SAFETY DATA SHEET

Prepared to U.S. OSHA, CMA, ANSI, Canadian WHMIS Standards, European Union CLP EC 1272/2008 and the Global Harmonization Standard

1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY UNDERTAKING

PRODUCT IDENTIFIER/TRADE/MATERIAL NAME: Fludarabine Phosphate for Injection, USP

DESCRIPTION: Fludarabine Phosphate Lyophilized Powder
CHEMICAL NAME: For Active Ingredient: 9H-Purin-6-amine, 2-fluoro-9-(5-0-phosphono-b-D-arabino-furanosyl) (2-fluoro-ara-AMP)
CHEMICAL FAMILY: For Active Ingredient: Purine Nucleoside Cytotoxic Agent
FORMULA: For Active Ingredient: $C_{10}H_{13}FN_5O_7P$
RELEVANT USE of the SUBSTANCE: Human Pharmaceutical
USES ADVISED AGAINST: Non-Pharmaceutical Use
OTHER DESIGNATIONS: NDC 45963-609-55, NDC 45963-062-151
HOW SUPPLIED: Fludarabine Phosphate 50 mg Lyophilized Powder

SUPPLIER OF THE SAFETY DATA SHEET

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NOTE: ALL United States Occupational Safety and Health Administration Standard (29 CFR 1910.1200), U.S. State equivalent Standards, Canadian WHMIS [Controlled Products Regulations], EU Directives through EC 1907: 2006, and European Union CLP EC 1272/2008, required information is included in appropriate sections based on the U.S. ANSI Z400.1-2010 format. This product has been classified in accordance with the hazard criteria of the countries listed above.

DATE OF PREPARATION: January 04, 2015 **DATE OF REVISION:** New

2. HAZARDS IDENTIFICATION

EU CLP REGULATION (EC) 1272/2008 LABELING AND CLASSIFICATION: According to Article 1, item 5 (a) of CLP Regulation (EC) 1272/2008, medicinal products in the finished state for human use, as defined in 2001/83/EC, are excepted from classification and other criteria of 1272/2008.

EU 67/548/EEC LABELING AND CLASSIFICATION: According to Article 1 of European Union Council Directive 92/32/EEC, medical products in the finished state for human use (as defined by European Union Council Directives 67/548/EEC and 87/21/EEC) are not subject to the regulations and administrative provisions of European Union Council Directive 92/32/EEC.

EMERGENCY OVERVIEW:

Product Description: This product is a white lyophilized cake.

Health Hazards: WARNING! THIS PRODUCT CONTAINS A CYTOTOXIC AGENT. EXPOSURE BY ALL ROUTES OF EXPOSURE MUST BE AVOIDED In the workplace, this product may cause irritation. May be harmful if swallowed. In therapeutic use this product can cause bone marrow suppression which can lead to serious infection or death. The most common non-hematologic adverse reactions were nausea, alopecia, vomiting, sepsis or pyrexia/infection with reduced number of blood neutrophils, diarrhea, constipation, fatigue, and fever. Severe and possible hypersensitivity reactions have been reported from therapeutic use. Can cause fetal harm. Suspected of carcinogenic and mutagenic effects, based on animal and microorganism test data. May cause harm to breast-fed babies. These effects may be possible as a result of workplace exposure. Refer to Section 11 (Toxicological Information) for additional information on adverse effects.

Flammability Hazards: This compound may be combustible and may ignite if subjected to direct flame or if heated to high temperature for a prolonged period. As a finely-divided organic compound, the accumulation of dusts can create a serious hazard of explosion. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds (including carbon, phosphorous and nitrogen oxides and hydrogen fluoride).

Reactivity Hazards: This product is not reactive.

Environmental Hazards: This product has not been tested for environmental harm; all release to the environment should be avoided. **Emergency Recommendations:** Emergency responders must wear personal protective equipment suitable for the situation to which they are responding.

3. COMPOSITION and INFORMATION ON INGREDIENTS

CHEMICAL NAME	CAS #	EINECS #	% w/w	LABEL ELEMENTS EU Classification (67/548/EEC) GHS and EU Classification (1272/2008 EC) Risk Phrases/Hazard Statements
ACTIVE INGREDIENT				
Fludarabine Phosphate 9H-Purin-6-amine, 2-fluoro-9-(5-0-phosphono-b-D-arabino-furanosyl) (2-fluoro-ara-AMP)	75607-67-9	For freebase: 244-525-5	Proprietary	SELF CLASSIFICATION EU 67/548 Classification: Reproductive Toxicity Cat. 2, Germ Cell Mutagenicity Cat. 2, Carcinogenic Cat. 3 Risk Phrase Codes: R61, R62, R46, R40, R64, R48/20/22 Hazard Symbols: T GHS and EU 1272/2008 Classification: Reproductive Toxicity Cat. 1B, Germ Cell Mutagenicity Cat. 1B, Carcinogenic Cat. 2, STOT RE Cat. 2, , Adverse Effects on or Via Lactation Hazard Codes: H360Df, H340, H351, H362, H372 Hazard Symbol/Pictogram: GHS08
EXCIPIENTS				
Sodium hydroxide	1310-73-2	215-185-5	Proprietary	EU 67/548 Classification: Not Applicable GHS & EU 1272/2008 Classification: Not Applicable
Disodium Phosphate Dihydrate	10028-24-7	231-448-7	Proprietary	EU 67/548 Classification: Not Applicable GHS & EU 1272/2008 Classification: Not Applicable
Water for Injections			Proprietary	EU 67/548 Classification: Not Applicable GHS & EU 1272/2008 Classification: Not Applicable

NOTE: Sodium Hydroxide is used to adjust pH of this product. This compound does not contribute any further hazard to this product and so is not addressed in this SDS. See Section 16 for full classification information of this product.

