SAFETY DATA SHEET

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

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Product identifier	Pralatrexate
Synonyms	*N*-{4-[1-(2,4-diaminopteridin-6-yl)pent-4-yn-2-yl]benzoyl}-*L*-glutamic acid, (2*S*)-2-[[4-[(1*RS*)-1-[(2,4-diaminopteridin-6-yl)methyl]but-3-ynyl]benzoyl] amino]pentanedioic acid, (*RS*)-10-propargyl-10-deazaaminopterin, PDX
Trade names	FOLOTYN® (formulated pralatrexate)
Chemical family	Folic acid analog
Relevant identified uses of the substance or mixture and uses advised against	Active pharmaceutical ingredient; indicated for the treatment of relapsed or refractory peripheral T-cell lymphoma
Note	The ecological properties of this substance have not been fully characterized. This data sheet will be updated as more data become available.
Issue Date	30 July 2010

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture

Regulation (EC) 1272/ 2008 [GHS]	Reproductive Toxicity - Category 1A. Germ Cell Mutagenicity - Category 2.. Acute toxicity - oral - Category 4. Specific Target Organ Toxicity (repeated exposure) - Category 1.
Directive 67/548/EEC or 1999/45/EC	T - R60 (Repro. Cat. 1), R61 (Repro. Cat. 1), R48/23/25, R68 (Muta. Cat. 3), R22

Label elements

CLP/GHS hazard pictogram

CLP/GHS signal word

Danger

CLP/GHS hazard statements

H302 - Harmful if swallowed. H341 - Suspected of causing genetic defects. H360FD - May damage fertility. May damage the unborn child. H372 - Causes damage to hematological system, gastrointestinal system, liver and bone marrow through prolonged or repeated exposure.

CLP/GHS precautionary statements

P201 - Obtain special instructions before use. P202 - Do not handle until all safety precautions have been read and understood. P260 - Do not breathe dust. P264 - Wash hands thoroughly after handling. P270 - Do not eat, drink or smoke when using this product. P281 - Use personal protective equipment as required. P308 + P313 - If exposed or concerned: get medical advice/attention. P301+P312: IF SWALLOWED: Call a Poison Center or doctor/physician if you feel unwell. P314 - Get medical advice/attention if you feel unwell. P330 - Rinse mouth. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.

EU symbol/indication of danger

T- Toxic.

Risk (R) Phrase(s)

R60 - May impair fertility. R61 - May cause harm to the unborn child. R68 - Possible risk of irreversible effects. R48/23/25 - Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed. R22 - Harmful if swallowed.

Safety Advice

S22 - Do not breathe dust. S36/37 - Wear suitable protective clothing and gloves. S53 - Avoid exposure - Obtain special instructions before use.

Other hazards

Pralatrexate is a cytotoxic anticancer agent. The most commonly occurring adverse effects with therapeutic use of pralatrexate include mucositis, thrombocytopenia, nausea and fatigue. Other adverse effects may include bone marrow suppression, hematological toxicity, gastrointestinal toxicity and liver toxicity. Reproductive, developmental and genotoxic effects have been observed in humans exposed to the mechanistically and structurally related compound, methotrexate.

US Signal word

Caution

SECTION 2 - HAZARDS IDENTIFICATION …continued

US Hazard overview

Cytotoxic drug. May adversely affect the developing fetus and/or cause adverse reproductive effects. May cause birth defects. May cause hematological system, gastrointestinal system, liver and bone marrow damage. May be genotoxic. May be harmful if swallowed.

Note

This substance is classified as dangerous/hazardous according to Directive 67/548/EEC, Regulation EC No 1272/2008 (EU CLP), and applicable US regulations. The EU symbol/indicator of danger, R Phrases and Safety Advice are based on Directive 67/548/EEC or 1999/45/EC. See Section 16 for full text of EU and GHS classifications.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	EU Classification	GHS Classification
Pralatrexate	146464-95-1	N/A	~100%	Toxic - T; R60, R61, R48/23/25, R68, R22	RT1A: H360FD; STOT-R1: H372; GCM2: H341; ATO4: H302

Note

The ingredient(s) listed above are considered dangerous/hazardous. The remaining components are non-dangerous/not hazardous and/or present at amounts below reportable limits. See Section 16 for full text of EU and GHS classifications. The EU classification is based on Directive 67/548/EEC and the GHS classification is based on Regulation (EC) 1272/2008.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures

Immediate Medical Attention Needed

Yes - delayed effects may occur.

