

# SAFETY DATA SHEET

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## SECTION 1 - IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/ UNDERTAKING

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### Contact information

#### General



Leucadia Pharmaceuticals, Inc.  
2325 Camino Vida Roble, Suite A  
Carlsbad, CA 92011  
Main: +1 (844) 538-2231 (Mon-Fri 8:00 AM - 6:00 PM Central)  
Email: info.sds@leucadiapharma.com

#### Emergency telephone number

Chemtrec (24-hour availability):  
+1 (800) 424-9300 (USA and Canada)  
+1 (703) 527-3887 (International; collect calls accepted)

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<b>Product identifier</b>	Fludarabine Phosphate for Injection, USP
<b>Synonyms</b>	9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono- $\beta$ -D-arabinofuranosyl)
<b>Trade names</b>	None identified
<b>Chemical family</b>	Purine Nucleoside
<b>Relevant identified uses of the substance or mixture and uses advised against</b>	Bulk pharmaceutical product; indicated for the treatment of cancer.
<b>Note</b>	This SDS is written to address potential worker health and safety issues associated with the handling of the bulk pharmaceutical product.

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## SECTION 2 - HAZARDS IDENTIFICATION

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<b>Classification of the substance or mixture</b>	<b>Drugs in the finished state and intended for the final user are not subject to labeling in the US, EU or Canada.</b> Consult prescribing/packaging information. <b>The classification and labeling listed below is for bulk drug product.</b>
<b>Globally Harmonized System [GHS]</b>	Reproductive Toxicity - Category 1B. Carcinogenic - Category 2.
<b>Label elements</b>	

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**SECTION 2 - HAZARDS IDENTIFICATION** ...continued

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**GHS hazard pictogram**



**GHS signal word**

Danger

**GHS hazard statements**

H360D - May damage the unborn child. H351 - Suspected of causing cancer.

**GHS precautionary statements**

P201 - Obtain special instructions before use. P281 - Use personal protective equipment as required. P308 + P313 - IF exposed or concerned: get medical advice/attention. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.

**Other hazards**

Fludarabine phosphate is a prodrug indicated for the treatment of chronic lymphocytic leukemia (CLL). Although the mechanism is not fully understood, the active metabolite appears to inhibit DNA synthesis. The most commonly reported adverse effects include myelosuppression (low red or white blood cell counts) leading to decreased resistance to infection, cough, fever, fatigue, weakness, and gastrointestinal upset (nausea, vomiting, diarrhea). Other commonly reported adverse effects include chills, edema, malaise, peripheral neuropathy (tingling, numbness, or pain in the extremities), visual disturbance, anorexia, mucositis (GI tract inflammation/ulceration), stomatitis (sore and inflamed mouth), and skin rash. Serious opportunistic infections have been reported.

**Note**

This mixture is classified as hazardous under GHS as implemented by Regulation EC No 1272/2008 (EU CLP), WHMIS 2015 (Health Canada), and Hazard Communication Standard No. 1910.1200 (US OSHA).

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**SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS**

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<u>Ingredient</u>	<u>CAS #</u>	<u>EINECS/ ELINCS#</u>	<u>Amount</u>	<u>GHS Classification</u>
Fludarabine phosphate	75607-67-9	244-525-5 (fludarabine)	1-5%	RT1B: H360D; STOT-R2: H373; Carc2: H351
Mannitol	69-65-8	200-711-8	1-5%	Not classified

**Note**

The ingredient(s) listed above are considered dangerous/hazardous. The remaining components are non-hazardous and/or present at amounts below reportable limits. Amounts are listed as ranges; the exact percentage of composition is withheld as a trade secret. See Section 16 for full text of GHS classifications.

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## SECTION 4 - FIRST AID MEASURES

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### Description of first aid measures

#### Immediate Medical Attention Needed

Yes

#### Eye Contact

If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.

#### Skin Contact

Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.

#### Inhalation

Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.

#### Ingestion

Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.

#### Protection of first aid responders

See Section 8 for Exposure Controls/Personal Protection recommendations.

#### Most important symptoms and effects, both acute and delayed

See Sections 2 and 11.

#### Indication of immediate medical attention and special treatment needed, if necessary

Medical conditions aggravated by exposure: None known or reported. Treat symptomatically and supportively.

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## SECTION 5 - FIREFIGHTING MEASURES

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#### Extinguishing media

Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.