4 FIRST-AID MEASURES

PROTECTION OF FIRST AID RESPONDERS: First-aid responders should not attempt to treat victims of exposure to this material without adequate personal protective equipment. Rescuers should be taken for medical attention, if necessary.

DESCRIPTION OF FIRST AID MEASURES: Victim(s) must be taken for medical attention. Remove victim(s) to fresh air, as quickly as possible. Upon contact of this product with skin, eyes, or mucous membranes, immediately decontaminate by flushing with water for at least 20 minutes! Remove contaminated clothing and shoes. Only trained personnel should administer supplemental oxygen and/or cardio-pulmonary resuscitation, when necessary. Take copy of label and SDS to physician or other health professional with victim(s). Wash clothing and thoroughly clean shoes before reuse.

Inhalation: If aerosols are inhaled, remove victim to fresh air. If necessary, use artificial respiration to support vital functions. Seek medical attention if adverse effect occurs after removal to fresh air.

Skin Exposure: If the product contaminates the skin and adverse effect occurs, begin decontamination with running water. Minimum flushing is for 20 minutes. Do not interrupt flushing. Remove exposed or contaminated clothing, taking care not to contaminate eyes. Seek medical attention if adverse effect occurs after flushing.

Eye Exposure: If particulates from this product enter the eyes, open victim's eyes while under gently running water. Use sufficient force to open eyelids. Have victim "roll" eyes. Minimum flushing is for 20 minutes. Do not interrupt flushing. Seek immediate medical attention after flushing if adverse effect occurs.

Ingestion Exposure: If this product is swallowed, CALL PHYSICIAN OR POISON CONTROL CENTER FOR MOST CURRENT INFORMATION. If professional advice is not available, do not induce vomiting. Rinse mouth with water immediately. Victim should drink large quantities of water. If milk is available, victim should drink it after drinking water. Never induce vomiting or give diluents (milk or water) to someone who is unconscious, having convulsions, or unable to swallow.

IMPORTANT SYMPTOMS AND EFFECTS: See Sections 2 (Hazard Identification) and 11 (Toxicological Information).

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: In therapeutic use, pre-existing bone marrow disease or insufficiency, renal insufficiency, interstitial lung disease and blood disorders may be may be aggravated. Workplace exposure may also aggravate these conditions.

IMMEDIATE MEDICAL ATTENTION AND SPECIAL TREATMENT NEEDED: Treat symptoms and eliminate exposure. There is no specific antidote for this drug. Treatment should be symptomatic and supportive. Persons developing hypersensitivity reactions should receive immediate medical attention.

5. FIRE-FIGHTING MEASURES

FLASH POINT: Not established.

AUTOIGNITION TEMPERATURE: Not established.

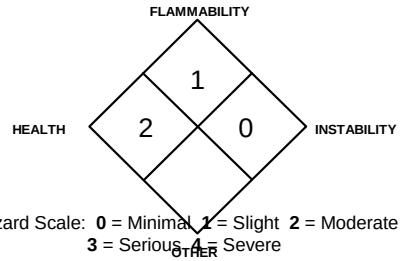
FLAMMABLE LIMITS & METHOD OF DETERMINATION (in air by volume, %): Not determined.

FIRE EXTINGUISHING MEDIA: Use extinguishing media appropriate for surrounding fire.

UNSUITABLE EXTINGUISHING MEDIA: None known.

SPECIFIC HAZARDS ARISING FROM THE PRODUCT: This product must be substantially pre-heated before ignition can occur. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds (including carbon, phosphorous and nitrogen oxides and hydrogen fluoride).

NFPA RATING



Hazard Scale: **0** = Minimal **1** = Slight **2** = Moderate **3** = Serious **4** = Severe

Explosion Sensitivity to Mechanical Impact: Not sensitive.

Explosion Sensitivity to Static Discharge: Large, finely-divided dust clouds of this product have the potential to ignite explosively.

SPECIAL PROTECTIVE ACTIONS FOR FIRE-FIGHTERS: Incipient fire responders should wear eye protection. Structural firefighters must wear Self-Contained Breathing Apparatus (SCBA) and full protective equipment. Contaminated protective equipment should be thoroughly washed with running water prior to removal of SCBA respiratory protection.

5. FIRE-FIGHTING MEASURES (Continued)

SPECIAL PROTECTIVE ACTIONS FOR FIRE-FIGHTERS (continued): Firefighters whose protective equipment becomes contaminated should thoroughly shower with warm, soapy water and should receive medical evaluation if they experience any adverse effects.

6. ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS: In the event of a spill, clear the area and protect people. Avoid aerosols of this product during spill response procedures.

PROTECTIVE EQUIPMENT:

Small Spills: For incidental spills (e.g., 5 g), wear double latex or nitrile disposable gloves and eye protection.

Large Spills: For large spills (e.g., greater than 5 g), protective apparel should be used with a respirator when there is any danger of airborne dusts being generated. Minimum Personal Protective Equipment should be rubber gloves, rubber boots, face shield, and Tyvek suit.