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.

SECTION 4 - FIRST AID MEASURES …continued

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	Contains a folic acid analog. Calcium leucovorin is a potent agent for neutralizing the toxic effects of methotrexate on the hematopoietic system and may therefore also neutralize the effects of pralatrexate. Treat symptomatically and supportively. If accidental exposure occurs to an individual who is also taking one or more concomitant medications, consult the respective package or prescribing information for potential drug interactions.

SECTION 5 - FIREFIGHTING MEASURES

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 toxic fumes of carbon monoxide, carbon dioxide, and oxides of nitrogen.
Flammability/ Explosivity	Not considered to be a fire hazard. No explosivity data available. 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.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe dust.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	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 solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container suitable for disposal in accordance with applicable waste disposal regulations (see Section 13). Decontaminate the area twice.

SECTION 6 - ACCIDENTAL RELEASE MEASURES …continued

Reference to other sections See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling Follow recommendations for handling potent cytotoxic pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Avoid breathing dust. Wash thoroughly after handling.

Conditions for safe storage including any incompatibilities Store in a refrigerator between 2-8°C away from incompatible materials. Avoid extreme temperatures. Keep out of reach of children. Protect from light and heat. Store locked up.

Specific end use(s) No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Pralatrexate	Allos	TWA-8 HR	0.4 µg/m

DNELs/PNECs None identified.

Exposure/Engineering controls Control exposures to below the OEL (if available). Otherwise, selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Open handling should not be performed when handling potent substances, or substances of unknown toxicity. Material should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for dusts and/or aerosols.

Respiratory protection 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 worn powered air-purifying respirator equipped with HEPA filters or combination filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use 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 air purifying respirators may not provide adequate protection.

Hand protection Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered. When the material is dissolved or suspended in an organic solvent, wear gloves that provide protection against the solvent.

Skin protection 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.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION …continued

Eye/face protection	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.
Environmental Exposure Controls	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.
Other protective measures	Wash hands in the event of contact with this substance, 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).

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Solid
Color	Off-white to yellow
Odor	No information identified.
Odor threshold	No information identified.
pH	No information identified.
Melting point/ freezing point	216-220°C
Initial boiling point and boiling range	No information identified.
Flash point	No information identified.
Evaporation rate	No information identified.
Flammability (solid, gas)	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Vapor pressure	No information identified.
Vapor density	No information identified.
Relative density	No information identified.
Water solubility	Insoluble unless pH is adjusted to 7.5-8.5

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Solvent solubility	Practically insoluble in chloroform and ethanol; >0.3 mg/mL in 0.1N sodium hydroxide and 0.1N hydrochloric acid
Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.

Other information

Molecular weight	477.5
Molecular formula	$C_{23}H_{23}N_7O_5$

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	Chemically stable; pharmacological stability not guaranteed beyond expiration date imprinted on package.
Possibility of hazardous reactions	Not expected to occur.
Conditions to avoid	Avoid exposure to light. Avoid extreme temperatures.
Incompatible materials	Strong oxidizers
Hazardous decomposition products	Products of decomposition may include nitrogen oxides, carbon monoxide and carbon dioxide.

