# SAFETY DATA SHEET

**Product Name: Methotrexate Injection, USP**

## 1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

| | | |
|---|---|---|
| **Manufacturer Name And Address** | Hospira, Inc.<br>275 North Field Drive<br>Lake Forest, Illinois 60045<br>USA | Hospira Australia Pty Ltd<br>1 Lexia Place<br>Mulgrave VIC 3170<br>AUSTRALIA |
| **Emergency Telephone #'s** | 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 | |
| **Material Name** | Methotrexate Injection, USP | |
| **Synonyms** | N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid; Amethopterin; 4-Amino-4-deoxy-10-methylpteroyl-L-glutamic Acid; 4-Amino-10-methylfolic acid. | |

## 2. HAZARD(S) IDENTIFICATION

**Emergency Overview**

Methotrexate Injection, USP is a solution containing methotrexate, a folic acid antagonist. Clinically, this product is used alone or with other agents to treat some types of cancers, to treat severe psoriasis, and rheumatoid arthritis. Methotrexate is a cytotoxic agent and in the workplace, should be considered a potential occupational reproductive hazard, and a potential carcinogen. Based on clinical use, possible target organs may include the bone marrow, gastrointestinal system, central nervous system, cardiovascular system, lungs, liver, kidney, skin, and gonads.

**U.S. OSHA GHS Classification**

| **Physical Hazards** | **Hazard Class** | **Hazard Category** |
|---|---|---|
| | Not Classified | Not Classified |

| **Health Hazards** | **Hazard Class** | **Hazard Category** |
|---|---|---|
| | Toxic to Reproduction | 1 |
| | Germ Cell Mutagenicity | 2 |
| | STOT – RE | 2 |

**Label Element(s)**

**Pictogram**

**Signal Word**

Danger

**Hazard Statement(s)**

May damage fertility or the unborn child
Suspected of causing genetic defects
May cause damage to organs through prolonged or repeated exposure

**Precautionary Statement(s)**

**Prevention**

Obtain special instructions before use
Do not handle until all safety precautions have been read and understood
Wear protective gloves/protective clothing/eye protection/face protection
Do not breathe vapor or spray
Wash hands thoroughly after handling

**Response**

Get medical attention if you feel unwell. If exposed or concerned: Get medical advice/attention.

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.

## 3. COMPOSITION/INFORMATION ON INGREDIENTS

**Ingredient Name** Methotrexate
**Chemical Formula** $C_{20}H_{22}N_8O_5$

| Component | Approximate Percent by Weight | CAS Number | RTECS Number |
|---|---|---|---|
| Methotrexate | ≤ 2.5 | 59-05-2 | MA1225000 |

Non-hazardous ingredients include Water for Injection. Hazardous ingredients present at less than 1% include sodium chloride; hydrochloric acid and/or sodium hydroxide are added to adjust the pH. Some formulations may contain 0.9% benzyl alcohol as a preservative.

## 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 aqueous product.

**Fire & Explosion Hazard** None anticipated for this aqueous product.

**Extinguishing Media** As with any fire, use extinguishing media appropriate for primary cause of fire such as carbon dioxide, dry chemical extinguishing powder or foam.

**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** Isolate the area around the spill. Put on suitable protective clothing and equipment as specified by site spill control procedures. Absorb liquid with suitable material and clean affected area with soap and water. Application of household bleach for 10 minutes can be used to further clean the affected spill areas. Dispose of materials according to the applicable federal, state, or local regulations.

## 7. HANDLING AND STORAGE

**Handling** Methotrexate is a cytotoxic agent. Appropriate procedures should be implemented during the handling and disposal of cytotoxic antineoplastics 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 site hygienist or safety professional for your facility requirements.

## 7. HANDLING AND STORAGE: continued

**Handling:** continued

Avoid ingestion, inhalation, skin contact, and eye contact. 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 storage recommendations noted on the product case label, the primary container label, or the product insert. Protect from light.

Dilute solutions of methotrexate may undergo photo-degradation when stored in the light. Under normal lighting conditions, solutions are stable for about 24 hours, but photodegradation results in a decrease in drug concentration of up to 12% after 48 hours. Photodegradation is more rapid in direct sunlight, with about an 11% drug loss from a 1 mg/mL solution after 7 hours.

**Special Precautions**

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

## 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

**Exposure Guidelines**

| | Exposure Limits | | | |
|---|---|---|---|---|
| **Component** | **OSHA-PEL** | **ACGIH-TLV** | **AIHA WEEL** | **Hospira EEL** |
| Methotrexate | 8-hr TWA: Not Established | 8-hr TWA: Not Established | 8-hr TWA: Not Established | 8-hr TWA: Not Established |

Notes: OSHA PEL: US Occupational Safety and Health Administration – Permissible Exposure Limit
ACGIH TLV: American Conference of Governmental Industrial Hygienists – Threshold Limit Value.
AIHA WEEL: Workplace Environmental Exposure Level
EEL: Employee Exposure Limit.
TWA: 8-hour Time Weighted Average.

