



MATERIAL SAFETY DATA SHEET

Product Name: Tomudex® (Raltitrexed disodium for Injection)

1. CHEMICAL PRODUCT AND COMPANY INFORMATION

Manufacturer Name And Address Hospira Inc.
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Lake Forest, Illinois USA
60045

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Hospira, Inc., Non-Emergency 224-212-2000

Product Name Tomudex® (Raltitrexed disodium for Injection)

Synonyms Raltitrexed Powder for Injection; *N*-{5-[3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl(methyl)amino]-2-thenoyl}-L-glutamic acid.

2. COMPOSITION/INFORMATION ON INGREDIENTS

Active Ingredient Name Raltitrexed

Chemical Formula $C_{21}H_{22}N_4O_6S$

Preparation Non-hazardous ingredients include mannitol and dibasic sodium phosphate heptahydrate. Hazardous ingredients present at less than 1% include sodium hydroxide.

Component	Approximate Percent by Weight	CAS Number	RTECS Number
Raltitrexed	100	112887-68-0	MA1253250

3. HAZARD INFORMATION

Carcinogen List

Substance	IARC	NTP	OSHA
Raltitrexed	Not Listed	Not Listed	Not Listed

Emergency Overview Tomudex® (Raltitrexed disodium for Injection) is a powder for solution for injection containing raltitrexed, a folate analog that inhibits thymidylate synthase, an enzyme involved in the synthesis of DNA. Clinically, raltitrexed is used in the treatment of advanced colorectal cancer and other solid cancers. This material is cytotoxic and in the workplace should be considered a possible eye irritant, a potential occupational reproductive hazard and potentially harmful to the fetus. Following an accidental over-exposure, possible target organs may include the gastrointestinal tract, bone marrow, liver, and fetus.

Occupational Exposure Information on the absorption of this product via inhalation or skin contact is not available.

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Potential	Avoid liquid aerosol or dust generation; avoid skin contact. In the workplace, there is increasing evidence that personnel (e.g. nurses, pharmacists, etc.) who prepare and administer parenteral antineoplastics (e.g. in hospitals) may be at some risk due to potential mutagenicity, teratogenicity, and/or carcinogenicity of these agents if workplace exposures are not properly controlled. The actual risk in the workplace is not known.
Signs and Symptoms	None known from occupational exposure. None anticipated from normal handling of intact container. In clinical use, raltitrexed produces mild to moderate bone marrow depression with leucopenia, anemia, and thrombocytopenia. The nadir of the white cell count usually occurs 7 to 14 days after treatment. Other adverse effects include gastrointestinal toxicity with nausea and vomiting, diarrhea, anorexia, weakness and malaise, fever, pain, headache, skin rashes, arthralgia, muscle cramps, weight loss, peripheral edema, alopecia, taste disturbance, and conjunctivitis. Mucositis and reversible increases in liver enzyme values may also occur.
Medical Conditions Aggravated by Exposure	Pre-existing hypersensitivity to raltitrexed; pre-existing gastrointestinal, bone marrow or liver ailments; pregnancy.

4. FIRST AID MEASURES

Eye contact	Remove from source of exposure. Flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.
Skin contact	Remove from source of exposure. Flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.
Inhalation	Remove from source of exposure. If signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.
Ingestion	Remove from source of exposure. If signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

5. FIRE FIGHTING MEASURES

Flammability	None anticipated for this product. However, most organic powders will combust at high temperatures.
Fire & Explosion Hazard	None anticipated for this product. As with all powders, avoid the creation of dusty atmospheres.
Extinguishing media	As with any fire, use extinguishing media appropriate for primary cause of fire.
Special Fire Fighting Procedures	No special provisions required beyond normal firefighting equipment such as flame and chemical resistant clothing and self contained breathing apparatus.

6. ACCIDENTAL RELEASE MEASURES

Spill Cleanup and Disposal	For spilled powder, isolate area around spill. Put on suitable protective clothing and equipment as specified by site spill procedures. Collect the spilled powder using techniques that minimize powder migration or the creation of airborne dust. Clean affected area with soap and water. Dispose of materials according to the applicable federal, state, or local regulations. If a spill occurs after reconstitution, absorb liquid with suitable material and clean affected area with
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soap and water. Absorb the liquid with an inert absorbent material (e.g. absorbent pad). Dispose of materials according to the applicable federal, state, or local regulations.