SECTION 11 - TOXICOLOGICAL INFORMATION

Information on toxicological effects

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

Acute toxicity

Compound	Type	Route	Species	Dose
Pralatrexate	--	--	--	--

Irritation/Corrosion	No data available.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Sensitization	No data available.
STOT-single exposure	No data available.
STOT-repeated exposure/Repeat-dose toxicity	A conservative estimate of the intravenous (IV) LD_{50} in mice and rats treated once weekly for up to 3 weeks is 370 and 110 mg/kg pralatrexate, respectively. Repeat-dose IV toxicity studies of up to 28 weeks and 9 months were conducted in rats and dogs, respectively. Animals were dosed in 7-week cycles (treatment was once per week for 6 weeks followed by 1 dose-free week). Target organs of toxicity in these studies included the hematological system, spleen, testes, gastrointestinal tract and/or the bone marrow. NOAELs of 5 and 0.1 mg/kg were identified in rats and dogs, respectively.
Reproductive toxicity	No studies were identified for pralatrexate. Reproductive organ toxicity, impaired spermatogenesis and decreased fertility have been reported in non-clinical studies with methotrexate.
Developmental toxicity	Pralatrexate was embryotoxic and/or fetotoxic in rats and rabbits treated with IV doses as low as 60 and 30 µg/kg/day, respectively.
Genotoxicity	Pralatrexate did not cause mutations in the Ames bacterial mutagenicity assay or the Chinese hamster cell chromosome aberration test. However these tests do not reliably predict genotoxicity for this class of compounds. Pralatrexate was also negative in the mouse *in vivo* micronucleus assay. Methotrexate has been shown to be genotoxic to germ cells in several test systems.
Carcinogenicity	No studies were identified for pralatrexate. This substance is not listed by NTP, IARC, ACGIH or OSHA as a carcinogen. Methotrexate is classified as IARC Group 3 (not classifiable as to its carcinogenicity to humans).
Aspiration hazard	No data available.
Human health data	Pralatrexate is a cytotoxic anticancer agent. The most commonly occurring adverse effects with therapeutic use of pralatrexate include mucositis, thrombocytopenia, nausea and fatigue. Other adverse effects may include bone marrow suppression, hematological toxicity, gastrointestinal toxicity and liver toxicity. Reproductive, developmental and genotoxic effects have been observed in humans exposed to the mechanistically and structurally related compound, methotrexate.

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Pralatrexate	--	--	--

Persistence and Degradability	No data available.
Bioaccumulative potential	No data available.

SECTION 12 - ECOLOGICAL INFORMATION …continued

Mobility in soil	No data available.
Results of PBT and vPvB assessment	Not performed.
Other adverse effects	No data available.
Note	The environmental characteristics of this substance have not been fully investigated. Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods	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.

SECTION 14 - TRANSPORT INFORMATION

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

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS complies with the requirements under US, EU and GHS (EU CLP - Regulation EC No 1272/2008) guidelines. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.
OSHA Hazardous	Yes. Caution. May adversely affect the developing fetus and/or cause adverse reproductive effects. May cause birth defects. May cause hematological system, gastrointestinal system, liver and bone marrow damage. May be genotoxic. May be harmful if swallowed.
WHMIS classification	Not required. Drugs are not subject to WHMIS. This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations and the SDS contains all of the information required by those regulations.
TSCA status	Drugs are exempt from TSCA.
SARA section 313	Not listed.
California proposition 65	Not listed. However, methotrexate is listed as a developmental toxicant.
Additional information	Methotrexate is listed as a hazardous drug by NIOSH.

SECTION 16 - OTHER INFORMATION

Full text of R phrases and EU Classifications	T - Toxic. R22 - Harmful if swallowed. R48/23/25 - Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed. R60 - May impair fertility. R61 - May cause harm to the unborn child. R68 - Possible risk of irreversible effects. Muta. Cat. 3 - Mutagenic Category 3. Repr. Cat. 1 - Toxic for reproduction Category 1.
Full text of H phrases, P phrases and GHS classification	ATO4 - Acute Toxicity (Oral) Category 4. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. RT1A - Reproductive toxicity Category 1A. GCM2 - Germ Cell Mutagenicity Category 2. H302 - Harmful if swallowed. H341 - Suspected of causing genetic defects. H360FD - May damage fertility. May damage the unborn child. H372 - Causes damage to hematological system, gastrointestinal system, liver and bone marrow through prolonged or repeated exposure.
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; 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

SECTION 16 - OTHER INFORMATION …continued

Abbreviations …continued

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; 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

Revisions

Updated formatting in accordance with General US, EU, and GHS (EU CLP) requirements.

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 potent 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 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.