

# MATERIAL SAFETY DATA SHEET

**Boehringer Ingelheim  
Pharmaceuticals, Inc.  
900 Ridgebury road  
Ridgefield, CT 06877**

Product name: **Spiriva® HandiHaler®**

DATE ISSUED: 3/25/04

**EMERGENCY TELEPHONE NUMBER  
1- (800) 424-9300**

## 1. SUBSTANCE IDENTIFICATION

CHEMICAL NAME: Tiotropium Bromide & lactose

GENERIC NAME: 6-alpha,7-alpha-Epoxy-8-methyl-8-azabicyclo(3.2.1)oct-3endo-yl-di-2-thienyl) glycolate Methylbromide monohydrate

MOLECULAR FORMULA: Mixture

TRADEMARK: Spiriva® HandiHaler®  
CHEMICAL FAMILY: Quarternary ammonium compound  
PRODUCT USE: Anticholinergic

MOLECULAR WEIGHT: mixture  
CAS NUMBER: 136310-93-5

## 2. COMPONENTS PER UNIT DOSE

| MATERIAL                              | EXPOSURE LIMITS                                  |
|---------------------------------------|--|
| Active Ingredient: Tiotropium bromide | 2 ug/m3** BIEL                                   |
| Inert Ingredients: Lactose            | 10 mg/m3* Inhalable Fraction<br>* ACGIH TLV 2002 |

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

## 3. HAZARD IDENTIFICATION

### EMERGENCY OVERVIEW

**Light green, hard gelatin capsule.**

The product is a pharmaceutical material. All precautions for handling drugs and pharmaceuticals should be followed.

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

TARGET ORGANS: Respiratory System

ACUTE EXPOSURE: Conjunctivitis, dry mouth. Eye contact can cause blurred vision or pupil dilation.

SIGNS AND SYMPTOMS OF EXPOSURE: Dry mouth, constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty and urinary retention.

MEDICAL CONDITIONS POTENTIALLY AGGRAVATED BY EXPOSURE: Narrow angle glaucoma, prostatic hyperplasia or bladder neck obstruction. Renal impairment.

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

ADVERSE REACTIONS TO PRODUCT: Spiriva is contraindicated in patients with a history of hypersensitivity to atropine derivatives including Ipratropium or any components of this product. Immediate hypersensitivity reactions, including angioedema may occur after administration. Inhaled medicines may cause paradoxical bronchospasms.

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#### 4. EMERGENCY FIRST AID PROCEDURES

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**INHALATION:** Remove from area to fresh air. Seek medical attention if respiratory irritation develops or if breathing becomes difficult.

**INGESTION:** Capsules are meant for administration by inhalation not ingestion. The active ingredient is poorly absorbed from the gastrointestinal tract. If ingested, get medical attention to determine whether vomiting or evacuation of stomach is necessary. Give 3-4 glasses of water, but **DO NOT** induce vomiting. If vomiting occurs, give fluids again. Do not give anything by mouth to an unconscious or convulsing person.

**SKIN CONTACT:** Remove contaminated clothing. Wash affected areas with plenty of water, and soap if available, for several minutes. Seek medical attention if irritation or rash develops and persists.

**INJECTION:** In case of accidental injection, wash and thoroughly disinfect, get medical attention.

**EYE CONTACT:** Flush eyes with large amounts of running water for 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:

Carbon dioxide or dry powder 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. The HandiHaler® device is plastic.

#### UNUSUAL FIRE AND EXPLOSION HAZARDS:

As with all dry powders it is advisable to ground mechanical equipment in contact with dry material to dissipate the potential buildup of static electricity. When heated to decomposition material may emit oxides of nitrogen, carbon, sulfur and Hydrogen bromide.

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### 6. SPILL AND ACCIDENTAL RELEASE MEASURES

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**STEPS TO BE TAKEN IN THE EVENT OF A SPILL OF COMPROMISED CAPSULES:** Wear approved respirator, eye protection, personal protective coverings and gloves. Do not allow product to reach sewer system or any body of water. Use HEPA filtered vacuum to pick up spilled powder. Avoid exposure to dust. Place spillage in appropriate container for waste disposal. Wash contaminated clothing before reuse. Ventilate area and wash spill site.

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### 7. PRECAUTIONS FOR SAFE HANDLING AND USE

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**HANDLING AND STORAGE PRECAUTIONS:** Store in tight container. Store away from foodstuffs. This material should be handled and stored as per label and other instructions to ensure product integrity.

**STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED FROM CAPSULES:** Wear approved respirator, eye protection, personal protective coverings and gloves. Use HEPA filtered vacuum or wet sweeping to clean up spillage. Avoid dust. Place spillage in appropriate container for waste disposal. Wash contaminated clothing before reuse. Ventilate area and wash spill site.

