

SAFETY DATA SHEET



Product Name: Methotrexate Injection, USP

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Manufacturer Name And Address	Hospira, Inc. 275 North Field Drive Lake Forest, Illinois 60045 USA	Hospira Australia Pty Ltd 1 Lexia Place Mulgrave VIC 3170 AUSTRALIA
Emergency Telephone #'s	CHEMTREC: North America: 800-424-9300; 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-pteridiny)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 Not Classified	Hazard Category Not Classified
Health Hazards	Hazard Class Toxic to Reproduction Germ Cell Mutagenicity STOT – RE	Hazard Category 1 2 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 C₂₀H₂₂N₈O₅

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

Component	Exposure Limits			
	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	<p>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 teratogenicity was 0.1 mg/kg/day in rats, the most sensitive species.</p> <p>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.</p> <p>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.</p>
Mutagenicity	Methotrexate was negative for mutagenicity in several bacterial assays (Ames test, <i>E. coli</i>), 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

Aquatic Toxicity	Not determined for product. Information for the active ingredient is as follows: EC50 = 260 mg/L in algae LC50 > 1000 mg/L in Daphnia EC50 = 85 mg/L in a fish embryo assay EC50 = 45 mg/L for growth inhibition in ciliates EC50 = 1220 mg/L for inhibition of luminescence in <i>V. fischeri</i>
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

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

<u>EU Classification*</u>	*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 S24: Avoid contact with the skin S25: Avoid contact with eyes S37/39: Wear suitable gloves and eye/face protection 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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Disclaimer:

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