

MATERIAL SAFETY DATA SHEET

Boehringer Ingelheim Pharmaceuticals,
Inc.
900 Ridgebury Rd
Ridgefield, CT 06877

Combivent® Respimat® Inhalation Spray

DATE ISSUED: November 14, 2008

EMERGENCY TELEPHONE NUMBER
(203) 798-5521

1. SUBSTANCE IDENTIFICATION

CHEMICAL NAME:

Ipratropium Bromide: 8-Azoniabicyclo (3.2.1)-octane, 3-(3hydroxy-1-oxo-2-phenylpropoxy)-8-(1-methylethyl)-,bromide, monohydrate (endo,syn)-, (±) and,
Albuterol Sulfate: (1,3-benzenedimethanol, α'-[[[(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® Respimat® Inhalation
Spray

MOLECULAR WEIGHT: 430.4 (Ipratropium
bromide) & 576.7 (Albuterol Sulfate)

CHEMICAL FAMILY: Bronchodilator

CAS NUMBER: 66985-17-9 (Ipratropium bromide)
& 51022-70-9 (Albuterol Sulfate)

SYNONMS:

2. COMPONENTS PER UNIT DOSE

MATERIAL	CAS NUMBERS	EXPOSURE LIMITS
Active Ingredients		
Albuterol Sulfate	51022-70-9	N/E
Ipratropium Bromide	66985-17-9	15 µg/M ³ *
Excipients		
Benzalkonium Chloride	8001-54-5	N/E
Edetate disodium	6381-92-6	N/E
Hydrochloric Acid	7647-01-0	5 PPM Ceiling
Nitrogen	7727-37-9	Simple Asphyxiant
Water	7732-18-5	N/A

*ECL: BIPI Exposure Control Limit. Where lower governmentally imposed limits are in effect, such limits should take precedence. Category 3A default banding control limits 10 - <100ug/m3.

3. HAZARD IDENTIFICATION

**EMERGENCY OVERVIEW:
Colorless 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.

ROUTES OF ENTRY: Inhalation, ingestion, eye and skin contact.

TARGET ORGANS: Liver, GI Tract, Adrenals, Male Reproductive Organs and Eyes

CONTRAINDICATIONS: 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: Coughing; Headache; Hypertension; Dizziness and Tremor; Muscle Spasms and Myalgia; Nausea, Dry Mouth, and Vomiting; Asthenia; Eye Pain; Hypokalemia; Papitations and Tachycardia; Rash; Chronic obstructive pulmonary disease and Dyspnea; Nasopharyngitis; Upper respiratory tract infections and Bronchitis, Nervousness; Fatigue; Chest Pain; Edema; Urinary tract infections; Increase 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® Respimat® Inhalation Spray** can produce paradoxical bronchospasm that can be life-threatening. If this occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Cardiovascular Effect: The albuterol sulfate contained in the **Combivent® Respimat® Inhalation Spray**, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients, as measured by pulse rate, blood pressure and/or symptoms. Although such effects are uncommon after administration of **Combivent® Respimat® Inhalation Spray** 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® Respimat® Inhalation Spray** 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

SIGNS AND SYMPTOMS OF EXPOSURE: Eye contact with product 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, and 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 or potential carcinogen by NTP, IARC Monographs or OSHA.

4. EMERGENCY FIRST AID PROCEDURES

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 areas with copious amounts of water. If irritation or rash develops and persists, seek medical attention.

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

5. FIRE AND EXPLOSION HAZARD DATA

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: When heated to decomposition, material emits toxic fumes of bromide, acid gases, and oxides of carbon and nitrogen.

6. SPILL AND ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN THE EVENT OF A SPILL: Wear approved respirator, eye protection 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.

7. PRECAUTIONS FOR SAFE HANDLING AND USE

HANDLING AND STORAGE PRECAUTIONS:

Store between 59°F (15°C) and 86°F (30°C). Avoid freezing. KEEP OUT OF REACH OF CHILDREN.

