Material Safety Data Sheet

LETROZOLE TABLETS USP 2.5 mg

SECTION 1 - PRODUCT IDENTIFICATION

Product Name: Letrozole Tablets USP 2.5 mg

Therapeutic Category: Treatment of breast cancer (nonsteroidal aromatase inhibitor)

Chemical Name: 4,4'-(1H-1,2,4-Triazol-1-ylmethylene)dibenzonitrile

Chemical Formula: $C_{17}H_{11}N_5$

Molecular Weight: 285.31

SECTION 2 – COMPOSITION/INFORMATION ON INGREDIENTS

Active: Letrozole (2.5 mg)

Inactive: Colloidal anhydrous silica, hypromellose, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, starch (corn), talc, and titanium dioxide.

SECTION 3 - HAZARDS IDENTIFICATION

Emergency Overview:
Refer to physicians' desk reference or package insert
May cause nausea, Bone pain and Arthralgia
Experimental Teratogen
May adversely affect the developing fetus

Primary Route(s) of Entry: Oral

Effects of Overexposure: Potential for exposure is reduced in this form (Tablets).
Skin: No hazard is expected from normal clinical use.
Eye: No hazard is expected from normal clinical use.
Inhalation: No hazard is expected from normal clinical use.
Ingestion: No hazard is expected from normal clinical use.

Therapeutic side effects: Bone pain, hot flushes, back pain, nausea, fatigue, dizziness, arthralgia and dyspnea.

Therapeutic organ effects: Letrozole has been found to accumulate in the skin, as well as produce changes in the liver and bone.

Reproductive Hazards: ***FDA Pregnancy Category D*** (see section 11). Given its inhibitory effect on estrogen synthesis, the potential exists for Letrozole to inhibit uterine implantation of the fertilized egg, produce menstrual irregularities, and adversely affect the developing fetus.

Carcinogenicity: See section 11.

Mutagenicity: Letrozole was clastogenic in two in vitro assays, and non-mutagenic in two in vitro assays and one in vivo assay (see Section 11).

Medical Conditions Aggravated by Exposure: Pregnancy; known hypersensitivity to letrozole or any other components of the formulation; pre-existing liver or kidney impairment.

SECTION 4 - EMERGENCY AND FIRST AID MEASURES

Skin Contact: Wash contaminated area with soap and water.
Eye Contact: Flush with running water for 15 minutes holding eyelids open.
Inhalation: No specific treatment is necessary since this product is not likely to be hazardous by inhalation if tablet is left intact.
Ingestion: Get medical attention immediately; induce vomiting if victim is conscious.

SECTION 5 - FIRE FIGHTING MEASURES

Flash Point: Not applicable
Method Used: Not applicable
Flammable Limits (% in air)
Lower: not applicable
Upper: not applicable
Autoignition Temperature: Not available
Extinguishing Media: Use media suitable for fire in surrounding area.
Special Fire Fighting Procedures and Precautions: Evacuate area and fight fire from safe distance.
Fire and Explosion Hazards: Not available
Fire-Fighting Equipment: Wear full protective clothing and positive pressure self-contained breathing apparatus.

Hazardous Products of Combustion: COx, NOx, SOx

NFPA Ratings:
Health = 1, Flammability = 0, Reactivity = 0, Special Hazard = None
Hazard Rating Scales:
0 = Minimal, 1 = Slight, 2 = Moderate, 3 = Serious, 4 = Severe, U = Unknown

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Steps to be taken if Material is Released or Spilled: Using appropriate protective equipment, sweep up and containerize spilled material. Avoid contamination of sewers and waterways.