#### Specific hazards arising from the substance or mixture

No information identified. May emit carbon monoxide, carbon dioxide, oxides of nitrogen, hydrochloric acid and other fluorine and/or phosphorous-containing compounds.

#### Flammability/Explosivity

No explosivity or flammability data identified. High concentrations of finely divided airborne organic particles can potentially explode if ignited.

#### Advice for firefighters

Wear full protective clothing and a self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode. Decontaminate all equipment after use.

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## SECTION 6 - ACCIDENTAL RELEASE MEASURES

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<b>Personal precautions, protective equipment and emergency procedures</b>	Take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe dust.
<b>Environmental precautions</b>	Do not empty into drains. Avoid release to the environment.
<b>Methods and material for containment and cleaning up</b>	DO NOT RAISE DUST. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize entry of powder into the air. Add excess liquid to allow the material to enter into solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container for disposal in accordance with applicable waste disposal regulations (see section 13). Decontaminate the area twice.
<b>Reference to other sections</b>	See Sections 8 and 13 for more information.

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## SECTION 7 - HANDLING AND STORAGE

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<b>Precautions for safe handling</b>	Follow recommendations for handling bulk formulated products (i.e., use of engineering controls and/or other personal protective equipment if needed). Wash thoroughly after handling. Avoid breathing dust.
<b>Conditions for safe storage including any incompatibilities</b>	Store under refrigeration, between 2°C and 8°C (34°F to 46°F) away from incompatible materials. Avoid extreme temperatures. Keep container upright and tightly closed. Store locked up.
<b>Specific end use(s)</b>	No information identified.

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## SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

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<b>Note</b>	Wash hands, face and other potentially exposed areas immediately in the event of physical contact.
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### **Control Parameters/ Occupational Exposure Limit Values**

<u>Compound</u>	<u>Issuer</u>	<u>Type</u>	<u>OEL</u>
Fludarabine phosphate	--	--	--
Mannitol	--	--	--

<b>Exposure/Engineering controls</b>	Selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Use local exhaust and/or enclosure at dust-generating points. Emphasis is to be placed on closed material transfer systems and process containment, with limited open handling of powders. High-energy operations such as milling, particle sizing, spraying or fluidizing should be done within an approved emission control or containment system.
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**SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION ...continued**

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<b>Respiratory protection</b>	Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine powder handling tasks, an approved and properly fitted air-purifying respirator with HEPA filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use a powered air-purifying respirator equipped with HEPA filters or combination filters or a positive-pressure air-supplied respirator if there is any potential for an uncontrolled release, when exposure levels are not known, or in any other circumstances where a lower level of respiratory protection may not provide adequate protection.
<b>Hand protection</b>	Wear nitrile or other impervious gloves if skin contact is possible. When the material is dissolved or suspended in an organic solvent, wear gloves that provide protection against the solvent.
<b>Skin protection</b>	Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.
<b>Eye/face protection</b>	Wear safety glasses with side shields, chemical splash goggles, or full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available.
<b>Environmental Exposure Controls</b>	Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel.
<b>Other protective measures</b>	Wash hands in the event of contact with this mixture, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors).

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**SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES**

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**Information on basic physical and chemical properties**

<b>Appearance</b>	Lyophilized solid powder/cake
<b>Color</b>	White
<b>Odor</b>	Odorless
<b>Odor threshold</b>	No information identified.
<b>pH</b>	7.2-8.2
<b>Melting point/ freezing point</b>	No information identified.

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**SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ...continued**

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<b>Initial boiling point and boiling range</b>	Not applicable.
<b>Flash point</b>	No information identified.
<b>Evaporation rate</b>	Not applicable.
<b>Flammability (solid, gas)</b>	No information identified.
<b>Upper/lower flammability or explosive limits</b>	No information identified.
<b>Vapor pressure</b>	Not applicable.
<b>Vapor density</b>	Not applicable.
<b>Relative density</b>	No information identified.
<b>Water solubility</b>	Soluble
<b>Solvent solubility</b>	No information identified.
<b>Partition coefficient (<i>n</i>-octanol/water)</b>	No information identified.
<b>Auto-ignition temperature</b>	No information identified.
<b>Decomposition temperature</b>	No information identified.
<b>Viscosity</b>	No information identified.
<b>Explosive properties</b>	No information identified.
<b>Oxidizing properties</b>	No information identified.
<b>Other information</b>	
<b>Molecular formula</b>	Not applicable (Mixture)
<b>Molecular weight</b>	Not applicable (Mixture)

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**SECTION 10 - STABILITY AND REACTIVITY**

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<b>Reactivity</b>	Stable under recommended storage conditions.
<b>Chemical stability</b>	Stable under recommended storage conditions.
<b>Possibility of hazardous reactions</b>	Hazardous polymerization will not occur.
<b>Conditions to avoid</b>	Avoid excessive heat.

