

SAFETY DATA SHEET

Product Name: Mirapex ® ER (Extended Release)

Date Issued: February 18, 2010

1. SUBSTANCE IDENTIFICATION

SUBSTANCE/MIXTURE NAME: Mirapex ® ER

EMERGENCY CONTACT NUMBER: (203) 798-5521 – 8:30 AM to 5:00 PM EST
(203) 798-4000

SUPPLIER ROUTINE CONTACT NUMBER: (203) 798-5521

SUPPLIER NAME: Boehringer-Ingelheim Pharmaceuticals,
Incorporated

900 Ridgebury Road
Ridgefield, Connecticut
06877-0368

RECOMMENDED USES: non-ergot dopamine agonist indicated for the treatment of the signs and symptoms of early Parkinson's disease

2. HAZARD IDENTIFICATION

HAZARD CLASSIFICATION: **WARNING - This is a medicinal compound designed to be prescribed by a health professional. Should the patient or any exposed employee observe any adverse symptoms, they should contact their health care professional immediately and discontinue taking this medication or evacuate the work environment. Follow all instructions and packaging labels.**

GHS HAZARD LABEL:

Product:

The product is a non-hazardous mixture of single components and need not be labeled according to EC-Directive 67/548, as amended

Active Ingredient



OTHER NON GHS CLASSIFIABLE HAZARDS: Active Ingredient has been given a "R43 – May cause sensitization by skin contact" designation

3. COMPOSITION/INFORMATION ON INGREDIENTS

EMERGENCY OVERVIEW:

Warning: Falling asleep during activities of daily living: Sudden onset of sleep may occur without warning

0.375 mg white to off-white, round, bevel-edged, extended-release tablets debossed with "ER" on one side and "0.375" on the other side

0.75 mg white to off-white, round, bevel-edged, extended-release tablets debossed with "ER" on one side and "0.75" on the other side

1.5 mg white to off-white, oval, extended-release tablets debossed with "ER" on one side and "1.5" on the other side

3 mg white to off-white, oval, extended-release tablets debossed with "ER" on one side and "3.0" on the other side

4.5 mg white to off-white, oval, extended-release tablets debossed with "ER" on one side and "4.5" on the other side

Material	Exposure Limits
Active Ingredient	
Pramipexole	6 µg/m ³
Inactive Ingredients	
Carbomer Homopolymer, Type A	N/E
Corn Starch	10 mg/m ³ (ACGIH)
Colloidal Silicon Dioxide	10 mg/m ³ Total Dust for Particles not otherwise classified
Hypromellose	N/E
Magnesium Stearate	10 mg/m ³ as Stearates (ACGIH)

COMMON NAME: Mirapex ® ER

MOLECULAR WEIGHT: 302.27

CHEMICAL FAMILY: Dopamine Receptor Agonist

CAS NUMBER: 104632-25-9

PRODUCT USE: Anti-Parkinson's

SYNONYMS: Pramipexole dichloride monohydrate; Sifrol ®, Mirapexin ®, Mirapex ®, Pexola ®

4. FIRST AID MEASURES

IMMEDIATE EFFECTS: Sudden onset of sleep may occur without warning;

DELAYED EFFECTS: Symptomatic orthostatic hypotension; hallucinations (risk increases with age); dyskinesia (caused or exacerbated by Mirapex® ER); renal impairment; Impulse control symptoms including compulsive behaviors (gambling, compulsive eating and shopping);

BY EXPOSURE ROUTE

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

INGESTION: Give 3-4 glasses of water, but **DO NOT** induce vomiting. If vomiting occurs, give fluids again. Get medical attention to determine whether vomiting or evacuation of stomach is necessary. 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.

