



TEVA PARENTERAL MEDICINES

Material Safety Data Sheet

Fludarabine Phosphate Injection, USP

1. PRODUCT IDENTIFICATION

Product Name Fludarabine Phosphate Injection, USP
Product Use Medical Treatment for B-cell Chronic Lymphocytic Leukemia (CLL)
Manufacturer Teva Parenteral Medicines, Inc.
Address 11 Hughes
 Irvine, CA 92618-1902

Chemtrec Emergency No. 1-800-424-9300 (United States)
 1-202-483-7617 (International Collect)

Business Phone 1-800-729-9991
Website Address <http://www.newsicor.com>

Common Names 2-Fluoro-ara-AMP, Fludara
Chemical Name 9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl)

Chemical Formula C₁₀H₁₃FN₅O₇P
Chemical Family Purine Nucleoside
How Supplied 25 mg/mL, 50mg/vial

Date of Preparation: May 3, 2004

2. COMPOSITION AND INGREDIENTS

CHEMICAL NAME	CAS#	Wt%	EXPOSURE LIMITS IN AIR				
			ACGIH		OSHA		Other
			TLV	CEIL	PEL	STEL	
Fludarabine Phosphate	75607-67-9	2.5	NE	NE	NE	NE	NE
Mannitol	69-65-8	2.5	NE	NE	NE	NE	NE
Sodium Hydroxide (for pH adj.)	1310-73-2	Trace	NE	2mg/m ³	2mg/m ³	NE	NE
Water (for injection)	7732-18-5	Balance	NE	NE	NE	NE	NE

NE - Not Established

CEIL - Ceiling Limit

NOTE: All WHMIS required information is included. It is located in appropriate sections based on the ANSI Z400.1 format
 CHEMTREC NUMBER: Use only in the event of a chemical emergency involving a spill, leak, fire, exposure or accident involving this drug.

3. HAZARD IDENTIFICATION

EMERGENCY OVERVIEW: Material is clear, colorless solution. Harmful or fatal if swallowed, inhaled or absorbed through skin. Overexposure may cause damage to the bone marrow, nervous and the male reproductive systems. May cause birth defects. Avoid breathing dust. Avoid contact with eyes, skin and clothing. Avoid exposure during pregnancy. Do not taste or swallow. Wash thoroughly after handling.

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3. HAZARD IDENTIFICATION cont.

Symptoms of Overexposure by Route of Exposure: This material is intended for intravenous injection under the supervision of physicians.

Inhalation: Inhalation of significant amounts of the product is not anticipated to occur because of the small size of individual containers. However, Fludarabine Phosphate is toxic if inhaled.

Contact with Skin or Eyes: High concentrations of Fludarabine Phosphate are toxic by skin absorption. Skin rashes have also been reported.

Ingestion: Although ingestion is not an anticipated route of occupational exposure, this material is toxic and may be harmful or fatal if swallowed. Symptoms similar to those identified under injection may occur, including severe myelosuppression (neutropenia-decrease neutrophilic white blood cells, thrombocytopenia-decrease platelets and anemia-decrease red blood cells).

Injection: Local redness and pain are the primary symptoms of accidental injection in an occupational setting. Medical personnel are not anticipated to experience over-exposures to the therapeutic doses of this product. See package insert for adverse reactions associated with therapeutic doses of this product.

Health Effects or Risks From Exposure (An explanation in lay terms):

Acute: The primary health effects anticipated in an occupational setting include irritation of eyes and skin as well as redness and local swelling after accidental injection. In case of over-exposure by injection, burning sensation, myelosuppression (neutropenia, thrombocytopenia and anemia), fever, chills, infection, nausea, vomiting, malaise, fatigue, anorexia and weakness may occur. Death can occur in the event of accidental overdose.

Chronic: This product may cause male reproductive disorders. Exposure during pregnancy may cause birth defects.

Target Organs: This product may produce adverse effects on the bone marrow and nervous system.

Pre-Existing Medical Conditions: Conditions aggravated by exposure may include skin, respiratory, blood, male reproductive and nervous system disorders.



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4. FIRST-AID MEASURES

Skin Exposure: Remove contaminated shoes and clothing and cleanse affected area(s) thoroughly by washing with mild soap and water. If irritation or redness develops and persists, seek medical attention.

Eye Exposure: If irritation or redness develops, move victim away from exposure and into fresh air. Flush eyes with clean water and seek medical attention. For direct contact, hold eyelids apart and flush the affected eye(s) with clean water for at least 15 minutes. Seek medical attention.