METHODS FOR CLEANUP AND CONTAINMENT:

Small Spills: Solids should be gently covered with wet absorbent pads.

Large Spills: Trained personnel following pre-planned procedures should handle non-incidental releases. Access to the spill areas should be restricted. Sweep up spilled product carefully, avoiding the generation of airborne dusts.

All Spills: Decontaminate the area of the spill thoroughly using detergent and water. All contaminated material should be labeled as cytotoxic waste. Move to a secure area. Do not mix with wastes from other materials. If necessary, discard contaminated response equipment or rinse with soapy water before returning such equipment to service. Dispose of in accordance with applicable international, national, state, and local procedures (see Section 13, Disposal Considerations).

ENVIRONMENTAL PRECAUTIONS: Prevent material from entering sewer or confined spaces, waterways, soil or public waters. Do not flush to sewer. For spills on water, contain, minimize dispersion and collect.

7. HANDLING and USE

NOTE: Consistent with the OSHA Bloodborne Pathogen regulation (29 CFR 1910.1030), observe Universal Precautions while using this product. Place used or product-contaminated hypodermic needles and syringes in a rigid “Sharps” container. Do not recap or clip used or product-contaminated hypodermic needles. Dispose of materials in accordance with regulations.

PRECAUTIONS FOR SAFE HANDLING: THIS PRODUCT CONTAINS A CYTOTOXIC AGENT. ALL WORK PRACTICES MUST BE DESIGNED TO REDUCE HUMAN EXPOSURE TO THE LOWEST LEVEL. All employees who handle this product should be thoroughly trained to handle it safely. Special attention must be paid in avoiding releasing airborne particles of this product in areas in which this material is handled or used. As with all chemicals, avoid getting this material ON YOU or IN YOU. Do not eat or drink while handling this material. After handling this material, wash face and hands thoroughly prior to eating, drinking, smoking or applying cosmetics. Ensure this material is used with adequate ventilation. Appropriate personal protective equipment must be worn (see Section 8, Exposure Controls - Personal Protection). Areas in which this product is used should be wiped down, so that this product does not accumulate. Particular care in working with this product must be practiced during manufacture of this product, in pharmacies and other preparation areas, and during patient administration. Operations of high risk associated with the use of this product include:

- Filling, packaging and handling of vials
- Withdrawal of needles from drug vials;
- Drug transfers using syringes and needles or filter straws;
- Opening ampoules; and
- Expulsion of air from drug-filled syringes.

DO NOT CLIP OR CRUSH NEEDLE WITH WHICH THIS PRODUCT WAS IN CONTACT. Preparation and administration of this product should meet the following provisions:

- Work should be performed in a designated area for working with hazardous drugs;
- Containment devices, such as a Biological Safety Cabinet, should be used; contaminated waste must be properly handled; and
- Work areas must be regularly decontaminated.

Good hygiene practices must be in place for workers handling this material, including change facilities and a work place clothing program. Workers whose clothing may have become contaminated should change into uncontaminated clothing before leaving the work premises. Contaminated protective clothing should be segregated in such a manner so that there is no direct personal contact by personnel who handle, dispose, or clean the clothing. Contaminated clothing is required to be disposed of properly or remain in the work place for cleaning. No contaminated clothing should be taken from the employee's place of work.

PRODUCT PREPARATION INSTRUCTIONS FOR MEDICAL PERSONNEL: Handle this material following standard medical practices and following the recommendations presented on the Package Insert.

CONDITIONS FOR SAFE STORAGE: Containers of this product must be properly labeled. Store containers in a cool, dry location, away from direct sunlight and sources of intense heat. The sterile powder is stable under refrigeration: 20 to 25°C (68 to 77°F). Store away from incompatible materials (see Section 10, Stability and Reactivity). Material should be stored in secondary containers. Keep containers tightly closed when not in use. Inspect all incoming containers before storage, to ensure containers are properly labeled and not damaged. Refer to NFPA 654, *Prevention of Fire and Dust Explosions from the Manufacturing, Processing and Handling of Combustible Particulate Solids* for additional information on storage. Have appropriate extinguishing equipment in the storage area (e.g., sprinkler system, portable fire extinguishers). Empty containers may contain residual material; therefore, empty containers should be handled with care and disposed of properly.

SPECIFIC END USE(S): This product human pharmaceutical. Follow all industry standards for use of this product.

8. EXPOSURE CONTROLS - PERSONAL PROTECTION

EXPOSURE LIMITS/CONTROL PARAMETERS:

Ventilation and Engineering Controls: Use with adequate ventilation. Ensure eyewash stations and deluge showers are available and accessible in areas where this product is used. Wipe down work areas routinely to prevent accumulation of material. Follow standard medical product handling procedures. During decontamination of work surfaces, workers should wear the same equipment recommended in Section 6 (Accidental Release Measures) of this SDS.

Occupational/Workplace Exposure Limits/Guidelines:

CHEMICAL NAME	CAS #	EXPOSURE LIMITS IN AIR							
		ACGIH-TLVs		OSHA-PELs		NIOSH-RELs		NIOSH	OTHER
		TWA mg/m^3	STEL mg/m^3	TWA mg/m^3	STEL mg/m^3	TWA mg/m^3	STEL mg/m^3	IDLH mg/m^3	mg/m^3
Fludarabine Phosphate	75607-67-9	THIS IS A CYTOTOXIC AGENT. ALL WORK PRACTICES MUST BE DESIGNED TO REDUCE HUMAN EXPOSURE TO THE LOWEST LEVEL.							
Mannitol	69-65-8	NE	NE	NE	NE	NE	NE	NE	NE

NE = Not Established See Section 16 for Definitions of Other Terms Used

International Occupational Exposure Limits: No additional exposure limits have been established by various countries for the components of this product. Exposure limits can be added; individual country authorities should be contacted to check on more current limits.