**Respiratory Protection**

Respiratory protection is normally not needed during intended product use. However, if the generation of 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 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**

When handling this material, disposable gloves should be worn at all times. Further, the use of double gloves is recommended. Disposable gloves made from nitrile, neoprene, polyurethane or natural latex generally have low permeability to this material. Persons known to be allergic to latex rubber should select a non-latex glove. Gloves should be changed regularly, and removed immediately after known contamination. Care should be taken to minimize inadvertent contamination when removing and/or disposing of gloves.

**Eye Protection**

As a minimum, the use of chemical safety goggles is recommended when handling this product.

**Engineering Controls**

If the generation of aerosols is likely, as a minimum, local exhaust ventilation is recommended to minimize employee exposure. The use of an enclosure, such as an approved ventilated cabinet designed to minimize airborne exposures, is also recommended.

## 9. PHYSICAL/CHEMICAL PROPERTIES

| | |
|---|---|
| **Appearance/Physical State** | A clear yellowish orange liquid in a vial |
| **Odor** | NA |
| **Odor Threshold** | NA |
| **pH** | 8.5 |
| **Melting point/Freezing Point** | NA |
| **Initial Boiling Point/Boiling Point Range** | NA |
| **Flash Point** | NA |
| **Evaporation Rate** | NA |
| **Flammability (solid, gas)** | NA |
| **Upper/Lower Flammability or Explosive Limits** | NA |
| **Vapor Pressure** | NA |
| **Vapor Density (Air =1)** | NA |
| **Relative Density** | NA |
| **Solubility** | Practically insoluble in water, in alcohol, in chloroform, and in ether; freely soluble in dilute solutions of alkali hydroxides and carbonates; slightly soluble in 6N hydrochloric acid. |
| **Partition Coefficient: n-octanol/water** | 0.0141 |
| **Auto-ignition Temperature** | NA |
| **Decomposition Temperature** | NA |
| **Viscosity** | 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** | Strong oxidizers |
| **Hazardous Decomposition Products** | Not determined. During thermal decomposition, it may be possible to generate irritating vapors and/or toxic fumes of carbon oxides (COx) and nitrogen oxides (NOx). |
| **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 |
|---|---|---|---|---|---|---|
| Methotrexate | 100 | LD50 | Oral | 135 | mg/kg | Rat |
| Methotrexate | 100 | LD50 | Oral | 146 | mg/kg | Mouse |
| Methotrexate | 100 | LD50 | Intravenous | 14 | mg/kg | Rat |
| Methotrexate | 100 | LD50 | Intravenous | 65 | mg/kg | Mouse |

LD50 is the dosage producing 50% mortality.

## 11. TOXICOLOGICAL INFORMATION: continued

| | |
|---|---|
| **Occupational Exposure Potential** | There are scientific studies that suggest 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 materials if workplace exposures are not properly controlled. The actual risk in the workplace is not known. |
| **Signs and Symptoms** | None anticipated from normal handling of this product. This material should be considered irritating to the skin, eyes and respiratory tract. In clinical use, adverse events include bone marrow suppression, headache, dizziness, drowsiness, diarrhea, fatigue, skin rash, hair loss, chills and fever. Ulcerations and bleeding of the mouth and gastrointestinal tract may also occur. Liver and kidney injury, immune-suppression, osteoporosis and pulmonary and neurotoxic reactions have also been reported. Abortion, fetal death and congenital malformations (cranial abnormalities) have been associated with methotrexate use during pregnancy. Therapeutic dosages can impair oogenesis or spermatogenesis, resulting in lowered sperm counts, menstrual dysfunctions, and infertility. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. Instances of malignant lymphoma arising during treatment with low-dose oral methotrexate have been reported, which regressed completely following withdrawal of methotrexate. |
| **Aspiration Hazard** | None anticipated from normal handling of this product. |
| **Dermal Irritation/ Corrosion** | None anticipated from normal handling of this product. Based on clinical use, inadvertent contact of this product with skin may produce mild irritation and redness. |
| **Ocular Irritation/ Corrosion** | None anticipated from normal handling of this product. Inadvertent contact of this product with eyes may produce irritation with redness with tearing and discomfort. |
| **Dermal or Respiratory Sensitization** | None anticipated from normal handling of this product. In clinical use, hypersensitivity reactions to methotrexate are reported to be rare. |
| **Reproductive Effects** | None anticipated from normal handling of this product. Folic acid antagonists such as methotrexate interfere with embryogenesis and are recognized teratogens. Embryonic mesenchymal tissue is sensitive to these compounds. In animals, methotrexate produced embryotoxic and teratogenic effects at relatively low dosages, typically in the low mg/kg/day range. The lowest LOAEL for teratogencity was 0.1 mg/kg/day in rats, the most sensitive species.<br><br>Impotence has been reported in three men with rheumatoid arthritis who were treated with weekly doses of 12.5 mg methotrexate. The sexual dysfunction was reversible when the drug was discontinued. Toxic effects of methotrexate on gonadal function are inferred from studies in which this agent, along with other agents used for cancer therapy, has been associated with oligospermia in men and amenorrhea in women.<br><br>At least 19 children or fetuses with a very uncommon and characteristic pattern of congenital anomalies have been born to women treated with methotrexate during the first trimester of pregnancy The most characteristic malformation induced by methotrexate is a "clover-leaf" skull with a large head, swept-back hair, low-set ears, prominent eyes, and wide nasal bridge. Limb defects and absent ossification centers have also been reported, as well as CNS abnormalities including anencephaly, hydrocephaly, and meningomyelocele. |
| **Mutagenicity** | Methotrexate was negative for mutagenicity in several bacterial assays (Ames test, E. coli), but was clastogenic in a mouse lymphoma cell assay and an SCE assay in human lymphocytes. |