Inhalation: Immediately move victim away from exposure and into fresh air. If respiratory symptoms or other symptoms of exposure develop, seek immediate medical attention. If victim is not breathing, clear airway and immediately begin artificial respiration. If breathing difficulties develop, oxygen should be administered by qualified personnel. Seek immediate medical attention.

Ingestion: If swallowed, seek emergency medical attention. If victim is drowsy or unconscious and vomiting, place on the left side with the head down and DO NOT give anything by mouth. If not vomiting and professional advice is not available, DO NOT induce vomiting. If possible, do not leave victim unattended and observe closely for adequacy of breathing.

Victims of chemical exposure must be taken for medical attention. Take a copy of the MSDS to the physician or health professional with victim. Physicians should refer to Section 11 (Toxicological Information) as well as the Physicians Desk Reference for additional treatment information.

Recommendations to Physicians: Fatal pulmonary toxicity has been reported following the injection of Fludarabine Phosphate in combination with pentostatin (deoxycoformycin).

5. FIRE-FIGHTING MEASURES

Flash Point: No data Autoignition Temperature: No data

Flammable Limits (in air by volume, %): Lower: No data Upper: No data

Fire Extinguishing Equipment: Use extinguishing agent suitable for type of surrounding fire.

Water Spray: OK Carbon Dioxide: OK Halon: OK

Foam: OK Dry Chemical: OK Other: Any "ABC" Class

Unusual Fire and Explosion Hazards: No unusual fire or explosion hazards are expected.

Explosion Sensitivity to Mechanical Impact: Not sensitive.

Explosion Sensitivity to Static Discharge: Not sensitive.

Special Fire Fighting Procedures: For fires beyond the incipient stage, emergency responders in the immediate hazard area should wear bunker gear. When the potential chemical hazard is unknown, in enclosed or confined spaces, or when explicitly required by DOT, a self-contained breathing apparatus should be worn. In addition, wear other appropriate protective equipment as conditions warrant (see Section 8). Isolate immediate hazard area and keep unauthorized personnel out. Contain spill if it can be done with minimal risk. Move undamaged containers from immediate hazard area if it can be done with minimal risk. Cool equipment exposed to fire with water, if it can be done with minimal risk.



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5. FIRE-FIGHTING MEASURES cont...

NFPA HAZARD CLASS: Health: 3 (High)
 Flammability: 0 (Least)
 Reactivity: 0 (Least)

6. ACCIDENTAL RELEASE MEASURES

Spill and Leak Response:

For small releases of this product, wear latex or nitrile gloves and safety glasses. Absorb spilled liquid and rinse area thoroughly with soap and water.

For large or uncontrolled releases, stay away from spill. Isolate immediate hazard area and keep unauthorized personnel out. Contain spill if it can be done with minimal risk. Wear appropriate protective equipment including respiratory protection as conditions warrant (see Section 8). Prevent spilled material from entering sewers, storm drains, other unauthorized treatment drainage systems, and natural waterways. Dike far ahead of spill for later recovery or disposal. Spilled material may be absorbed into an appropriate absorbent material. Notify appropriate federal, state, and local agencies. Immediate cleanup of any spill is recommended.

7. HANDLING and STORAGE

Work and Hygiene Practices: As with all chemicals, avoid getting this product ON YOU or IN YOU. Do not eat, drink, smoke or apply cosmetics while handling the product. Wash hands thoroughly after handling.

Particular care in working with this product must be practiced in pharmacies and other preparation areas, during manufacture of this product, and during patient administration. Precautions should be taken during the following activities:

- Withdrawal of needles from drug vials.
- Drug transfers using syringes and needles or filter straws.
- Expulsion of air from drug-filled syringes.

Storage and Handling Practices: Employees must be trained to properly use the product. Ensure vials are properly labeled. Keep away from sources of ignition and any incompatible materials or conditions (see Section 10).

Protective Practices During Maintenance of Contaminated Equipment: When cleaning non-disposable equipment, wear latex or nitrile gloves (double gloving is recommended), goggles, and lab coat. Wash equipment with soap and water. All needles, syringes, vials and other disposable items contaminated with this product should be disposed of properly.



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8. EXPOSURE CONTROLS - PERSONAL PROTECTION

Ventilation and Engineering Controls: Use with adequate ventilation. Follow standard medical product handling procedures.