PERSONAL PROTECTIVE EQUIPMENT: Use of personal protective equipment must be in compliance with U.S. OSHA 29 CFR Subpart I (beginning at 1910.132), Canadian CSA Standards Z94.4-02 and Z94.3-02, EU EN 529:2005, CEN/TR 15419:2006, and CR 13464:1999. Please reference applicable regulations and standards for relevant details.

Respiratory Protection: Maintain airborne contaminant concentrations below exposure limits listed above if applicable. If necessary, use only respiratory protection authorized under appropriate regulations. Oxygen levels below 19.5% are considered IDLH by U.S. OSHA. In such atmospheres, use of a full-facepiece pressure/demand SCBA or a full facepiece, supplied air respirator with auxiliary self-contained air supply is required under U.S. OSHA's Respiratory Protection Standard (1910.134-1998).

Eye Protection: No eye protection is normally needed during medical administration of this product. During operations in which dusts of the product may be generated, splash goggles or safety glasses should be considered.

Hand Protection: During medical administration of this product, medical latex or nitrile gloves should be worn to avoid absorption of the product. During manufacture or other similar industrial operations, wear the appropriate hand protection for the process. Use double gloves for spill response, as stated in Section 6 (Accidental Release Measures) of this SDS.

Body Protection: Use appropriate protective clothing for the task (e.g., lab coat, etc.). If necessary, refer to the U.S. OSHA Technical Manual (Section VII: Personal Protective Equipment) or other appropriate regulations.

9. PHYSICAL and CHEMICAL PROPERTIES

The following information is for the product.

FORM: Powdered solid.
COLOR: As described in Section 2.
ODOR: Odorless.
ODOR THRESHOLD: Not applicable.
HOW TO DETECT THIS SUBSTANCE (identification properties): The appearance of this product is a distinguishing characteristic.

The following information is for the Fludarabine Phosphate active ingredient.

FORM: Crystalline solid.
COLOR: White.
MOLECULAR FORMULA: $C_{10}H_{13}FN_5O_7P$
MOLECULAR WEIGHT: 365.2
ODOR: Odorless.
ODOR THRESHOLD: Not applicable.
DECOMPOSITION TEMPERATURE: > 199.8°C (> 392°F)
FLASH POINT: 476.4°C (889.6°F) [predict.]
BOILING POINT @ 760 mmHg: 864.2°C (1587.5°F) [predict.]
MELTING POINT: ~ 213-218°C (~ 415.4-424.4°F)
RELATIVE VAPOR DENSITY (air = 1): Not available.
EVAPORATION RATE (n-BuAc = 1): Not available.
SPECIFIC GRAVITY (water = 1): 2.394 g/cm^3 [predict.]
pH: Not available.
VAPOR PRESSURE @ 25°C: 0 mmHg [predict.]
SOLUBILITY IN WATER: Soluble.
OTHER SOLUBILITY: Not available.
COEFFICIENT OF OIL/WATER DISTRIBUTION (PARTITION COEFFICIENT): Log P: -3.366 [predict.]

10. STABILITY and REACTIVITY

CHEMICAL STABILITY: This product is not reactive.

DECOMPOSITION PRODUCTS: *Combustion:* If exposed to extremely high temperatures, the products of thermal decomposition may include irritating fumes and toxic gases (e.g. carbon, phosphorous and nitrogen oxides and hydrogen fluoride). *Hydrolysis:* None known.

MATERIALS WITH WHICH SUBSTANCE IS INCOMPATIBLE: This product is generally compatible with other common materials in a medical facility, may be incompatible with strong acids and bases.

POSSIBILITY HAZARDOUS REACTION/POLYMERIZATION: Will not occur.

CONDITIONS TO AVOID: Avoid heat, light, and contact with incompatible chemicals.

11. TOXICOLOGICAL INFORMATION

SYMPTOMS OF EXPOSURE BY ROUTE OF EXPOSURE: This product is a cytotoxic and anti-neoplastic agent that may cause significant health effects from workplace exposure. Although toxicity of this product is mainly by injection, as a cytotoxic product, all exposure must be minimized. The anticipated symptoms of exposure, by route of exposure are described further in this section.

Inhalation: If aerosols (from powder or solution) of this product are inhaled, irritation of the nose and upper respiratory system may occur. Symptoms of such exposure may include sneezing, coughing, and nasal congestion.

11. TOXICOLOGICAL INFORMATION (Continued)

SYMPTOMS OF EXPOSURE BY ROUTE OF EXPOSURE:

Contact with Skin or Eyes: It is anticipated that this product may irritate contaminated skin or eyes. Symptoms of skin contact may include itching and redness. Symptoms of eye contact can include redness, pain, and watering (mechanical irritation).

Skin Absorption: No data is available on potential absorption of this product through intact skin. Due to the cytotoxic active ingredient, a hazard of skin absorption may be present; all skin contact must be avoided.

