediate medical attention.

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#### 5. FIRE AND EXPLOSION HAZARD DATA

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Flash Point	Flammable Limits	
	Upper	Lower
N/A	N/A	N/A

FIRE EXTINGUISHING MEDIA: Water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials.

**SPECIAL FIRE FIGHTING PROCEDURES:** As with all fires, evacuate personnel to safe area. Firefighters should use self-contained breathing equipment and protective clothing. Use water spray to keep fire-exposed containers cool and protect against all exposures.

#### UNUSUAL FIRE AND EXPLOSION HAZARDS

Pressurized containers may explode when heated. When heated to decomposition, material emits toxic fumes of bromide, acid gases and phosgene.

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## 6. SPILL AND ACCIDENTAL RELEASE MEASURES

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**STEPS TO BE TAKEN IN THE EVENT OF A SPILL:** Wear approved respirator and chemically compatible gloves if containers have been compromised. Vacuum or sweep up spillage. Avoid creating dust. Place spillage in appropriate container for waste disposal. Wash contaminated clothing before reuse. Ventilate area, wash down spill site, and control wash water.

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## 7. PRECAUTIONS FOR SAFE HANDLING AND USE

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#### HANDLING AND STORAGE PRECAUTIONS:

##### WARNING - CONTENTS UNDER PRESSURE

Do not puncture or incinerate container except at a facility capable of handling pressurized canisters. Store between 59°F (15°C) and 86°F (30°C) KEEP OUT OF THE REACH OF CHILDREN.

Avoid contact with eyes, skin or clothing. Avoid breathing dust or aerosol. Store in airtight container and protect from light.

**OTHER PRECAUTIONS:** Wash thoroughly after handling material. Wear fresh clothing daily. Wash contaminated clothing before reuse.

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## 8. CONTROL MEASURES

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**ENGINEERING CONTROLS:** Not generally required when handling containers. (See section 2 for exposure limits.) Use appropriate respiratory protection based on an industrial hygiene survey.)

**RESPIRATORY PROTECTION:** The need for respiratory protection should be determined by an industrial hygiene survey. (See Section 2 for exposure limits.) NIOSH/MSHA approved respirators for protection should be used if respirators are found to be necessary.

**VENTILATION:** General ventilation should be adequate to maintain exposure levels below recommended established exposure limits. If general ventilation is not sufficient, local exhaust is recommended.

**PERSONAL PROTECTIVE EQUIPMENT:** Not generally required when handling final product. If containers are compromised or exposure to the active ingredient or mixture is likely wear:

Eye Protection: Safety glasses w/ sideshields or goggles

Hand Protection: Neoprene gloves

Protective Clothing: Laboratory coats

Other: Eye wash

**WORK/HYGIENIC PRACTICES:** Do not permit eating, drinking or smoking near this material.

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## 9. PHYSICAL/CHEMICAL CHARACTERISTICS

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**APPEARANCE AND ODOR:** Milky white liquid supplied in a metered dose inhaler. Inhaler consists of a white mouth piece with a clear sleeve and an orange protective cap.

Boiling Point: N/A  
Vapor Pressure (mmHg): N/A  
Vapor Density: N/A  
Water Solubility: Soluble

Specific Gravity: N/A  
Melting Point: N/D  
Evaporation Rate: F-11 63  
pH: N/A

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## 10. REACTIVITY DATA

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**STABILITY:** Stable.

**CONDITIONS TO AVOID:** None known.

**INCOMPATIBLE MATERIALS:** Alkalis, iodine, mercury salts and tannic acid.

**HAZARDOUS DECOMPOSITION OR BY-PRODUCTS:** When heated to decomposition, material emits toxic fumes of bromide, acid gases and phosgene.

**HAZARDOUS POLYMERIZATION:** Will not occur.

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## 11. TOXICOLOGICAL INFORMATION

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ACUTE TOXICITY:

**Albuterol Sulfate & Ipratropium Bromide mixture:**

**6-Month Dog Inhalation Toxicity Study:** the “no effect level” was determined to be the dose level administered in this study (7 ug/kg/day Ipratropium Bromide and 41 ug/kg/day Albuterol Sulfate)

**Thirteen-Week Rat Nose-Only Inhalation Toxicity Study:** the no effect dose level for the formulation was determined to be 500 g/kg/day Ipratropium Bromide and 2857 g/kg/day Albuterol Sulfate. The maximum tolerated dose exceeded the maximum feasible targeted inhaled dose of 500 g/kg/day Ipratropium Bromide and 2857 g/kg/day Albuterol Sulfate achieved.