GENERAL ADVICE

Seek medical attention after exposure to this compound; physician or health care provider should treat symptomatically. Wash any contaminated clothing before reuse. First responders should wear personal protective equipment as defined in:

SECTION 5 for FIRE FIGHTING

SECTION 6 for ACCIDENTAL RELEASES, or

SECTION 8 for EXPOSURE CONTROL/PERSONAL PROTECTION

ADVERSE REACTION TO PRODUCT: Most common adverse events (incidences $\geq 5\%$ and greater than placebo) in early Parkinson's disease without levodopa were: somnolence; nausea; constipation; fatigue; dry mouth; muscle spasms; and falls

OVERDOSAGE: There is no clinical experience with significant over-dosage. One patient took 11 mg/day of pramipexole for 2 days for an investigational use. Blood pressure remained stable, although pulse rate increased to between 100 and 120 beats per minute. No other adverse events were reported related to the increased dose.

There is no known antidote for over-dosage of a dopamine agonist. Management of over-dose may require general supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring.

5. FIRE AND EXPLOSION HAZARD DATA

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

SPECIFIC HAZARDS ARISING FROM THE CHEMICAL: As with any organic powder (in a manufacturing environment), this material can present a dust explosion hazard. It can burn in a fire, producing acid fumes including acid gases (Hydrochloric, Nitric, and Sulfuric Acids) and oxides of carbon, nitrogen and sulfur.

SPECIAL PROTECTIVE EQUIPMENT: Firefighters should use self-contained breathing equipment and protective clothing (Turn-out Gear). Firefighters should avoid breathing fumes from product.

PRECAUTIONS FOR FIRE FIGHTERS: As with all fires, evacuate personnel to safe area. Use water spray to keep fire-exposed containers cool and protect against all exposures.

FURTHER INFORMATION: Collect contaminated extinguishing water; do not allow water to reach sewage or effluent systems.

6. ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS: For the final product consumption, personal protective equipment should not be necessary. Keep Mirapex ER® Tablets out of reach from children.

In case of large spills or crushing of multiple tablets where there is a powder residue, a qualified person should determine the need for respiratory protection. NIOSH/MSHA approved respirators for protection should be used if respirators are found to be necessary.

PERSONAL PROTECTIVE EQUIPMENT

Eye Protection: Safety glasses with side shields or goggles

Hand Protection: Gloves

Protective Clothing: Laboratory coats

Other: Eye wash & safety shower

Only trained employees should respond to any chemical release, review and act according to your companies' defined internal release or spill procedures. Employee's who have not been trained in appropriate spill response methods, should evacuate the area, closing all doors as they exit. If possible without endangering themselves, employees should remove any source of ignition.

ENVIRONMENTAL PRECAUTIONS: Whenever possible, employees should take all necessary steps to prevent this material from entering any catch basin, drain, ground water, sink, surface water, or toilet.

METHODS AND MATERIALS FOR CONTAINMENT AND CLEAN-UP: Wear approved respirator, eye protection and chemically compatible gloves if containers have been compromised. HEPA 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. HANDLING AND STORAGE

PRECAUTIONS FOR SAFE HANDLING: For final product, protect from exposure to direct sunlight and high humidity. Keep out reach from children. This material should be handled and stored as per label and other instructions to ensure product integrity.

PERSONAL HYGIENE: In manufacturing environments, employees should wear protective equipment, as defined in Section 8 – Exposure Control/Personal Protection. The required PPE should be removed before entering common area (cafeteria, hallway, or lavatory) or an office environment. Employees using this substance should consult with their internal safety policies and procedures for chemical handling.

CONDITIONS FOR SAFE STORAGE: Prevent the formation of dust. Store tablets in original container at 25°C (77°F) with a range of 15°C to 30°C (59°F to 86°F). Store away from foodstuffs.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

MATERIAL	WEIGHT %	EXPOSURE LIMITS
Active Ingredient: (S)-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate	< 2%	6 µg/M ³
Inactive Ingredients: Carbomer Homopolymer, Type A Corn Starch Colloidal Silicon Dioxide	98%	N/E 10 mg/m ³ (ACGIH) 10 mg/m ³ Total Dust for Particles not otherwise classified
Hypromellose Magnesium Stearate		N/E 10 mg/m ³ as Stearates (ACGIH)

APPROPRIATE ENGINEERING CONTROLS: Not generally required when handling final product containers.