Ingestion: Ingestion of this product is not anticipated to be a significant route of occupational exposure. Ingestion of this product (i.e., through poor hygiene practices) may irritate the mouth, throat, and other tissues of the gastrointestinal system. Other effects may occur as described under 'Other Potential Health Effects'.

Injection: Accidental injection of this product, by a contaminated needle or via laceration or puncture wound from a contaminated object may cause toxic effects. Local redness and pain are the primary symptoms in an occupational setting. Other symptoms are described under 'Other Potential Health Effects'.

OTHER POTENTIAL HEALTH EFFECTS-Therapeutic Doses: In therapeutic use this product can cause bone marrow suppression which can lead to serious infection or death. The most common non-hematologic adverse reactions were nausea, alopecia, vomiting, sepsis or pyrexia/infection with neutropenia, diarrhea, constipation, fatigue, and fever. Can cause fetal harm. Hypersensitivity reactions have been reported from therapeutic use. Suspected of carcinogenic and mutagenic effects, based on animal and microorganism test data. May cause harm to breast-fed babies. These effects may be possible as a result of workplace exposure. The actual risk in the workplace is not known. In therapeutic use the following additional adverse effects described by body system have included:

HAZARDOUS MATERIAL IDENTIFICATION SYSTEM

HEALTH HAZARD	(BLUE)	2*
FLAMMABILITY HAZARD	(RED)	1
PHYSICAL HAZARD	(YELLOW)	0

PROTECTIVE EQUIPMENT

EYES	RESPIRATORY	HANDS	BODY
	SEE SECTION 8		SEE SECTION 8

For Routine Industrial Use and Handling Applications

Hazard Scale: **0** = Minimal **1** = Slight **2** = Moderate **3** = Serious **4** = Severe * = Chronic hazard

- ***Blood System:*** Frequent: Bone marrow suppression, anemia, decrease in the number of white blood cells, abnormally low level of neutrophils in the blood, blood platelet decrease. Severe bleeding can occur in association with bone marrow suppression. Rare: Bone marrow fibrosis, trilineage bone marrow disorder characterized by a decline of red blood cells resulting in pancytopenia (reduction of red and white blood cells and platelets), sometimes resulting in death, have been reported.
- ***Body as a Whole:*** Fever, chills, lack or loss of strength and energy, weakness, infections.
- ***Cardiovascular System:*** Cardiovascular edema. Rarely: heart failure and arrhythmia.
- ***Digestive System:*** Nausea and vomiting, anorexia, diarrhea, mouth inflammation and gastrointestinal bleeding and hemorrhage, elevations of pancreatic enzyme levels.
- ***Eyes:*** Visual disturbances, optic nerve inflammation, optic neuropathy, blindness
- ***Genitourinary System:*** Rare cases of hemorrhagic cystitis have been reported.
- ***Infections:*** Serious and sometimes fatal infections, including opportunistic infections and reactivations of latent viral infections such as VZV (herpes zoster), Epstein-Barr virus and JC virus (progressive multifocal leukoencephalopathy) have been reported. Rare cases of Epstein Barr virus (EBV) associated lympho-proliferative disorders. Cases of progressive multifocal leukoencephalopathy have been reported. Most cases had a fatal outcome. Many of these cases were confounded by prior and/or concurrent chemotherapy.
- ***Hypersensitivity Reactions***: Anaphylactoid reactions. Pulmonary hypersensitivity characterized by difficulty breathing, cough and interstitial pulmonary infiltrate have been observed. Life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia, autoimmune Idiopathic Thrombocytopenic Purpura (ITP) (a bleeding disorder in which the immune system destroys platelets, which are necessary for normal blood clotting), Evans syndrome, and acquired hemophilia, cases of Myelodysplastic Syndrome (syndrome with poorly formed or dysfunctional blood cells) and acute myeloid leukemia, have been reported.
- ***Liver***: Elevations of hepatic enzyme levels.
- ***Metabolic System:*** Tumor lysis syndrome has been reported frequently. Complications from this may include abnormally high blood uric acid, phosphate and potassium levels, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperkalemia, hematuria, urate crystalluria, and renal failure. The onset of this syndrome may be heralded by flank pain and hematuria.
- **Neoplasms:** Worsening or flare up of pre-existing skin cancer lesions, as well as new onset of skin cancer.
- ***Nervous System:*** Objective weakness, agitation, confusion, seizures, peripheral neuropathy. Rarely wrist-drop and reports of cerebral hemorrhage.
- ***Reproductive System:*** Can cause harm to fetus during pregnancy based on animal data. May cause adverse fertility effects.
- ***Respiratory System:*** Frequent: Pneumonia, interstitial lung disease. Cases of severe pulmonary toxicity have been reported which resulted in ARDS (Adult Respiratory Distress Syndrome), respiratory distress, pulmonary hemorrhage, pulmonary fibrosis, pneumonitis and respiratory failure.
- ***Skin:*** Skin toxicity, skin rashes, eythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and pemphigus (rare group of blistering autoimmune diseases that affect the skin and mucous membranes)..

HEALTH EFFECTS OR RISKS FROM EXPOSURE: An Explanation in Lay Terms. Exposure to this product may cause the following health effects:

Acute: Accidental ingestion may be harmful. Eye contact with dusts may cause mechanical irritation. Inhalation of dusts from product may also cause effects described under 'Other Potential Health Effects'.