7. HANDLING AND STORAGE

Handling

Raltitrexed is a cytotoxic agent. Appropriate procedures should be implemented during the handling and disposal of cytotoxic antineoplastic agents to minimize potential exposures. Several guidelines on handling cytotoxic antineoplastic agents have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Consult your hygienist or safety professional for your site requirements.

Avoid ingestion, inhalation, skin contact, and eye contact. If handling a powder, precautions may include the use of a containment cabinet during the weighing, reconstitution and/or solubilization of this antineoplastic agent. The use of disposable gloves and respiratory protection is recommended. Proper disposal of contaminated vials, syringes, or other materials is required when working with this material.

Storage

No special storage is required for hazard control. However, employees should be trained on the proper storage procedures for antineoplastic agents. For product protection, follow temperature and/or light storage recommendations noted on the product case label, the primary container label, or the product insert.

Special Precautions

Persons with known allergies to raltitrexed, women who are pregnant, or women who want to become pregnant, should consult a health and/or safety professional prior to handling open containers of this material.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Exposure Guidelines

Component	Type	Exposure limits			Note
		mg/m ³	ppm	µg/m ³	
Raltitrexed	Not Applicable	N/A	N/A	N/A	None Established

Respiratory protection

Respiratory protection is normally not needed during intended product use. However, if the generation of dusts or aerosols is likely, and engineering controls are not considered adequate to control potential airborne exposures, the use of an approved air-purifying respirator with a HEPA cartridge (N99 or equivalent) is recommended under conditions where airborne dust or aerosol concentrations are not expected to be excessive. For uncontrolled release events, or if exposure levels are not known, provide respirators that offer a high protection factor such as a powered air purifying respirator or supplied air. A respiratory protection program that meets OSHA's 29 CFR 1910.134 and ANSI Z88.2 requirements must be followed whenever workplace conditions require respirator use. Personnel who wear respirators should be fit tested and approved for respirator use as required.

Skin protection

If skin contact with the product formulation is likely, the use of latex or nitrile gloves is recommended.

Eye protection

Eye protection is normally not required during intended product use. However, if eye contact is likely to occur, the use of chemical safety goggles (as a minimum) is recommended.

Engineering Controls

Engineering controls are normally not needed during the intended use of this product.

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9. PHYSICAL/CHEMICAL PROPERTIES

Appearance/Physical State	Solid
Color	Sterile lyophilized pale yellow-brown to brown powder
Odor	NA
Odor Threshold:	NA
pH:	6.9 TO 7.9 for reconstituted solution
Melting point/Freezing point:	170°C with decomposition
Initial Boiling Point/Boiling Point Range:	NA
Evaporation Rate:	NA
Flammability (solid, gas):	NA
Upper/Lower Flammability or Explosive Limits:	NA
Vapor Pressure:	NA
Vapor Density:	NA
Specific Gravity:	NA
Solubility:	NA
Partition coefficient: n-octanol/water:	NA
Auto-ignition temperature:	NA
Decomposition temperature:	NA

10. STABILITY AND REACTIVITY

Reactivity	Not determined.
Chemical Stability	Stable under standard use and storage conditions.
Hazardous Reactions	Not determined.
Conditions to avoid	Not determined.
Incompatibilities	Not determined.
Hazardous decomposition products	Not determined. During thermal decomposition, it may be possible to generate irritating vapors and/or toxic fumes of carbon oxides (COx), nitrogen oxides (NOx), and sulfur oxides (SOx).
Hazardous Polymerization	Not anticipated to occur with this product.

11. TOXICOLOGICAL INFORMATION

Acute Toxicity

Not determined for the product formulation. Information for the ingredients is as follows:

Ingredient(s)	Percent	Test Type	Route of Administration	Value	Units	Species
Raltitrexed	100%	LD50	Oral	>500 875-1249	mg/kg mg/kg	Rat Mouse

Aspiration Hazard None anticipated from normal handling of this product.