Respiratory Protection: Not normally required for routine, medical administration of this product. A NIOSH certified air-purifying respirator with a type 95 filter may be used under conditions where airborne concentrations are expected to be excessive. Protection provided by air purifying respirators is limited (see manufacturer's respirator selection guide). Use a positive pressure air supplied respirator if there is potential for uncontrolled release, exposure levels are not known, or any other circumstances where air-purifying respirators may not provide adequate protection. A respiratory protection program that meets OSHA's 29 CFR 1910.134 and ANSI Z88.2 requirements must be followed whenever workplace conditions warrant a respirator's use.

Eye Protection: Approved eye protection to safeguard against potential eye contact, irritation or injury is recommended. Depending on conditions of use, a face shield may be necessary.

Hand Protection: Use latex, nitrile, or rubber gloves. Check gloves for leaks. Wash hands before and after using gloves.

Body Protection: No special body protection required for routine, medical administration of this product. Wear lab coat, gown, or smock, as appropriate for procedure.

Product Preparation Instructions for Medical Personnel: Follow standard procedure for handling pharmaceutical materials and recommendations presented on the Package Insert.

9. PHYSICAL and CHEMICAL PROPERTIES

Relative Vapor Density (air = 1):	ND	Evaporation Rate (n-BuAc=1):	ND
Specific Gravity (water = 1):	ND	Melting/Freezing Point:	0°C (32°F))
Solubility in Water:	Soluble	Boiling Point:	100°C
Vapor Pressure, mm Hg @ 25°C.	ND	pH:	ND
Odor Threshold: ND			
Appearance and Color: Clear, colorless solution			

ND = No Data

10. STABILITY and REACTIVITY

Stability: Stable under normal conditions of storage and handling.

Materials With Which Substance is Incompatible: This product is generally compatible with other common materials in a medical facility.

Hazardous Polymerization: Will not occur.

Hazardous Combustion Products: Protect from light and excessive heat.

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11. TOXICOLOGICAL INFORMATION

Toxicity Data: The following information is for Fludarabine Phosphate

IV LD50(rat-male) = 910 mg/kg IV LD50(rat-female) = 1050 mg/kg
 IV LD50(mouse-male) = 1404 mg/kg IV LD50(mouse-female) = 1235 mg/kg
 IV LD50(mouse-combined) = 1321 mg/kg

IV LD50-five daily doses(mouse-male) = 593 mg/kg
 IV LD50-five daily doses(mouse-female) = 496 mg/kg
 IV LD50-five daily doses(mouse-combined) = 542 mg/kg

Suspected Cancer Agent: This product as well as all components of this product have **NOT** been identified as carcinogens by NTP, IARC or OSHA.

Irritancy of Product: This product may be irritating to contaminated skin, eyes and other tissues.

Sensitization to the Product: This product is not expected to cause sensitization although individual sensitivities may vary.

Reproductive Toxicity Information: Listed below is information concerning the effects of Fludarabine Phosphate on human and animal reproductive systems. This material is classified as a Pregnancy Category D (Risk to Fetus).

Mutagenicity: Fludarabine phosphate was not mutagenic to several strains of *Salmonella typhimurium*, including TA-98, TA-100, TA-1535 and TA-1537. Also, it was not mutagenic to Chinese Hamster Ovarian (CHO) cells at the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus under both activated and non-activated metabolic conditions. Chromosomal aberrations were observed in an in-vitro assay using CHO cells under metabolically activated conditions. Fludarabine phosphate was determined to cause increased sister chromatid exchanges (SCE) using an in-vitro SCE assay under both metabolically activated and non-activated conditions. In addition, fludarabine phosphate has also been shown to be mutagenic as indicated by an increase in the number of micronucleated erythrocytes (red blood cells) in the in-vivo mouse micronucleus test at doses up to 1000 mg/kg.

Embryotoxicity/Teratogenicity/Reproductive Toxicity: Studies in mice, rats and dogs have demonstrated dose-related adverse effects on the male reproductive system. Observations consisted of a decrease in mean testicular weights in mice and rats with a trend toward decreased testicular weights in dogs and degeneration and necrosis of spermatogenic epithelium of the testes in mice, rats and dogs. The possible adverse effects on fertility in humans have not been adequately evaluated.