Use appropriate respiratory protection based upon industrial hygiene survey(s). Minimize dust generation. Use closed equipment where possible. Use spot ventilation to remove dust from the work area. If operations generate dusts, use explosion-proof ventilation equipment to control airborne levels.

INDIVIDUAL PROTECTION MEASURES:

RESPIRATORY PROTECTION: A qualified person should determine the need for respiratory protection. NIOSH/MSHA approved respirators for protection should be used if respirators are found to be necessary.

PERSONAL PROTECTIVE EQUIPMENT

Eye Protection: Safety glasses with side shields or goggles
Hand Protection: Gloves
Protective Clothing: Laboratory coats
Other: Eye wash & safety shower

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AND ODOR: Odorless White to Off-white round or oval tablet with ER debossed on one side and the tablet strength on the other side

Auto-ignition temperature: N/D
Boiling Point: N/D
CAS Number: 104632-25-9
Decomposition temperature: N/D
Evaporation rate: N/D

Flammability (solid, gas): N/D
Flash point: N/D
Initial boiling point and boiling range: N/D
Melting point: 296 to 301°C
Molecular Formula: $C_{10}H_{17}N_3S \cdot 2HCl \cdot H_2O$

Odor threshold: N/D
Partition coefficient: n-octanol/water: N/D
pH: N/D
Relative density: N/D
Solubility: 20% in Water; 8% in Methanol; 0.5% in ethanol
Upper/lower explosive/flammable limits: N/D
Vapor density: N/D
Vapor pressure (mm Hg): N/D
Viscosity: N/D
Volatiles, %: N/D

10. STABILITY AND REACTIVITY

STABILITY: Stable at ambient temperatures

POSSIBILITY OF HAZARDOUS REACTIONS:

Potentially Hazardous Conditions	Conditions that may cause these Reactions
Polymerize: N/D	
Release excessive heat: N/D	
Release excessive pressure: N/D	
Other hazardous conditions: N/D	

CONDITIONS TO AVOID: Direct Sunlight, Flames/Heat, and High Humidity

INCOMPATIBLE MATERIALS: Direct Sunlight, Flames/Heat, and High humidity

HAZARDOUS DECOMPOSITION OR BY-PRODUCTS: When heated to decomposition or under fire conditions, material emits: acid gases (Hydrochloric, Nitric, and Sulfuric Acids) and oxides of carbon, nitrogen and sulfur.

11. TOXICOLOGICAL INFORMATION

TOXICITY: Data for active ingredient

Acute toxicity: LD ₅₀ female rat 548 mg/kg :LD ₅₀ male rat 809 mg/kg	Reproductive toxicity: See below
Aspiration hazard: N/D	Serious eye irritation: No eye irritation (rabbit)
Carcinogenicity: Not listed as carcinogen or potential carcinogen by NTP, IARC Monographs or OSHA.	Skin irritation: Non irritant (rabbit)
Germ cell mutagenicity: N/D	STOST-single exposure: N/D
Skin sensitization: mild sensitizing potential (guinea pig)	STOST-repeated exposure: N/D

MOST LIKELY ROUTE OF EXPOSURE: The most likely routes of exposure for final product is ingestion or inhalation. The most likely route of exposure during manufacturing processes is: inhalation, dermal absorption, mucous membranes, injection or ingestion.

SYMPTOMS RELATED TO THE PHYSICAL, CHEMICAL AND TOXICOLOGICAL CHARACTERISTICS:

- Pregnancy:** *Pregnancy Category C* – There are no adequate and well controlled studies in pregnant women. Mirapex® ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day. Administration of 1.5 mg/kg/day of pramipexole to pregnant rats during the period of organogenesis resulted in a high incidence of total resorption of embryos. These findings are thought to be due to the prolactin-lowering effect of pramipexole. Because of pregnancy disruption and early embryonic loss in these studies, the teratogenic potential of pramipexole could not be adequately evaluated.
- Nursing Mothers:** A single dose, radio-labeled study showed that the drug-related material was present in rat milk at concentrations three to six times higher than in plasma at equivalent time points.
- It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from pramipexole, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
- Renal Impairment:** The elimination of pramipexole is dependant upon renal function. Pramipexole clearance is extremely low in dialysis patients, as a negligible amount of pramipexole is removed by dialysis. In populations with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance.
- Gender:** Pramipexole clearance is about 30% lower in women than in men. But this difference can be accounted for by difference in body weight.