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Dermal Irritation/Corrosion	None anticipated from normal handling of this product.
Ocular Irritation/Corrosion	None anticipated from normal handling of this product. However, inadvertent contact of this product with eyes may produce irritation with redness and discomfort.
Dermal or Respiratory Sensitization	None anticipated from normal handling of this product.
Reproductive Effects	Fertility studies in the rat indicate that raltitrexed can cause impairment of male fertility. In these studies, fertility returned to normal three months after dosing ceased. In developmental toxicity studies in animals, raltitrexed caused embryolethality and fetal abnormalities in pregnant rats. When this material was given to mice as a single intraperitoneal dosage of 15 mg/kg on gestational day 9, tail defects, cleft palate and other facial defects were noted.
Mutagenicity	Raltitrexed was not mutagenic in the Ames test or in supplementary tests using E. coli or Chinese hamster ovary cells. This material caused increased levels of chromosome damage in an in vitro assay of human lymphocytes. An in vivo micronucleus study in the rat indicated that at cytotoxic dose levels, this material may cause chromosome damage in the bone marrow.
Carcinogenicity	The carcinogenic potential of raltitrexed has not been evaluated.
Target Organ Effects	Following an accidental over-exposure, possible target organs may include the gastrointestinal tract, bone marrow, liver, and fetus.

12. ECOLOGICAL INFORMATION

Aquatic Toxicity	Not determined for product The no-observed-effect-concentration (NOEC)(96hr) = 1000 mg/L in Bluegill sunfish The NOEC(72hr) = 1000 mg/L in Rainbow trout The NOEC(96hr) = 320 mg/L The NOEC(14d) on cell density was 125 mg/L in green algae The NOEC(14d) on growth rate was 1000 mg/L in green algae The NOEC(21d) on cell density was 96 mg/L in blue-green algae The NOEC(21d) on growth rate was 48 mg/L in blue-green algae.
Persistence/Biodegradability	Not determined for product. Raltitrexed was not considered biodegradable.
Bioaccumulation	Not determined for product. Raltitrexed has a low potential for bioaccumulation.
Mobility in Soil	Not determined for product.

13. DISPOSAL CONSIDERATIONS

Waste Disposal	All waste materials must be properly characterized. Further, disposal should be performed in accordance with the federal, state or local regulatory requirements.
Container Handling and Disposal	Dispose of container and unused contents in accordance with federal, state and local regulations.

14. TRANSPORTATION INFORMATION

ADR/ADG/ DOT STATUS: Not regulated
IMDG STATUS: Not regulated
ICAO/IATA STATUS: Not regulated
Transport Comments: None

15. REGULATORY INFORMATION

USA Regulations

Substance	TSCA Status	CERCLA Status	SARA 302 Status	SARA 313 Status	PROP 65 Status
Raltitrexed	Not Listed	Not Listed	Not Listed	Not Listed	Not Listed

RCRA Status Not Listed
U.S. OSHA Classification Possible Eye Irritant
 Target Organ Toxin
 Reproductive Toxin

GHS Classification *In the EU, classification under GHS/CLP does not apply to certain substances and mixtures, such as medicinal products as defined in Directive 2001/83/EC, which are in the finished state, intended for the final user.:

Hazard Class Not Applicable

Hazard Category Not Applicable

Signal Word Not Applicable

Symbol Not Applicable

Prevention P260 - Do not breathe dust/fume/gas/mist/vapors/spray.

Hazard Statement Not Applicable

Response: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists, get medical attention. Wash hands after handling.

EU Classification*

*Medicinal products are exempt from the requirements of the EU Dangerous Preparations Directive. Information provided below is for the pure drug substance Raltitrexed

Classification(s): Not Applicable

Symbol: Not Applicable

Indication of Danger: Not Applicable

Risk Phrases: Not Applicable

Safety Phrases: S23 - Do not breathe vapor.

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- S24 - Avoid contact with skin.
- S25 - Avoid contact with eyes.
- S37/39 - Wear suitable gloves and eye/face protection.

16. OTHER INFORMATION:

Notes:

ACGIH TLV	American Conference of Governmental Industrial Hygienists – Threshold Limit Value
CAS	Chemical Abstracts Service Number
CERCLA	US EPA law, Comprehensive Environmental Response, Compensation, and Liability Act
DOT	US Department of Transportation Regulations
EEL	Employee Exposure Limit
IATA	International Air Transport Association
LD50	Dosage producing 50% mortality
NA	Not applicable/Not available
NE	Not established
NIOSH	National Institute for Occupational Safety and Health
OSHA PEL	US Occupational Safety and Health Administration – Permissible Exposure Limit
Prop 65	California Proposition 65
RCRA	US EPA, Resource Conservation and Recovery Act
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
STEL	15-minute Short Term Exposure Limit
TSCA	Toxic Substance Control Act
TWA	8-hour Time Weighted Average

MSDS Coordinator: Hospira GEHS
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