11. TOXICOLOGICAL INFORMATION (Continued)

HEALTH EFFECTS OR RISKS FROM EXPOSURE (continued):

Chronic: Can cause harm to fetus and adverse fertility effects, based on animal data. Repeated workplace exposure to the skin contact may cause dermatitis (dry, red skin). Chronic therapeutic use or workplace exposure may cause effects described under 'Other Potential Health Effects'.

TARGET ORGANS: It is anticipated that for Occupational Exposure the target organs are: **Acute:** Skin, eyes, respiratory system. **Chronic:** Possible fetal harm. In therapeutic use this product may have an impact on the body systems described under 'Other Potential Health Effects'.

IRRITANCY OF PRODUCT: This product is may cause mechanical eye irritation and may be irritating to the respiratory system. Prolonged skin contact may be irritating.

SENSITIZATION TO THE PRODUCT: In therapeutic use, this product has been reported to cause serious hypersensitivity reactions (by injection) including, anaphylactoid reactions, pulmonary hypersensitivity characterized by difficulty breathing, cough and interstitial pulmonary infiltrate have been observed. Life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia, autoimmune Idiopathic Thrombocytopenic Purpura (ITP) (a bleeding disorder in which the immune system destroys platelets, which are necessary for normal blood clotting), Evans syndrome, and acquired hemophilia, cases of Myelodysplastic Syndrome (syndrome with poorly formed or dysfunctional blood cells) and acute myeloid leukemia have also been reported.

TOXICITY DATA: Currently, the following toxicity data are available for the active ingredient. Data are available for excipients, but are not provided in this SDS. Contact Actavis for more information.

FLUDARABINE PHOSPHATE:

TDLo (Intravenous-Child) 18,750 mg/kg/5 days-intermittent: Brain and Coverings: encephalitis; Sense Organs and Special Senses (Eye): visual field changes

TDLo (Intravenous-Human) 4.380 mg/kg/168 days-intermittent: Blood: lymphoma, including Hodgkin's disease; Tumorigenic: protects against induction of experimental tumors, active as anti-cancer agent

TDLo (Intravenous-Man) 17,760 mg/kg/5 days-intermittent: Brain and Coverings: demyelination; Behavioral: hallucinations, distorted perceptions; Behavioral: coma

TDLo (Intravenous-Man) 11,655 mg/kg/5 days-intermittent: Sense Organs and Special Senses (Eye): visual field changes, ptosis; Behavioral: somnolence (general depressed activity)

TDLo (Intravenous-Woman) 14,245 mg/kg/5 days: Sense Organs and Special Senses (Eye): effect, not otherwise specified; Behavioral: excitement; Skin and Appendages: sweating

FLUDARABINE PHOSPHATE (continued):

TDLo (Intravenous-Woman) 23,125 mg/kg/5 days-intermittent: Brain and Coverings: encephalitis; Sense Organs and Special Senses (Eye): visual field changes; Behavioral: somnolence (general depressed activity)

LD_{50} (Intravenous-Mouse) 1236 mg/kg: Behavioral: somnolence (general depressed activity)

LD_{50} (Intravenous-Rat [male]) 910 mg/kg

LD_{50} (Intravenous-Rat [female]) 1050 mg/kg

LD_{50} (Intravenous-Mouse [male]) 1404 mg/kg

LD_{50}(Intravenous-Mouse [male]) 593 mg/kg/5 days

LD_{50} (Intravenous-Mouse [female]) 1235 mg/kg

LD_{50} (Intravenous-Mouse [male/female]) 1321 mg/kg

LD_{50} (Intravenous-Mouse [female]) 496 mg/kg/5 days

Cytogenetic Analysis (Human Lymphocyte) 1 mg/L/72 hours-continuous

CARCINOGENIC POTENTIAL OF COMPONENTS: The following information is available for the active ingredient.

No animal carcinogenicity studies with Fludarabine Phosphate have been conducted. However, positive findings in carcinogenicity studies with other cytotoxic medicines and the positive genotoxicity findings with Fludarabine Phosphate suggest that Fludarabine Phosphate has carcinogenic potential.

The remaining components of this product are not found on the following lists: U.S. EPA, U.S. NTP, U.S. OSHA, U.S. NIOSH, GERMAN MAK, IARC, or ACGIH and therefore are neither considered to be nor suspected to be cancer-causing agents by these agencies.

REPRODUCTIVE TOXICITY INFORMATION: There are no adequate and well-controlled studies of Fludarabine Phosphate in pregnant women; however, Fludarabine Phosphate can cause fetal harm when administered to a pregnant woman. In the workplace, the risk to the fetus should be communicated and the appropriate action should be taken to prevent exposure in accordance with company policy and regulatory requirements. This product is rated by the FDA for therapeutic risk as Pregnancy Risk Category D (There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks).

Mutagenicity: Fludarabine Phosphate has been shown not to cause gene mutations in bacterial and mammalian cells *in vitro*. Chromosomal aberrations were observed in an *in vitro* assay using Chinese hamster ovary (CHO) cells under metabolically activated conditions. Fludarabine phosphate has also been shown to be clastogenic in the *in vivo* mouse micronucleus test. In addition, Fludarabine Phosphate was shown to cause increased sister chromatid exchanges using an *in vitro* sister chromatid exchange (SCE) assay under both metabolically activated and non-activated conditions.

