MATERIAL SAFETY DATA SHEET

Product Name: Methotrexate Injection, USP

1. CHEMICAL PRODUCT AND COMPANY INFORMATION

Manufacturer Name And Address	Hospira Inc. 275 North Field Drive Lake Forest, Illinois USA 60045 Hospira Australia Pty Ltd 1 Lexia Place Mulgrave, VIC 3170 Australia
Emergency Telephone	CHEMTREC: North America: 800-424-9300; International 1-703-527-3887; Australia (02) 8014 4880
Hospira, Inc., Non-Emergency	224-212-2000
Product 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. COMPOSITION/INFORMATION ON INGREDIENTS

Active Ingredient Name	Methotrexate
Chemical Formula	$C_{20}H_{22}N_8O_5$
Preparation	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.

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

3. HAZARD INFORMATION

Carcinogen List

Substance	IARC	NTP	OSHA
Methotrexate	3 - not classifiable as to carcinogenicity to humans	Not Listed	Not Listed

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, harmful to the fetus, and a potential human carcinogen. Based on clinical use, possible target organs may

	include the bone marrow, gastrointestinal system, central nervous system, cardiovascular system, lungs, liver, kidney, skin, gonads, and the fetus.
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	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, immunosuppression, 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.
Medical Conditions Aggravated by Exposure	Pre-existing hypersensitivity to methotrexate. Pre-existing bone marrow, cardiovascular, gastrointestinal, central nervous system, pulmonary, liver, kidney, gonadal, or skin ailments; or 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 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.
Special Fire Fighting Procedures	Firefighters should wear self-contained breathing apparatus. Protective equipment and clothing should be worn to minimize contact with the respiratory tract, skin and eyes.

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 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.

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.

Diluted 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. The bicarbonate ion catalyses this reaction.

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 this material.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Exposure Guidelines

	Exposure limits				
Component	**Type**	**mg/m3**	**ppm**	**µg/m3**	**Note**
Methotrexate	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 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	Liquid
Color	Clear Yellowish Orange
Odor	None
Odor Threshold:	NA
pH:	8.5
Melting point/Freezing point:	NA
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:	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

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

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 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.

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, have been associated with oligospermia in men and amenorrhea in women.

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.

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.

Target Organ Effects

This material should be considered irritating to the skin, eyes and respiratory tract. Based on clinical use, possible target organs may include the bone marrow, gastrointestinal system, central nervous system, cardiovascular system, lungs, liver, kidney, skin, gonads, and the fetus.

12. ECOLOGICAL INFORMATION

Aquatic Toxicity

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 V. fischeri

Persistence/Biodegradability

Not degradable in a 28-day Ready biodegradation assay in activated sludge.
Not determined. Based on a log octanol:water partition coefficient of less than 3, this material is not anticipated to bioaccumulate.

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 occurs 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 by the waste generator. Disposal should be performed in accordance with the federal, state or local regulatory requirements.

Container Handling and Disposal

Dispose of containers and unused contents in accordance with federal, state and local regulations.

14. TRANSPORTATION INFORMATION

DOT STATUS Not regulated

ICAO/IATA STATUS: Not regulated

IMDG STATUS: Not regulated

15. REGULATORY INFORMATION

USA Regulations

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

US RCRA Status Not Listed

U.S. OSHA Classification
Possibly Toxic by Ingestion
Target Organ Toxin
Reproductive Toxin
Possible Irritant

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.

Get medical attention if you feel unwell.

EU Classification*

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

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Classification(s): Not Applicable

Symbol: Not Applicable

Indication of Danger: Not Applicable

Risk Phrases: Not Applicable

Safety Phrases: Not Applicable

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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