**OTHER PRECAUTIONS HANDLING BROKEN CAPSULES:** Avoid contact with eyes, skin or clothing. Avoid breathing dust or mist. Use with adequate dust control and local ventilation. Wash hands thoroughly after handling. Wear fresh clothing daily.

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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.)

**RESPIRATORY PROTECTION:** Not generally required when handling containers. 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 or nitrile gloves

Protective Clothing: Laboratory coats

Other: Eye wash

WORK/HYGIENIC PRACTICES: Keep away from foodstuffs, beverages and feed. Immediately remove all soiled and contaminated clothing. Wash hands before breaks and at the end of work.

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## 9. PHYSICAL/CHEMICAL CHARACTERISTICS

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APPEARANCE AND ODOR OF ACTIVE INGREDIENT: White odorless crystalline powder in green gelatin capsules.

Boiling Point: N/D  
Vapor Pressure (mm Hg): N/A  
Vapor Density: N/A  
Water Solubility: 30g/l @ 20oC

Specific Gravity: N/A  
Melting Point: 226oC  
Evaporation Rate: N/A  
Volatiles, %: N/A

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## 10. REACTIVITY DATA

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STABILITY: Stable.

CONDITIONS TO AVOID: None known.

INCOMPATIBLE MATERIALS:

HAZARDOUS DECOMPOSITION OR BY-PRODUCTS: When heated to decomposition material may emit oxides of nitrogen, carbon, sulfur and Hydrogen bromide.

HAZARDOUS POLYMERIZATION: Will not occur.

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## 11. TOXICOLOGICAL INFORMATION

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### Toxicity for Active Ingredient:

Acute Toxicity: LD 50 3,500 mg/kg rat (female)  
LD 50 1,336 mg/kg mouse

Repeated dose study in rats:

Oral NOEL: 13 weeks 0.1 mg/kg/day

Inhalation NOEL: 13 weeks 0.07 mg/kg/day

Repeated dose study in dogs:

Oral NOEL: 13 weeks 0.005 mg/kg/day

Inhalation NOEL: 12 months 0.005 mg/kg/day

Carcinogenicity, Mutagenicity, Fertility Impairment: No evidence of tumorigenicity in 104 week rat, 83 week mouse and 101 week mouse studies at 25, 35 and 0.5 times the recommended human daily dose. No evidence of mutagenicity or clastogenicity in gene mutation, hamster cell, chromosomal aberration in human lymphocytes and mouse micronucleus formation or unscheduled DNA synthesis in rat hepatocytes.

Toxicity for Inactive Ingredient:

LD50 - ROUTE: Intraperitoneal; DOSE: >10 gm/kg

LD50 - ROUTE: Oral; DOSE: >10 gm/kg

LD50 - ROUTE: Subcutaneous; DOSE: >5 gm/kg

### REPRODUCTIVE EFFECTS

Rat TDLo - ROUTE: Oral; DOSE: 375 mg/kg; DURATION: female 4-18D of pregnancy  
TOXIC EFFECTS: *Specific Developmental Abnormalities* - Musculoskeletal system

#### TUMORIGENIC EFFECTS

Mouse TDLo - ROUTE: Subcutaneous; DOSE: 1000 gm/kg/29w continuous  
TOXIC EFFECTS: *Tumorigenic* - Equivocal tumorigenic agent by RTECS criteria  
*Tumorigenic* - Tumors at site of application

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## 12. ECOLOGICAL INFORMATION

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- The toxicity to aquatic life was evaluated using Daphnids and this organism showed no observable effects with the active moiety at the 32 mg/ with a 48-hour exposure time. The 48-hour EC-50 was 69 mg/l.
- The material is not classified as readily biodegradable, but the material is also known to hydrolyze at aquatic pH levels.
- The octanol water partition coefficient is low, Log P o/w = -2.28. This suggests the material will remain in the water column.

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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.

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## 14. TRANSPORT INFORMATION

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|                           |     |                        |     |
|---------------------------|-----|------------------------|-----|
| DOT Proper Shipping Name: | N/A | Packing Group:         | N/A |
| Hazard Class:             | N/A | Identification Number: | N/A |

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## 15. REGULATORY INFORMATION

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## 16. OTHER INFORMATION

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ABBREVIATIONS:  
N/A - Not applicable  
N/D - Not determined  
N/E - Not established  
N/K - Not known

#### PREPARATION INFORMATION

Prepared by: Environmental Affairs & Safety  
Date: 3/25/04  
Replaces: 3/19/04

Revisions:

- Section 1: Added HandiHaler®
- Section 4: Added ingestion information
- Section 5: Revised information in Special Firefighting Procedures

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REFERENCES:

Tiotropium Bromide Monohydrate MSDS Version 1.2 - Boehringer Ingelheim GmbH  
Spiriva Package Insert- 1/2004