# MATERIAL SAFETY DATA SHEET

## Product Name: Tomudex® (Raltitrexed disodium for Injection)

## 1. CHEMICAL PRODUCT AND COMPANY INFORMATION

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| **Manufacturer Name And Address** | Hospira Inc.<br>275 North Field Drive<br>Lake Forest, Illinois USA<br>60045<br><br>Hospira Healthcare Corporation<br>1111, Dr. Frederick-Philips Boulevard, Suite 450 & 600<br>St-Laurent, Quebec Canada H4M 2X6 |
| **Emergency Telephone** | CHEMTREC: North America: 800-424-9300;<br>International 1-703-527-3887; Australia - 61-290372994; UK - 44-870-8200418 |
| **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

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| **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 |

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| **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 Potential** | Information on the absorption of this product via inhalation or skin contact is not available. Avoid liquid aerosol or dust generation; avoid skin contact. In the workplace, there is increasing |

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| | 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

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| **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

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| **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

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| **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 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**

| | Exposure limits | | | | |
|---|---|---|---|---|---|
| **Component** | **Type** | **mg/m3** | **ppm** | **µg/m3** | **Note** |
| 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.

## 9. PHYSICAL/CHEMICAL PROPERTIES

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| **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$^{o}$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

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| **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<br>875-1249 | mg/kg<br>mg/kg | Rat<br>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

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| **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

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| **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

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**Classification(s):** Not Applicable

**Symbol:** Not Applicable

**Indication of Danger:** Not Applicable

**Risk Phrases:** Not Applicable

**Safety Phrases:** S23 - Do not breathe vapor.

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

## 16. OTHER INFORMATION:

Notes:

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| 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
Date Prepared: 10/19/2012
Obsolete Date: 11/07/2011

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