**Albuterol Sulfate**

**Rat LD50** - ROUTE: Intraperitoneal; DOSE: 295 mg/kg TOXIC EFFECTS: *Sense Organs and Special Senses (Nose, Eye, Ear, and Taste)* – Lacrimation *Lung, Thorax, or Respiration* - Respiratory depression

LD50 - ROUTE: Intravenous; DOSE: 59100 ug/kg TOXIC EFFECTS: *Behavioral* - Altered sleep time (including change in righting reflex) *Lung, Thorax, or Respiration* - Respiratory depression

LD50 - ROUTE: Oral; DOSE: >2500 mg/kg

LD50 - ROUTE: Subcutaneous; DOSE: >2500 mg/kg TOXIC EFFECTS: *Lung, Thorax, or Respiration* - Other changes *Skin and Appendages* - Hair

**Mouse LD50** - ROUTE: Intraperitoneal; DOSE: 200 mg/kg

LD50 - ROUTE: Intravenous; DOSE: 48700 ug/kg TOXIC EFFECTS: *Behavioral* - Altered sleep time (including change in righting reflex) *Lung, Thorax, or Respiration* - Respiratory depression

LD50 - ROUTE: Oral; DOSE: 1950 mg/kg

LD50 - ROUTE: Subcutaneous; DOSE: 737 mg/kg TOXIC EFFECTS: *Sense Organs and Special Senses (Nose, Eye, Ear, and Taste)* – Lacrimation *Behavioral* - Convulsions or effect on seizure threshold

**Ipratropium Bromide**

**Rat LD50** - Oral; DOSE: 1663 mg/kg TOXIC EFFECTS: *Behavioral* - Convulsions or effect on seizure threshold. *Behavioral* – Ataxia *Lung, Thorax, or Respiration* - Dyspnea

**Mouse LD50** - Oral; DOSE: 1001 mg/kg TOXIC EFFECTS: *Behavioral* - Convulsions or effect on seizure threshold. *Behavioral* – Ataxia *Lung, Thorax, or Respiration* – Dyspnea

**Dog LD50** -Oral; DOSE: 1300 mg/kg TOXIC EFFECTS: *Behavioral* - Convulsions or effect on seizure threshold *Behavioral* – Ataxia *Lung, Thorax, or Respiration* – Dyspnea

**Human TDLO:** Inhalation; Dose: 1 ug/kg TOXIC EFFECTS: Gastrointestinal –other changes

ACUTE TOXICITY for Excipients:

**Freon F-11 Animal Toxicity Data:**

1. LD50 Guinea pig inhalation 250,000 ppm/30 min
2. LD50 Rat inhalation 100,000 ppm/30 min
3. LD50 Rat oral 3725 mg/kg
4. LC50 Mouse inhalant 10,000 ppm/ 30 minutes
5. LC50 Hamster inhalation 571 g/cu m/4 hr

#### **Freon F-11 Human Toxicity Data**

1. By inhalation, large, acute doses have resulted in cardiac sensitization (arrhythmia) or bronchial constriction leading to death.
2. Human exposure to 1000 ppm, 8 hr/day, 5 days/wk for a total of 18 exposures had no untoward subjective effects, & there were no changes in the electrocardiogram or pulmonary function tests. The venous blood levels of F11 after 8 hr were as high as 4.69 ug/ml. The gradual attainment of this level represents a low uptake of the gas.
3. Bradycardia is the usual response in human subjects inhaling 10% of CFC 11. ... It is reasonable to suggest that bradycardia in man originates from irritation of the upper respiratory tract, & that cardiac effects can be initiated prior to absorption of CFC 11 in the lungs.
4. Gas of low toxicity but not entirely inert.
5. May be central nervous system depressant in high concentration.

#### **Freon F-12 Non-Human Toxicity Values:**

1. LD50 Mouse inhalation 760,000 ppm/30 min
2. LD50 Guinea pig inhalation >800,000 ppm/30 min
3. LD50 Rabbit inhalation >800,000 ppm/30 min
4. LD50 Rat single oral >1 g/kg
5. LD50 Rat inhalation >800,000 ppm/30 min

#### **Freon F-12 Human Toxicity Data**

1. Fatal case of bronchopneumonia /reported/ in man who punctured freezing coil of refrigerator containing F-12. It is probable that he aspirated cold concentrated vapor or liq, or was exposed to degradation products of refrigerant compound.
2. If inhaled at 5% by vol concentration induces dizziness in man. If inhaled at 15% concentration, loss of consciousness results.
3. Studies on ... Volunteers showed that inhalation of 10,000 ppm of fF12 for 2.5 hr causes 7% reduction in standardized psychomotor scores.
4. At concentration of 1000 ppm for 8 hr/day, 5 days/wk for total of 17 repetitive exposures, there were no untoward subjective responses & no abnormal physiological responses of lungs or heart.
5. Concentration as high as 27,000 ppm of F12 for 15 to 60 sec caused increase in airway resistance & electrocardiographic changes