Fludarabine Phosphate was teratogenic in rats and rabbits when administered intravenously. Intravenous doses of 0, 1, 10 or 30 mg/kg/day were given to pregnant rats on days 6 to 15 of gestation. At 10 and 30 mg/kg/day, there was an increased incidence of various skeletal malformations. Doses of 0, 1, 5 or 8 mg/kg/day were given to pregnant rabbits on days 6 to 15 of gestation. Dose-related teratogenic effects manifested by external deformities and skeletal malformations were observed in rabbits at the 5 and 8 mg/kg/day dosage levels. Drug-related deaths or toxic effects on maternal and fetal weights were not observed. There are no adequate and well-controlled studies in pregnant women, however, a single case report of congenital malformations associated with first trimester, in utero, fetal exposure has been published.

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11. TOXICOLOGICAL INFORMATION cont.

Target Organ Toxicity Information: Fludarabine Phosphate can severely suppress bone marrow function resulting in anemia, thrombocytopenia, and neutropenia. Life-threatening and sometimes fatal autoimmune hemolytic anemia has been reported to occur in patients receiving injections of Fludarabine Phosphate. It has also been associated with severe neurologic and central nervous system effects including blindness, coma and death.

ACGIH Biological Exposure Indices: Currently there are no Biological Exposure Indices (BEIs) associated with the components of this product.

12. ECOLOGICAL INFORMATION

All work practices must be aimed at eliminating environmental contamination.

Environmental Stability: This product will be relatively stable under ambient environmental conditions.

Effect of Materials on Plants or Animals: No specific information is available on the effect of Fludarabine Phosphate on plants or animals in the environment. Due to the small product size and dilute concentration of the components, this product is not anticipated to cause adverse effects.

Effect of Chemicals on Aquatic Life: No specific information is available on the effect of Fludarabine Phosphate on plants or animals in the aquatic environment. Due to the small product size and dilute concentration of the components, this product is not anticipated to cause adverse effects.

13. DISPOSAL CONSIDERATIONS

Preparing Wastes for Disposal: This material, if discarded as produced, is not a RCRA "listed" or "characteristic" hazardous waste. Use resulting in chemical or physical change or contamination may subject it to regulation as a hazardous waste. Along with properly characterizing all waste materials consult state and local regulations regarding the proper disposal of this material.

U.S. EPA Waste Number: None

14. TRANSPORTATION INFORMATION

This Material is not Hazardous as Defined by 49 CFR 172.101 by the U. S. Department of Transportation

Proper Shipping Name: Not applicable

Hazard Class Number and Description: Not applicable

UN Identification Number: Not applicable

Packing Group: Not applicable

DOT Label(s) Required: Not applicable

North American Emergency Response Guidebook Number (1996): Not applicable.

MARINE POLLUTANT: No component of this product is listed as a Marine Pollutant (49 CFR 172.101, Appendix B)

Transport Canada Transportation of Dangerous Goods Regulations: Not applicable



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15. REGULATORY INFORMATION

U.S. REGULATIONS:

U.S. SARA Reporting Requirements: The components of this product are not subject to the reporting requirements of Sections 302, 304 and 313 of Title II of the Superfund Amendments and Reauthorization Act.

U.S. SARA Threshold Planning Quantity: Not applicable

U.S. TSCA Inventory Status: Fludarabine Phosphate is a “drug” as defined by the Federal Food, Drug and Cosmetic Act and is therefore not a chemical substance under TSCA.

California Safe Drinking Water and Toxic Enforcement Act (Proposition 65): This product does not contain a chemical which is known to the State of California to cause cancer, developmental or other reproductive effects.

Other U.S. Federal Regulations: Based on this product’s use, the requirements of the OSHA Bloodborne pathogen Standard (29 CFR 1910.1030) are applicable.

CANADIAN REGULATIONS:

Canadian DSL/NDSL Status: Fludarabine Phosphate is regulated by the Food and Drug Administration of Health Canada and is therefore exempt from the requirements of CEPA.

ANSI Labeling (Based on 129.1, Provided to Summarize Occupational Exposure Hazards **WARNING!** HARMFUL OR FATAL IF SWALLOWED, INHALED OR ABSORBED THROUGH SKIN. OVEREXPOSURE MAY CAUSE DAMAGE TO THE BONE MARROW, NERVOUS AND MALE REPRODUCTIVE SYSTEMS. MAY CAUSE BIRTH DEFECTS. Fludarabine Phosphate should be administered under the supervision of a qualified physician. Avoid over-exposure. Avoid breathing dust. Avoid exposure during pregnancy. Avoid contact with eyes, skin and clothing. Do not eat, drink or smoke when handling Fludarabine Phosphate. Do not taste or swallow. Wash thoroughly after handling. Clean up spills promptly.

16. OTHER INFORMATION

Issue Date: 05/03/04

Previous Issue Date: None

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