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**SECTION 10 - STABILITY AND REACTIVITY ...continued**

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**Incompatible materials** No information identified.  
**Hazardous decomposition products** Not available.

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**SECTION 11 - TOXICOLOGICAL INFORMATION**

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**Note** As limited data for the mixture were identified, the data below describes the ingredient(s).

**Information on toxicological effects**

**Route of entry** May be absorbed by inhalation, skin contact and ingestion.

**Acute toxicity**

<u>Compound</u>	<u>Type</u>	<u>Route</u>	<u>Species</u>	<u>Dose</u>
Fludarabine phosphate	LD <sub>50</sub>	Intravenous (IV)	Mouse	1321 mg/kg
	LD <sub>50</sub>	IV	Male Rat	910 mg/kg
Mannitol	LD <sub>50</sub>	Oral	Rat	13.5 g/kg
	LD <sub>50</sub>	Oral	Mice	14 g/kg

**Irritation/Corrosion** No studies identified.

**Sensitization** No studies identified.

**STOT-single exposure** In mice and dogs, dose-dependent effects were observed in the hematopoietic, gastrointestinal, renal, and hepatic systems at  $\geq 490$  and  $\geq 13.1$  mg/kg/day fludarabine phosphate, respectively. Effects in the male reproductive system were also observed in male mice at this dose. In rats, dose dependent effects were observed in the lymph nodes, thymus, heart, lungs, and stomach at  $\geq 800$  mg/kg fludarabine phosphate.

**STOT-repeated exposure/Repeat-dose toxicity** In a 13-week study in rats, IV doses of fludarabine phosphate  $\geq 50$  mg/kg/day resulted in decreased red blood cell and clinical chemistry parameters, and microscopic abnormalities in the male reproductive organs, adrenal, kidney, liver, and spleen. The NOAEL was 10 mg/kg/day.

In a 13-week study in dogs, IV doses of fludarabine phosphate  $\geq 50$  mg/kg/day caused decreases in red and white blood cell parameters, lymphoid depletion of the thymus, and inflammation of the stomach. The NOAEL was considered 10 mg/kg/day for female dogs and 1 mg/kg/day for male dogs.

**Reproductive toxicity** No definitive studies were identified. In the repeat-dose rat study described above, microscopic abnormalities were observed in the male reproductive organs at IV doses of 50 mg/kg/day; the NOAEL was 10 mg/kg/day.

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**SECTION 11 - TOXICOLOGICAL INFORMATION ...continued**

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<b>Developmental toxicity</b>	In pregnant rats, IV doses of fludarabine phosphate $\geq 10$ mg/kg/day resulted in fetuses with increased incidence of skeletal variation. Maternal toxicity was observed at $\geq 30$ mg/kg/day. Doses of 40 mg/kg/day (the highest dose tested) caused decreased offspring viability and delayed skeletal maturation. The NOAEL was 1 mg/kg/day. In pregnant rabbits, postimplantation loss, external and skeletal malformations in the head, limbs, digits, and tail were observed at 8 mg/kg/day in the presence of maternal toxicity. The NOAEL for maternal toxicity was 1 mg/kg/day, but equivocal for fetal toxicity.
<b>Genotoxicity</b>	Fludarabine was positive in a sister chromatid exchange assay, and a chromosome aberration assay, but was negative in an Ames assay and a Chinese hamster ovary HGPRT cell assay. It was positive in an <i>in vivo</i> mouse micronucleus test but was negative in an <i>in vivo</i> mouse dominant lethal test. Overall, the data suggest it may cause chromosome breaks, but is unlikely to be mutagenic to germ cells.
<b>Carcinogenicity</b>	Not conducted. None of the components of the product present at levels greater than or equal to 0.1% are listed by ACGIH or OSHA as a carcinogen.
<b>Aspiration hazard</b>	No studies identified
<b>Human health data</b>	See "Section 2 - Other Hazards"
<b>Additional information</b>	The toxicological properties of this mixture have not been fully characterized.

