SAFETY DATA SHEET

XATMEP™ (methotrexate) ORAL SOLUTION, 2.5 mg/mL
PRESCRIPTION DRUG PRODUCT

1. PRODUCT AND COMPANY INFORMATION

PRODUCT NAME	XATMEP (methotrexate) Oral Solution, 2.5 mg/mL, is a clear, yellow to orange solution.
SYNONYMS	Methotrexate disodium (active pharmaceutical ingredient)
CAS NUMBER	Not applicable. XATMEP (methotrexate) Oral Solution, 2.5 mg/mL, is a formulated prescription drug product. CAS # for the active ingredient, methotrexate disodium, is 7413-34-5
INDICATIONS	XATMEP (methotrexate) is a folate analog metabolic inhibitor indicated for the: - Treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a multi-phase, combination chemotherapy maintenance regimen. - Management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJRA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory drugs (NSAIDs).
SUPPLIER	Silvergate Pharmaceuticals, Inc. 6251 Greenwood Plaza Blvd., Suite 101 Greenwood Village, CO 80111 USA Tele: (720)-266-4524 Fax: (720)-439-3037
EMERGENCY PHONE NUMBER	1-855-379-0383

2. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW	Xatmep contains methotrexate, a folic acid antagonist. Methotrexate is used to treat some types of cancers, severe psoriasis, and rheumatoid arthritis. It is a cytotoxic agent. It may cause genetic defects and may damage fertility or the unborn child.
OSHA Hazards Target Organs	Prescription drug product contains a **BOXED WARNING**: **WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY** ***See full prescribing information for complete boxed warning.*** • **Methotrexate can cause severe or fatal toxicities. Monitor closely and modify dose or discontinue for the following toxicities: bone marrow suppression (5.1), infections (5.2), renal (5.3), gastrointestinal (5.4), hepatic (5.5), pulmonary (5.6), hypersensitivity and dermatologic (5.7).**

BOXED WARNING, CONTINUED:

- **Methotrexate can cause embryo-fetal toxicity and fetal death. Use in polyarticular juvenile idiopathic arthritis is contraindicated in pregnancy (4). Consider the benefits and risks of XATMEP and risks to the fetus when prescribing XATMEP to a pregnant patient with a neoplastic disease. Advise patients to use effective contraception during and after treatment with XATMEP (5.9, 8.1, 8.3).**

Global Harmonized System (GHS) Classification:

GHS06
Severe Toxic: Material is a serious health or physical hazard or poison.

GHS08
Health Hazard: Muta.1B May cause genetic defects
Repr. 1A May damage fertility or fetus

GHS07
Acute Toxic: The material may cause immediate serious health effects.

Health: CAUTION: Pharmaceutical product available only with prescription.
Inhalation: May be harmful if inhaled. May cause respiratory tract irritation.
Ingestion: May be harmful if ingested without a medical professional's supervision. XATMEP (methotrexate) Oral Solution is a cytotoxic agent.

Eyes: May cause eye irritation.
Skin: Non-irritating to intact skin; may cause irritation to abraded skin.

3. COMPOSITION/INFORMATION ON INGREDIENTS

Ingredients of Methotrexate Oral Solution	Percentage	CAS Number
Methotrexate disodium	2.7 (≈ 2.5 methotrexate)	7413-34-5
Citric acid, anhydrous USP	*	77-92-9
Sodium citrate, anhydrous USP	*	68-04-2
Methylparaben sodium NF	*	5026-62-0
Propylparaben sodium NF	*	
Sucralose NF	*	56038-13-2
Purified water USP	*	N/A
May contain HCl or NaOH for pH	*	7647-01-0 1310-73-2

* Proprietary information

4. FIRST AID MEASURES

Eye Contact: In case of contact, immediately flush eyes with water for 20 minutes. Remove contact lenses if able. Seek medical attention, if irritation persists.

Skin Contact: Wash with soap and water. Remove contaminated clothing and wash thoroughly before reuse. Remove and clean shoes. Seek medical attention if irritation develops.

Inhalation: If inhaled, remove to fresh air. Seek medical attention. If difficulty breathing, give oxygen. If not breathing, give artificial respiration.

Ingestion: Do not induce vomiting unless directed to do so by medical personnel. Seek medical attention. Never give anything by mouth to an unconscious person.

5. FIRE FIGHTING MEASURES

Flammability: Non-flammable. It is an aqueous based solution.

Suitable Extinguishing Media: Use water spray (fog), foam, carbon dioxide, or dry chemicals.

Hazardous Decomposition Products: Carbon oxides, nitrogen oxides.

Fire Fighting Procedures: During fire-fighting activities, wear appropriate protective equipment including self-contained breathing apparatus.

6. ACCIDENTAL RELEASE MEASURES

Personnel Precautions: Immediately contact emergency personnel. Use suitable personal protective equipment. Keep unnecessary personnel away.

Clean-Up Procedures: Contain the spilled materials. Avoid creating dust. Carefully absorb spilled materials and place in a suitable closed container for appropriate disposal. Wear gloves and if necessary, other protective clothing.

Environmental Precautions: Do not let product rinse down drains. Minimize contact with soils to prevent run-off to surface waterways.