SECTION 7 - HANDLING AND STORAGE

Storage Temperature: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].
Shelf Life: See container packaging.
Special Sensitivity: None known.
Handling and Storage Precautions: None known.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Eye Protection: Not required under normal conditions of therapeutic administration and use.
Skin Protection: Not required under normal conditions of therapeutic administration and use. Protective gloves should be worn if tablet is crushed.
Respiratory Protection: Not required under normal conditions of therapeutic administration and use.
Ventilation Requirements: Not required under normal conditions of therapeutic administration and use.
Additional Measures: None

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Appearance: Yellow round, biconvex, film coated tablets.
Boiling Point: Not applicable

Melting/Freezing Pt.: Not applicable
pH: Not available
Specific Gravity: Not available
Solubility (For Drug Substance): Freely soluble in Dichloromethane, slightly soluble in ethanol, practically insoluble in water.
Odor Threshold: Not available
Odor Characteristics: Not available
Vapor Pressure (mm Hg): Not applicable
Vapor Density: Not applicable
% Volatile by Wt: Not applicable

SECTION 10 - STABILITY AND REACTIVITY

Stable (yes/no): Yes
Hazardous Polymerization: Will not occur.
Conditions and Materials to Avoid: Protect from temperatures exceeding 86ºF (30ºC).
Incompatibility: None known
Hazardous Decomposition Products: None known

SECTION 11 - TOXICOLOGY INFORMATION

No toxicological data on finished product; data is for drug substance.

Eye Irritation: Not an irritant (rabbit).

Skin Irritation/Sensitization: Not an irritant (rabbit)

Oral Toxicity:
LD_{50} > 2000 mg/kg (rat)
LD_{50} > 2000 mg/kg (mouse)
LD_{50} = 200 mg/kg (dog)

Dermal Toxicity: No data available.

Inhalation Toxicity: No data available

Chronic/Carcinogenicity:
In a two-year carcinogenicity study in mice at oral doses of 0.6 to 60 mg/kg/day, and in rats at oral doses of 0.1 to 10 mg/kg/day, a dose-related increase in the incidence of benign ovarian stromal tumors was observed. This effect was seen in rats at the 10 mg/kg dose. In female rats, ovarian hyperplasia was observed at doses equal to or greater than 0.1 mg/kg/day.

Mutagenicity:
Positive in the following tests: Potential clastogen in the *in vitro* CHO K1 and CCL 61 Chinese hamster ovary cells
Negative in the following tests: *in vitro* Ames and E. coli bacterial assays, and an *in vivo* rat micronucleus assay.

Reproductive Effects: Letrozole may cause fetal harm when administered to pregnant women.

Studies in rats at doses equal to or greater than 0.003 mg/kg administered during the period of organogenesis, have shown that letrozole is embryotoxic and fetotoxic, as indicated by intrauterine mortality, increased resorption, increased post implantation loss, decreased numbers of live fetuses and fetal anomalies including absence and shortening of renal papilla, dilation of ureter, edema and incomplete ossification of frontal skull and metatarsals. Letrozole was also teratogenic in rats, causing fetal domed heads and cervical/centrumvertebral fusion at a dose of 0.03 mg/kg.

In rabbits, Letrozole is embryotoxic at doses equal to or greater than 0.002 mg/kg and fetotoxic at 0.02 mg/kg.

There are no studies in pregnant women. Letrozole Tablets is indicated for postmenopausal women. The patient should be apprised of the potential hazard to the fetus and potential risk for loss of the pregnancy It is also not known whether letrozole is excreted in human milk. Caution should be exercised when letrozole is administered to pregnant women.

SECTION 12 - ECOLOGICAL INFORMATION

No ecological data on finished product; data is for drug substance.

Biological elimination:
1 % (CO_2)
Initial conc. 23.4 mg/l
Not readily degradable
Method: OECD 301B * 1981 Mmod. Sturm (ready)

Biological elimination:
1 % (CO_2)
Initial conc. 26.3 mg/l
Not readily degradable
Method: OECD 301B * 1981 Mmod. Sturm (ready)

Fish toxicity:
LC_0: 37 mg/l

LC_{50}: > 37 mg/l
LC_{100}: > 37 mg/l
(Species: rainbow trout (salmo gairdneri, oncorhynchus mykiss), Exp. time: 96 h)
Method: OECD 203 * 1984 acute tox.
Not toxic with reference to the 7th Amendment to Directive
67/548/EEC, 92/32/EEC