Embryotoxicity/Teratogenicity: Fludarabine Phosphate was embryo-lethal in both rats and rabbits. In rats, repeated intravenous doses of Fludarabine Phosphate at 1.5 times and 4.5 times the recommended human oral dose (40 mg/m^2) administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations (cleft palate, exencephaly, and fetal vertebrae deformities) and decreased fetal body weights. Maternal toxicity was not apparent at 1.5 times the human oral dose, and was limited to slight body weight decreases at 4.5 times the human oral dose. In rabbits, repeated intravenous doses of Fludarabine Phosphate at 2.4 times the human oral dose administered during organogenesis increased embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. Fludarabine Phosphate was teratogenic in both rats and rabbits. A significant increase in malformations including cleft palate, hydrocephaly, adactyly, brachydactyly, fusions of the digits, diaphragmatic hernia, heart/great vessel defects, and vertebrae/rib anomalies were seen in all dose levels (≥ 0.3 times the human oral dose).

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. It is not known whether Fludarabine Phosphate is excreted in human milk. Many drugs can be present in breast milk, causing adverse effects to breast-fed babies. This drug should not be used by pregnant or nursing women.

11. TOXICOLOGICAL INFORMATION (Continued)

ACGIH BIOLOGICAL EXPOSURE INDICES (BEIs): Currently, ACGIH Biological Exposure Indices (BEIs) have not been determined for the components of this product.

12. ECOLOGICAL INFORMATION

ALL WORK PRACTICES MUST BE AIMED AT ELIMINATING ENVIRONMENTAL CONTAMINATION.

MOBILITY: This product has not been tested for mobility in soil.

PERSISTENCE AND BIODEGRADABILITY: This product has not been tested for persistence or biodegradability.

BIO-ACCUMULATION POTENTIAL: This product has not been tested for bio-accumulation potential.

ECOTOXICITY: This product may be harmful to aquatic and terrestrial organisms; all releases to terrestrial, atmospheric and aquatic environments should be avoided. No aquatic toxicity data are available for the active ingredient.

OTHER ADVERSE EFFECTS: This product does not contain any component with known ozone depletion potential.

RESULTS OF PBT AND vPvB ASSESSMENT: No Data Available. PBT and vPvB assessments are part of the chemical safety report required for some substances in European Union Regulation (EC) 1907/2006, Article 14.

ENVIRONMENTAL EXPOSURE CONTROLS: Controls should be engineered to prevent release to the environment, including procedures to prevent spills, atmospheric release and release to waterways.

13. DISPOSAL CONSIDERATIONS

WASTE TREATMENT/DISPOSAL METHODS: Waste disposal must be in accordance with appropriate Federal, State, and local regulations.

PRECAUTIONS TO BE FOLLOWED DURING WASTE HANDLING: Wear proper protective equipment when handling waste materials.

U.S. EPA WASTE NUMBER: Not applicable to wastes consisting only of this product.

PRECAUTIONS TO BE FOLLOWED DURING WASTE HANDLING: Wear proper protective equipment when handling waste materials.

EWC WASTE CODE: Wastes from natal care, diagnosis, treatment, or prevention of disease in humans: cytotoxic and cytostatic medicines, 18-01-08.

14. TRANSPORTATION INFORMATION

U.S. DEPARTMENT OF TRANSPORTATION REGULATIONS: This product is not classified as dangerous goods, per U.S. DOT regulations, under 49 CFR 172.101.

TRANSPORT CANADA, TRANSPORTATION OF DANGEROUS GOODS REGULATIONS: This product is not classified as Dangerous Goods, per regulations of Transport Canada.

INTERNATIONAL AIR TRANSPORT ASSOCIATION (IATA): This product is not classified as Dangerous Goods, by rules of IATA.

INTERNATIONAL MARITIME ORGANIZATION (IMO) DESIGNATION: This product is not classified as Dangerous Goods by the International Maritime Organization.

EUROPEAN AGREEMENT CONCERNING THE INTERNATIONAL CARRIAGE OF DANGEROUS GOODS BY ROAD (ADR): This product is not classified by the United Nations Economic Commission for Europe to be dangerous goods.

TRANSPORT IN BULK ACCORDING TO THE IBC CODE: Not applicable.

ENVIRONMENTAL HAZARDS: This product does not meet the criteria of environmentally hazardous according to the criteria of the UN Model Regulations (as reflected in the IMDG Code, ADR, RID, and ADN) and no component is specifically listed in Annex III under MARPOL 73/78.

15. REGULATORY INFORMATION

UNITED STATES 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 III of the Superfund Amendments and Reauthorization Act.

U.S. SARA Threshold Planning Quantity (TPQ): There are no specific Threshold Planning Quantities for any component of this product. The default Federal SDS submission and inventory requirement filing threshold of 10,000 lb (4,540 kg) therefore applies, per 40 CFR 370.20.

U.S. CERCLA Reportable Quantities (RQ): Not applicable.

U.S. TSCA Inventory Status: This product is regulated under Food and Drug Administration standards; it is not subject to requirements under TSCA.

Other U.S. Federal Regulations: Regulations of the FDA under the Federal Food, Drug and Cosmetic Act are applicable when this material is used in pharmaceutical preparations. Under the Hazard Communication Standard (HCS), Section (b)(5)(ii) drugs are subject to labeling requirements by the FDA under the Federal Food, Drug and Cosmetic Act and are exempt from labeling provisions of the HCS; this section of the HCS exempts only labeling requirements and not requirements for a Safety Data Sheet for drugs.