See Section 13 for Waste Disposal Information.

7. HANDLING AND STORAGE

Handling: Methotrexate is cytotoxic. Appropriate procedures should be implemented during the handling and disposal of cytotoxic agents to minimize potential exposures. Use of disposable gloves when handling a liquid is recommended.

Special Precautions: Women who are pregnant or intend to become pregnant should avoid exposure to methotrexate. Any person with known hypersensitivity to methotrexate or any of the components of XATMEP (methotrexate) Oral Solution should avoid handling and contact with the product.

Avoid contact with eyes. Do not ingest. Wash thoroughly after handling.

Storage: Store XATMEP refrigerated (2°C- 8°C/36°F - 46°F) in a tightly closed container. Patients may store XATMEP either refrigerated or at room temperature (20°C - 25°C/ 68°F - 77°F). If stored at room temperature, discard after 60 days. Excursion permitted to 15°C - 30°C/59°F - 86°F [see USP Controlled Room Temperature]. Avoid freezing and excessive heat.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

General Product Information: **This is a prescription drug product**.

Eye/Face Protection: Safety glasses or goggles should be worn when handling liquid.

Hand/Arm Protection: Wear impervious disposable gloves when handling liquid.

Respiratory Protection: Respiratory protection is not required, but recommended. Avoid inhalation of liquid.

Skin/Body Protection: Laboratory coat or work uniform is appropriate when handling liquid.

Hygiene Measures: Wash hands and exposed arms thoroughly before and after handling. Do not eat, drink, or smoke without first washing hands before and after handling.

Special Precautions: This is a prescription drug product whose prescribing information includes a **BOXED WARNING** provided in Section 1. See full prescribing information for complete boxed warning.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance	Clear, yellow to orange solution
Odor	No descriptive odor.
pH	~ 6.3
Melting point	Not applicable
Flash point	Not available
Ignition/Auto-ignition temperature	Not available
Upper and Lower explosion limit	Not available
Density	~ 1
Partition co-efficient (n-octanol/water)	Not available

10. STABILITY AND REACTIVITY

Stability	The product is stable through the expiration dating period on the label when stored in refrigerated conditions (2°C- 8°C/36°F - 46°F). It is stable at controlled room temperatures for 60 days.

Conditions to Avoid	Temperatures above 8°C for extended periods of time. Avoid freezing and exposure to excessive heat.
Incompatibility	Not established
Hazardous Decomposition Products	No data available
Hazardous Polymerization/Reactions	No data available

11. TOXICOLOGICAL INFORMATION

Toxicity Data

Component	Test	Species	Route	Result
Methotrexate	LD_{50}	Rat	Oral	135 mg/kg
	LD_{50}	Mouse	Oral	146 mg/kg
	LD_{50}	Rat	Intravenous	14 mg/kg
	LD_{50}	Mouse	Intravenous	65 gm/kg
	LD_{50}	Rat	Intraperitoneal	6 mg/kg
	LD_{50}	Mouse	Intraperitoneal	50 mg/kg

Carcinogenicity: Based on available data, the classification criteria are not met.
Rat: No route specified; 90 mg/kg/day NOAEL Not carcinogenic
Mouse: No route specified; 135 mg/kg/day NOAEL Not carcinogenic

No component of this product is listed as a carcinogen by OSHA, NTP, or IARC.

Reproductive Toxicity Information: Methotrexate causes embryo-fetal toxicity, including fetal death. Methotrexate is contraindicated in pregnant women with pJIA. Methotrexate inhibits dihydrofolic acid reductase. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication.

12. ECOLOGICAL INFORMATION

Toxicity	No data available
Persistence and degradability	No data available
Bio-accumulative potential	No data available
Other adverse effects	No data available

13. DISPOSAL CONSIDERATION

Dispose of waste in accordance with applicable Federal, State and local regulations.
See “HAZARDOUS DRUGS” OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html.*
Do not allow product to reach sewage system.

Containers should not be re-used for any purpose. Dispose of in accordance with applicable Federal, State and local regulations.

14. TRANSPORT INFORMATION

This SDS should accompany all shipments for reference in the event of spillage or accidental release. Only authorized and trained personnel with appropriate national and international regulatory requirements should prepare hazardous goods for transport.

15. REGULATORY INFORMATION

US Federal Regulations	Hazardous per OSHA Hazard Communication Standard Criteria (29 CFR § 1910.1200). FDA-approved prescription drug product. FDCA §505(b)(2).
California Prop. 65	Methotrexate sodium is listed as a chemical known to the State of California to cause birth defects or other reproductive harm.
NJ, MA, PA	State Right-To-Know lists: Not listed in concentrations presented in this drug product formulation.

16. OTHER INFORMATION

CAS: Chemical Abstracts Service number (division of American Chemical Society)
CFR: US code of federal regulations
FDCA: Federal Food, Drug, and Cosmetic Act
IARC: International Agency for Research on Cancer
LD_{50}: Median lethal dose
NF: National Formulary
NOAEL: No observed adverse effect level
NTP: National Toxicology Program
OSHA: US Occupational Safety and Health Administration
USP: United States Pharmacopeia

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