Daphnia toxicity:
EC_0: 35 mg/l
EC_{50}: > 35 mg/l
EC_{100}: > 35 mg/l
(Species: daphnia magna (water flea), Exp. time: 48 h)
Method: OECD 202.I
Not toxic with reference to the 7th Amendment to Directive
67/548/EEC, 92/32/EEC

Algae toxicity:
EC_{50}: > 100 mg/l
(Species: Scenedesmus subspicatus 86.81 sag. green algae, Exp time: 72 h)
Method: OECD 201 * 1984. Growth inhibition
Not toxic with reference to the 7th Amendment to Directive
67/548/EEC, 92/32/EEC

Bacteria toxicity (respiration inhibition):
EC_0: 20.2 mg/l
EC_{50}: > 20.2 mg/l
EC_{100}: > 20.2 mg/l
(Species: activated sludge, Exp. time: 696 h)
Method: evaluated

Bioaccumulation in water organisms is not likely based on the n-octanol/water partition coefficient (log pOW < 3.0). When low concentrations are discharged correctly into adapted biological sewage treatment plants, interference with the degradation activity of activated sludge is not likely.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste Disposal Method: All wastes must be disposed of in accordance with local, state and federal laws and regulations. (Contact local or state environmental agency for specific rules).

EPA Hazardous Waste Number: None.

SECTION 14 - TRANSPORTATION INFORMATION

Non-Hazardous and Not Regulated when Transporting through air, ground or sea freight:

IATA / ICAO – Non Hazardous - Not Regulated
IATA Proper shipping name: N/A
IATA UN / ID No: N/A
IATA Hazard Class: N/A
IATA Packing Group: N/A
IATA Label: N/A

IMDG – Non Hazardous - Not Regulated
IMDG Proper shipping name: N/A
IMDG UN / ID No: N/A
IMDG Hazard Class: N/A
IMDG Flash Point N/A
IMDG Label: N/A

DOT – Non Hazardous - Not Regulated
DOT Proper shipping name: N/A
DOT UN / ID No: N/A
DOT Hazard Class: N/A
DOT Flash Point N/A
DOT Packing Group: N/A
DOT Label: N/A

SECTION 15 - REGULATORY INFORMATION

OSHA (Occupational Safety & Health Administration): This Material Safety Data Sheet contains the information required by the Federal OSHA Hazard Communication Standard (29 CFR 1910.1200).

OSHA PSM (Process Safety Management): Not listed (29 CFR 1910.119, Appendix A)

NJ TCPA (Toxic Catastrophe Prevention Act): This product contains NONE of the substances subject to the reporting requirements of Section N.J.A.C. 7:31 of this act.

TSCA (Toxic Substance Control Act): Not applicable

CERCLA (Comprehensive Response Compensation & Liability Act): Not listed

SARA Title III (Superfund Amendments & Reauthorization Act):
Section 302 Extremely Hazardous Substances: Not listed

Section 311/312 Hazard Categories: None
Section 313 Reportable Ingredients: Not listed

RCRA (Resource Conservation & Recovery Act): Not listed

Other State Regulatory Information:
New Jersey: NJ RTK Threshold Planning Quantity = 10,000 lbs.

Other USA Regulations: None

California Proposition 65: The following statement is made in order to comply with the California Safe Drinking Water and Toxic Enforcement Act of 1986. *This product does not contain any ingredient known to the State of California to cause cancer or reproductive toxicity.*

Canada: WHMIS Ingredient Disclosure List Not listed

EEC Classification (European Economic Community):
Warning Symbol: not available.
Risk Phrases: not available.
Safety Phrases: not available.

SECTION 16 - OTHER INFORMATION

To the best of our knowledge, the information contained herein is accurate. However, We does not assume any liability whatsoever for the accuracy or completeness of the information contained herein except for the product's administration/use as intended. Final determination of the suitability of any material is the sole responsibility of the user. All materials may present unknown hazards and should be used with caution. Although certain hazards are described herein, we cannot guarantee that these are the only hazards which exist.