Carcinogenesis: Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to mice at dose up to 10 mg/kg/day. Pramipexole was administered in the diet to mice at dose up to 8 mg/kg/day. No significant increases in tumors occurred in either species.

Mutagenesis: Pramipexole was not mutagenic or clastogenic in a battery of *in vitro* (bacterial reverse mutation; V79/HGRPT gene mutation; chromosomal aberration in CHO cells) and *in vivo* (mouse micronucleus) assays.

Impairment of Fertility: In rat fertility studies, pramipexole at a dose of 2.5 mg/kg/day prolonged estrus cycles and inhibited implantation. These effects were associated with reductions in serum levels of prolactin, a hormone necessary for implantation and maintenance of early pregnancy in rats.

12. ECOLOGICAL INFORMATION

AQUATIC OR TERRESTRIAL TOXICITY:

Active Ingredient: Toxicity to fish – LC₅₀ > 100.0 mg/l (Brachydanio rerio) Exposition time 96 h, Method OECD Guideline 203

Toxicity to daphnia – EC₅₀ 70.0 mg/l (Daphnia magna) Exposition time 48 h, Method OECD Guideline 202

Toxicity to algae – EC₅₀ (Biomass) 240.0 mg/l (Desmodesmus subspicatus) Exposition time 72 h, Method OECD Guideline 201

Toxicity to algae – EC₅₀ (Growth rate) 32.0 mg/l (Desmodesmus subspicatus) Exposition time 72 h, Method OECD Guideline 201

PERSISTENCE AND DEGRADABILITY: Readily biodegradable. 80% Exposition time 28 d

BIOACCUMULATIVE POTENTIAL: N/D

MOBILITY IN SOIL: N/D

OTHER ADVERSE EFFECTS: Whenever possible, employees should take all necessary steps to prevent this material from entering any catch basin, drain, ground water, sink, surface water, or toilet.

13. DISPOSAL CONSIDERATIONS

DISPOSAL METHODS: Dispose of in accordance with local, state and federal regulations. Recommended method is incineration. Product must not be disposed of together with household trash. Do not allow product to enter any sewer drain line.

Contaminated Packaging: Containers that can not be cleaned should be disposed of in the same manner as the contents. Uncontaminated containers can be recycled.

14. TRANSPORT INFORMATION

D.O.T. Proper Shipping Name:	Not Regulated
Hazard Class:	N/A
Identification Number:	N/A
Packing Group:	N/A
Label:	N/A
Emergency Response Guidebook:	N/A

ENVIRONMENTAL HAZARDS: N/D

SPECIAL PRECAUTIONS FOR USERS: N/D

15. REGULATORY INFORMATION

SAFETY, HEALTH, AND ENVIRONMENTAL REGULATIONS SPECIFIC FOR THIS PRODUCT: 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.

This product is a non-hazardous mixture of single components and need not be labeled according to EC-Directive 67/548, as amended.

National legislation/regulations

Water Hazard Class:	VVWWS WGK 1 slightly water contaminating Annex 4 VwVwS (Germany) dated May 17, 1999
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16. OTHER INFORMATION

OTHER INFORMATION:

Active Ingredient

R20/21/22 Harmful by inhalation, in contact with skin and if swallowed

R52 Harmful to aquatic organisms

ABBREVIATIONS:

N/E: Not Established

N/A: Not Applicable

N/D: Not Determined

PPE: Personal Protective Equipment

Prepared by: Environmental Affairs & Safety

Date Prepared: February 18, 2010

Replaces: New

Sections Revised:

NOTICE:

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REFERENCES

BIPI Chemical Development

BIPI Pharmaceuticals

BI MSDS Mirapex ® ER dated May 19, 2009

BIEL Mirapex ®

Highlights of Prescribing Information Mirapex ® ER December 2009