California Safe Drinking Water and Toxic Enforcement Act (Proposition 65): No component of this product is on the California Proposition 65 Lists.

CANADIAN REGULATIONS:

Canadian DSL Inventory Status: This product regulated by the Therapeutic Products Programme (TPP) of Health Canada and so it excepted from requirements of the DSL/NDSL Inventory.

15. REGULATORY INFORMATION (Continued)

CANADIAN REGULATIONS (continued):

Canadian Environmental Protection Act (CEPA) Priorities Substances Lists: The components of this product are not on the CEPA Priorities Substances Lists.

Canadian WHMIS Classification and Symbol: The WHMIS Requirements of the Hazardous Products Act does not apply in respect of the advertising, sale or importation of any cosmetic, device, drug or food within the meaning of the Food and Drugs Act.

EUROPEAN REGULATIONS:

Safety, Health, and Environmental Regulations/Legislation Specific for the Product: When formulated in a finished medicinal product for human use, this material is subject to Directive 2001/83/EC and subsequent amendments to the directive.

Chemical Safety Assessment: No Data Available. The chemical safety assessment is required for some substances according to European Union Regulation (EC) 1907/2006, Article 14.

16. OTHER INFORMATION

ANSI LABELING (Based on 129.1, Provided to Summarize Occupational Exposure Hazards): DANGER! CONTAINS CYTOTOXIC AGENT. ALL EXPOSURE MUST BE MINIMIZED. ACCIDENTAL INJECTION CAN BE FATAL. MAY BE HARMFUL IF SWALLOWED, OR IF INHALED. MAY CAUSE HARM DURING PREGNANCY. MAY CAUSE MUTAGENIC EFFECTS. CAN CAUSE SEVERE ADVERSE EFFECTS ON NEUROLOGICAL, NERVOUS, IMMUNE AND BLOOD FORMING SYSTEMS. CAN CAUSE SERIOUS, LIFE-THREATENING HYPERSENSITITY REACTIONS BY INJECTION. COMBUSTIBLE IF EXPOSED TO HIGH TEMPERATURES. Do not taste or swallow. Avoid contact with skin, eyes, and clothing. Keep container closed. Use gloves, safety glasses, and appropriate respiratory and body protection. **FIRST-AID:** If exposed, seek immediate medical attention. If swallowed, do not induce vomiting. If alert, give victim up to three glasses of water. Never give anything by mouth to an unconscious person. In case of contact, immediately flush skin with copious amounts of warm water for 20 minutes. Remove contaminated clothing and shoes. If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. **IN CASE OF FIRE:** Use water fog, dry chemical or CO_2, or alcohol foam. **IN CASE OF SPILL:** Refer to Safety Data Sheet for complete spill response procedures. Spill response should be performed by persons properly trained to do so. Decontaminate area with bleach and detergent solution and triple rinse area. Place spill debris in a suitable container. Refer to SDS for additional information.

SPECIAL HANDLING AND DISPOSAL REQUIRED

GLOBAL HARMONIZATION AND EU CLP REGULATION (EC) 1272/2008 LABELING AND CLASSIFICATION: According to Article 1, item 5 (a) of CLP Regulation (EC) 1272/2008, medicinal products in the finished state for human use, as defined in 2001/83/EC, are excepted from classification and other criteria of 1272/2008.

EU LABELING AND CLASSIFICATION 67/548/EEC: According to Article 1 of European Union Council Directive 92/32/EEC, medical products in the finished state for human use (as defined by European Union Council Directives 67/548/EEC and 87/21/EEC) are not subject to the regulations and administrative provisions of European Union Council Directive 92/32/EEC.

CLASSIFICATION FOR COMPONENTS:

CLP Regulation (EC) 1272/2008:

Fludarabine Phosphate: This is a self-classification.

Classification: Reproductive Toxicity Category 1B, Germ Cell Mutagenicity Category 1B, Carcinogenic Category 2, Adverse Effects on or Via Lactation, Specific Target Organ Toxicity (Injection-Neurological, Immune, Central Nervous and Blood Forming Systems) Repeated Exposure Category 2

Hazard Statement Codes: H360Df: May damage the unborn child. Suspected of damaging fertility. H340: May cause genetic effects. H351: Suspected of causing cancer. H362: May cause harm to breast-fed children. H372: Causes damages to organs (neurological, central nervous, peripheral nervous, immune, bone marrow and, reproductive systems) through prolonged or repeated exposure by injection.

All Other Components: No classification has been published or is applicable.

Full Text EU 67/548/EEC:

Fludarabine Phosphate: This is a self-classification.

Classification: Reproductive Toxicity Category 2, Mutagenic Category 2, Carcinogenic Category 3, Harmful

Risk Phrases: R61: May cause harm to the unborn child. R62: Possible risk of impaired fertility. R46: May cause heritable genetic damage. R40: Limited evidence of a carcinogenic effect. R48/20/22: Harmful: danger of serious damage to health by prolonged exposure through inhalation and if swallowed. R64: May cause harm to breast-fed babies.

All Other Components: No classification has been published or is applicable.

REFERENCES AND DATA SOURCES: Contact the supplier for information.

METHODS OF EVALUATING INFORMATION FOR THE PURPOSE OF CLASSIFICATION: Bridging principles were used to classify this product.

REVISION DETAILS: New.

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