#### **Freon F-114 Non-Human Toxicity Values:**

1. CFC-114 caused no effects in mice, rats, guinea-pigs, cats, or dogs after intermittent exposure to concentrations as high as 711 g/cu m (100 000 ppm). At higher dose levels (995-1422 g/cu m; 140,000-200,000 ppm) signs of intoxication were noted in guinea-pigs, dogs, rats, and mice.
2. Exposure at 20% by volume caused tremors and convulsions in dogs. after single 8-hour exposures the animals recovered, but repeated exposures for 8 hours daily were fatal after 3 or 4 days. single 16-hour exposures were also lethal to dogs.
3. Dogs survived 21 eight-hr exposures at 142,000 - 150,000 ppm CFC-114; the animals showed slight blood changes & symptoms ranging from in coordination to occasional convulsions.
4. Dogs survived eight-hr exposures at 200,000 ppm CFC-114; however a single 16-hr exposure or three to four 8-hr exposures were lethal. High concentration produced clinical signs of tremors, convulsions, & incoordination.
5. Concentrations around 1% caused slight irritation in guinea pigs; concentrations of 2 to 4.7% caused distinct irritation and increased respiration, but no pathological changes after 2 hours.
6. An increase in red blood cells, hemoglobin, & /immature/ forms of polymorphonuclear leucocytes were reported in dogs following exposure to vapors

## F 114 Human Toxicity Data

1. In one study, ten subjects were exposed to CFC-11, CFC-12, and CFC-114; two mixtures of CFC-11 and CFC-12; & a mixture of CFC-12 and CFC-114 )breathing concentration between 16 & 150 g/cu m [2300 & 21,400 ppm]) for 15, 45, or 60 sec. Significant acute reduction of ventilatory lung capacity was reported in each case, as well as bradycardia & increased variability in heart rate & atrioventricular block. It was concluded that the mixtures exerted stronger respiratory effects than individual chlorofluorocarbons at the same level of exposure.

**TERATOGENICITY: Ipratropium bromide:** PREGNANCY CATEGORY B: No evidence of teratogenic effects have been reported following oral administration or inhalation of Ipratropium bromide in animals (Pakes et al, 1980; Massey & Gotz, 1985). A slight reduction in weight of rat fetuses fed 500 mg/kg of Ipratropium bromide during organogenesis was reported by Nishimura et al (1978). Consult physician if you suspect you are pregnant, pregnant or nursing.

**Albuterol:** 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/m<sup>2</sup> basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 10 times the recommended human daily inhalation dose on mg/m<sup>2</sup> basis). 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 t 50 mg/kg (approximately 1000 times the maximum recommended human daily inhalation does on a mg/m2 basis).

### TUMORIGENIC EFFECTS:

Albuterol Sulfate - in a 2 year rat study there was a significant dose-related increase in the incidence of benign tumors. The relevance of these findings to humans is not known. An 18 month study in mice and a lifelong study in hamsters revealed no evidence of tumorigenicity.

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## 12. ECOLOGICAL INFORMATION

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**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.

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## 13. DISPOSAL CONSIDERATIONS

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**WASTE DISPOSAL CONSIDERATIONS:** Dispose of in accordance with local, state and federal regulations. Recommended method is incineration at a facility capable of handling pressurized canisters.

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## 14. TRANSPORT INFORMATION

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D.O.T. Proper Shipping Name: Consumer commodity  
Hazard Class: ORM-D  
Identification Number: N/A  
Packing Group: N/A  
Label: None  
Emergency Response Guidebook - N/A

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## 15. REGULATORY INFORMATION

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This product contains trichloromonofluoromethane (CFC-11), dichlorodifluoromethane (CFC-12) and dichlorotetrafluoroethane (CFC-114), which have been designated as Class I, Ozone Depleting Substances, in 40 CFR 82, Subpart A, Appendix A.

Medical aerosols are excluded from the definition of a "controlled product" under 40 CFR Part 82 - Protection of Stratospheric Ozone.

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## 16. OTHER INFORMATION

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### ABBREVIATIONS:

BIPI - Boehringer Ingelheim Pharmaceuticals, Inc.

N/A - Not Applicable

N/E - None established

### PREPARATION INFORMATION

Prepared by: Environmental Affairs & Safety.

Date Revised: 2/3/03

Replaces: 06/98

REVISION INFORMATION: Updated Sections 2, 3, 5, 8, 11, & 13

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### SEE CURRENT PACKAGE INSERT FOR FURTHER INFORMATION

### REFERENCES

1. Physician's Desk Reference, 55<sup>th</sup> Edition, 2001.
2. MICROMEDEX Systems Integrated Index Copyright© 1974 - 2002
3. IND for Combivent