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**SECTION 12 - ECOLOGICAL INFORMATION**

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**Toxicity**

<u>Compound</u>	<u>Type</u>	<u>Species</u>	<u>Concentration</u>
Fludarabine phosphate	--	--	--
Mannitol	--	--	--

<b>Persistence and Degradability</b>	No data available.
<b>Bioaccumulative potential</b>	No data available.
<b>Mobility in soil</b>	No data available.
<b>Results of PBT and vPvB assessment</b>	Not performed.
<b>Other adverse effects</b>	No data available.
<b>Note</b>	Ecological characteristics of this mixture were not available. Releases to the environment should be avoided.



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## SECTION 13 - DISPOSAL CONSIDERATIONS

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<b>Waste treatment methods</b>	Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Do not send down the drain or flush down the toilet. All wastes containing the material should be properly labeled. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.
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## SECTION 14 - TRANSPORT INFORMATION

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<b>Transport</b>	Based on the available data, this mixture is not regulated as a hazardous material/dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG.
<b>UN number</b>	None assigned.
<b>UN proper shipping name</b>	None assigned.
<b>Transport hazard classes and packing group</b>	None assigned.
<b>Environmental hazards</b>	This mixture is not regulated as an environmental hazard or a marine pollutant.
<b>Special precautions for users</b>	Due to lack of data, avoid release to the environment.
<b>Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code</b>	Not applicable.

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## SECTION 15 - REGULATORY INFORMATION

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<b>Safety, health and environmental regulations/legislation specific for the substance or mixture</b>	This SDS generally complies with the requirements listed under current guidelines in the US, EU and Canada. Consult your local or regional authorities for more information.
<b>Chemical safety assessment</b>	Not conducted.
<b>TSCA status</b>	Drugs are exempt from TSCA.
<b>SARA section 313</b>	Not listed.
<b>California proposition 65</b>	Not listed.
<b>Additional information</b>	No other information identified.

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## SECTION 16 - OTHER INFORMATION

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**Full text of H phrases and GHS classifications**

RT1B - Reproductive toxicity Category 1B. H360D - May damage the unborn child. H373 - May cause damage to bone marrow, gastrointestinal system, and/or central nervous system through prolonged or repeated exposure. STOT-R2 - Specific Target Organ Toxicity Following Repeated Exposure Category 2. Carc2 - Carcinogenicity Category 2. H351 - Suspected of causing cancer.

**Sources of data**

Information from published literature and internal company data.

**Abbreviations**

ACGIH - American Conference of Governmental Industrial Hygienists; ADR/RID - European Agreement Concerning the International Carriage of Dangerous Goods by Road/Rail; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number; CLP - Classification, Labelling, and Packaging of Substances and Mixtures; DNEL - Derived No Effect Level; DOT - Department of Transportation; EINECS - European Inventory of New and Existing Chemical Substances; ELINCS - European List of Notified Chemical Substances; EU - European Union; GHS - Globally Harmonized System of Classification and Labeling of Chemicals; IARC - International Agency for Research on Cancer; IDLH - Immediately Dangerous to Life or Health; IATA - International Air Transport Association; IMDG - International Maritime Dangerous Goods; LOEL - Lowest Observed Effect Level; LOAEL - Lowest Observed Adverse Effect Level; NIOSH - The National Institute for Occupational Safety and Health; NOEL - No Observed Effect Level; NOAEL - No Observed Adverse Effect Level; NTP - National Toxicology Program; OEL - Occupational Exposure Limit; OSHA - Occupational Safety and Health Administration; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; STOT - Specific Target Organ Toxicity; STEL - Short Term Exposure Limit; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System

**Issue Date**

13 November 2017

**Revisions**

This is the first version of this SDS.

**Disclaimer**

The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions.

No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a pharmaceutical product. The above information is offered in good faith and with the belief that it is accurate. As of the date of issuance, we are providing all information relevant to

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**SECTION 16 - OTHER INFORMATION ...continued**

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**Disclaimer ...continued**

the foreseeable handling of the material. However, in the event of an adverse incident associated with this product, this Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.