## 11. TOXICOLOGICAL INFORMATION: continued

| | |
|---|---|
| **Carcinogenicity** | Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. |
| **Carcinogen Lists** | **IARC:** Group 3 - not classifiable as to carcinogenicity to humans **NTP:** Not listed **OSHA:** Not listed |
| **Specific Target Organ Toxicity – Single Exposure** | NA |
| **Specific Target Organ Toxicity – Repeat Exposure** | Based on clinical use, possible target organs may include the bone marrow, gastrointestinal system, nervous system, cardiovascular system, lungs, liver, kidney, skin, and gonads. |

## 12. ECOLOGICAL INFORMATION

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|---|---|
| **Aquatic Toxicity** | Not determined for product. Information for the active ingredient is as follows:<br><br>EC50 = 260 mg/L in algae<br>LC50 > 1000 mg/L in Daphnia<br>EC50 = 85 mg/L in a fish embryo assay<br>EC50 = 45 mg/L for growth inhibition in ciliates<br>EC50 = 1220 mg/L for inhibition of luminescence in V. fischeri |
| **Persistence/ Biodegradability** | Not degradable in a 28-day Ready biodegradation assay in activated sludge. |
| **Bioaccumulation** | Not determined. Based on a log octanol:water partition coefficient of less than 3, this material is not anticipated to bioaccumulate. |
| **Mobility in Soil** | Not determined. |
| **General Notes** | In stability studies, photodegradation occurred rapidly in direct sunlight, with about an 11% drug loss from a 1 mg/mL solution after 7 hours. |

## 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 |
| **Proper Shipping Name** | NA |
| **Hazard Class** | NA |
| **UN Number** | NA |
| **Packing Group** | NA |
| **Reportable Quantity** | NA |
| **ICAO/IATA STATUS** | Not regulated |
| **Proper Shipping Name** | NA |
| **Hazard Class** | NA |
| **UN Number** | NA |
| **Packing Group** | NA |
| **Reportable Quantity** | NA |
| **IMDG STATUS** | Not regulated |
| **Proper Shipping Name** | NA |
| **Hazard Class** | NA |
| **UN Number** | NA |
| **Packing Group** | NA |
| **Reportable Quantity** | NA |

Notes: DOT - US Department of Transportation Regulations

## 15. REGULATORY INFORMATION

| | |
|---|---|
| **US TSCA Status** | Exempt |
| **US CERCLA Status** | Not listed |
| **US SARA 302 Status** | Not listed |
| **US SARA 313 Status** | Not listed |
| **US RCRA Status** | Not listed |
| **US PROP 65 (Calif.)** | This product is, or contains chemical(s) known to the State of California to cause developmental toxicity. |

Notes: TSCA, Toxic Substance Control Act; CERCLA, US EPA law, Comprehensive Environmental Response, Compensation, and Liability Act; SARA, Superfund Amendments and Reauthorization Act; RCRA, US EPA, Resource Conservation and Recovery Act; Prop 65, California Proposition 65

**GHS/CLP 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 | Hazard Category | Pictogram | Signal Word | Hazard Statement |
|---|---|---|---|---|
| NA | NA | NA | NA | NA |

**Prevention**

Obtain special instructions before use
Do not handle until all safety precautions have been read and understood
Wear protective gloves/protective clothing/eye protection/face protection
Do not breathe vapor or spray
Wash hands thoroughly after handling
Avoid release to the environment

**Response**

Get medical attention if you feel unwell. If exposed or concerned: Get medical advice/attention.

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.

## 15. REGULATORY INFORMATION: continued

| | |
|---|---|
| **EU Classification*** | *Medicinal products are exempt from the requirements of the EU Dangerous Preparations Directive. |
| **Classification(s)** | NA |
| **Symbol** | NA |
| **Indication of Danger** | NA |
| **Risk Phrases** | NA |
| **Safety Phrases** | S23: Do not breathe vapor/spray<br>S24: Avoid contact with the skin<br>S25: Avoid contact with eyes<br>S37/39: Wear suitable gloves and eye/face protection<br>S61: Avoid release to the environment |

## 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 |
| $LD_{50}$ | 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 |
| STOT - SE | Specific Target Organ Toxicity – Single Exposure |
| STOT - RE | Specific Target Organ Toxicity – Repeated Exposure |
| TSCA | Toxic Substance Control Act |
| TWA | 8-hour Time Weighted Average |

MSDS Coordinator: Hospira GEHS
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