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

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

8. CONTROL MEASURES

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 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 is likely, wear:

Eye Protection: Safety glasses with side shields or goggles

Hand Protection: Neoprene Gloves

Protective Clothing: Laboratory coats

Other: Eye wash & safety shower

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

9. PHYSICAL/CHEMICAL CHARACTERISTICS

APPEARANCE AND ODOR: Colorless liquid supplied Respimat® drug Inhaler. Inhaler consists of a Gray mouth piece with an orange protective cap.

Boiling Point: N/A

Specific Gravity: N/A

Vapor Pressure (mm Hg): N/A

Melting Point: N/A

Vapor Density: N/A

Evaporation Rate: N/A

Water Solubility: Soluble

pH: N/A

10. REACTIVITY DATA

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 or under fire conditions, material emits: toxic fumes of bromide, acid gases, and oxides of carbon and nitrogen.

HAZARDOUS POLYMERIZATION: Will not occur

11. TOXICOLOGICAL INFORMATION

ACUTE TOXICITY:

Albuterol Sulfate & Ipratropium Bromide Mixture:

6-month Dog Inhalation Toxicity Study: the "no effect" was determined to be the dose level administered in this study (7 µg/kg/day Ipratropium Bromide and 41 µg/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 µg/kg TOXIC EFFECTS: *Behavioral – Altered sleep time (including change in righting reflex) Lung, Thorax, or Respiration – Respiratory depression*

LD₅₀ – ROUTE: Oral; DOSE: > 2500mg/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 µg/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 1µg/kg TOXIC EFFECTS: Gastrointestinal – other changes

Excipient Data

Benzalkonium Chloride

Acute Oral Toxicity - Rat LD₅₀ – 240 mg/kg

Edetate Disodium

Acute Oral Toxicity - Rat LD₅₀ – > 2000 mg/kg

Hydrochloric Acid

Acute Oral Toxicity - Rabbit LD₅₀ – 900 mg/kg

TERATOGENICITY:

Pregnancy Category C – There are no adequate and well controlled studies of **Combivent® Respimat® Inhalation Spray**, ipratropium bromide or albuterol sulfate, in pregnant women. Animal reproductive studies have not been conducted with **Combivent® Respimat® Inhalation Spray**. However, albuterol sulfate has been shown to be teratogenic in mice. **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 at doses of 10 mg/kg/day in mice, 1000 mg/kg/day in rats and 125 mg/kg/day in rabbits. These doses correspond in each species, respectively, to approximately 340, 68,000 and 17,000 times the maximum recommended daily inhalation dose in adults 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 100 and 240 times the recommended daily inhalation dose in adults on a mg/M² basis). These studies demonstrate no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses 90 mg/kg/day and above in rats (approximately 6,100 times the recommended daily inhalation dose in adults on a mg/M² basis) embryo toxicity was observed as increased resorption. 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. A reproductive 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 recommended human daily inhalation dose on a mg/M² 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 at 50 mg/kg (approximately 1000 times the maximum recommended human daily inhalation dose on a mg/M² basis).

Nursing Mothers – It is not known whether the components of **Combivent® Respimat® Inhalation Spray** are excreted in human milk.

TUMORIGENIC EFFECTS:

Albuterol Sulfate – in a 2 year rat study there was a significant dose-related increase in the incidences 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.

12. ECOLOGICAL INFORMATION

This is no data on the ecotoxicity of this product.

13. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL CONSIDERATIONS: Dispose of in accordance with local, state and federal regulations. Recommended method is incineration.

14. TRANSPORT INFORMATION

D.O.T. Proper Shipping Name: Not Regulated
Hazard Class: N/A
Identification Number: N/A
Packing Group: N/A
Label: None
Emergency Response Guidebook: N/A

15. REGULATORY INFORMATION

This material is **not** listed on the US TSCA Inventory. Therefore, it can only be used for TSCA exempt purposes such as R&D or drug use.

16. OTHER INFORMATION

ABBREVIATIONS:

BIPI: Boehringer Ingelheim Pharmaceuticals, Inc.
N/E: Not Established
N/A: Not Applicable
N/D: Not Determined

Prepared by: Environmental Health & Safety
Date Prepared: November 14, 2008
Replaces: New
Sections Revised:

NOTICE:

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REFERENCES:

Physician's Desk Reference 55th Edition 2001

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IND for Combivent

BIPI MSDS for Combivent® Inhalation Aerosol