



Pemetrexed Disodium for Injection

Eli Lilly and Company
Material Safety Data Sheet

Effective Date: 05-Feb-2004

Section 1 - Chemical Product and Company

Manufacturer:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Manufacturer's Emergency Phone:
1-317-276-2000
CHEMTREC:
1-800-424-9300 (North America)
1-703-527-3887 (International)

Common Name: Pemetrexed Disodium for Injection

Chemical Name: L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt

Synonym(s): 231514 Disodium for injection; 289739 for injection; MTA disodium for injection; MTA for injection; Pemetrexed sodium for injection

Trademarks(s): Alimta

Lilly Item Code(s): VL7623; VL7640

See attached glossary for abbreviations.

Section 2 - Composition / Information on Ingredients

Ingredient	CAS	Concentration %
Pemetrexed Disodium	150399-23-8	50
Mannitol	69-65-8	50

Exposure Guidelines:

Pemetrexed - LEG 0.3 micrograms/m³ TWA for 8 or 12 hours. Excursion Limit 3.6 micrograms/m³ for no more than a total of 30 minutes.

Mannitol - Exposure Guideline 10 mg/m³ TWA for 8 or 12 hours.

Section 3 - Hazards Identification

Appearance: White lyophilized plug

Physical State: Solid

Odor: Odorless

Emergency Overview



Special
R = Reproductive

Emergency Overview Effective Date: 22-Sep-2000

Lilly Laboratory Labeling Codes:

Health 2

Fire 1

Reactivity 0

Special R

Primary Physical and Health Hazards: Mutagen. Irritant (eyes, skin). Reproductive, Blood and Bone Marrow Effects.

Caution Statement: Pemetrexed Disodium for Injection alters genetic material and may be irritating to the eyes and skin. Effects of exposure may include reproductive tissue changes, fetal changes, decreased fetal weight, decreased offspring survival, decreased blood cell counts, and lymphoid tissue and bone marrow changes.

Routes of Entry: Inhalation and skin contact.

Effects of Overexposure: May be irritating to the eyes and skin. Decreased fetal weight and viability have been reported in animal studies with pemetrexed disodium. Pemetrexed is a folic acid antimetabolite, this class of compounds is known to cause developmental effects. Effects of overexposure to pemetrexed disodium may include bone marrow suppression resulting in decreased blood cell counts, inflammation of mucous membranes, skin rash, fatigue, fetal effects, and reproductive tissue changes.

Patients are instructed to take folic acid and vitamin B12 to reduce treatment-related toxicity. Skin rash has been reported in patients not pretreated with a cortiosteroid (dexamethasone).

Medical Conditions Aggravated by Exposure: None known.

Carcinogenicity:

Pemetrexed disodium - Not listed by IARC, NTP, ACGIH, or OSHA.

Mannitol - Not listed by IARC, NTP, ACGIH, or OSHA. Two-year dietary studies demonstrated no evidence of carcinogenicity in mice and rats.

Section 4 - First Aid Measures

Eyes: Hold eyelids open and flush with a steady, gentle stream of water for 15 minutes. See an ophthalmologist (eye doctor) or other physician immediately.

Skin: Remove contaminated clothing and clean before reuse. Wash all exposed areas of skin with plenty of soap and water. Get medical attention if irritation develops.

Inhalation: Move individual to fresh air. Get medical attention if breathing difficulty occurs. If not breathing, provide artificial respiration assistance (mouth-to-mouth) and call a physician immediately.

Ingestion: Do not induce vomiting. Call a physician or poison control center. If available, administer activated charcoal (6-8 heaping teaspoons) with two to three glasses of water. Do not give anything by mouth to an unconscious person. Immediately transport to a medical care facility and see a physician.

Notes to Physician:

Pemetrexed disodium - If overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. Management of pemetrexed overdose should include consideration of the use of leucovorin or thymidine rescue.

Section 5 - Fire Fighting Measures

Flash Point: No applicable information found

UEL: No applicable information found

LEL: No applicable information found

Extinguishing Media: Use water, carbon dioxide, dry chemical, foam, or Halon.

Unusual Fire and Explosion Hazards: As a finely divided material, may form dust mixtures in air which could explode if subjected to an ignition source.

Hazardous Combustion Products: May emit toxic fumes when exposed to heat or fire.

Section 6 - Accidental Release Measures

Spills: Use double pairs of latex disposable gloves which must be disposed of within an hour, goggles, impermeable body covering, and approved HEPA-filtered or supplied-air respirator. If material spills occur in production area, use either wet clean-up methods, ensuring that no airborne dusts or aerosols are formed, or appropriate vacuum cleaners having high efficiency particulate air (HEPA) filters.

It is recommended that areas handling final finished product have cytotoxic spill kits available. Spill kits should include impermeable body covering, shoe covers, latex and utility latex gloves, goggles, approved HEPA respirator, disposable dust pan and scoop, absorbent towels, spill control pillows, disposable sponges, sharps container, disposable garbage bag, and a hazardous waste label.

Section 7 - Handling and Storage

Storage Conditions: Store at Controlled Room Temperature 20 to 25 C (68 to 77 F) [see USP]. Pemetrexed is not light sensitive.

Section 8 - Exposure Controls / Personal Protection

See Section 2 for Exposure Guideline information.

For appropriate handling precautions in specific laboratory, manufacturing, or clinical health care operations, consult with a health and safety or technical services representative.

In clinical health care settings, follow OSHA Technical Manual, Section VI, Chapter 2 - Controlling Occupational Exposure to Hazardous Drugs. This chapter covers protection of employees during cytotoxic drug preparation, administration, disposal, and the handling of human waste products potentially contaminated with cytotoxic drug substances.

GENERAL: For all work environments, wear eye protection, avoid skin contact, wear gloves, and take other appropriate precautions.

Respiratory Protection: When the exposure guidelines may be exceeded, use an approved HEPA-filtered or supplied-air respirator.

Eye Protection: Chemical goggles and/or face shield.

Ventilation: Extensive local exhaust, ventilated enclosure (HEPA-filtered balance enclosure, fume hood, or Class II or III vertical flow biosafety cabinet), or enclosed process equipment.

Other Protective Equipment: Chemical-resistant gloves and impermeable body covering to minimize skin contact. If handled in a ventilated enclosure, as in a laboratory setting, respirator and goggles or face shield may not be required. Safety glasses are always required.

Additional Exposure Precautions: In production settings, airline-supplied, hood-type respirators are preferred. Shower and change clothing if skin contact occurs.

Section 9 - Physical and Chemical Properties

Appearance: White lyophilized plug

Odor: Odorless

Boiling Point: No applicable information found

Melting Point: No applicable information found

Density: No applicable information found

pH: No applicable information found

Evaporation Rate: No applicable information found

Water Solubility: Soluble

Vapor Density: No applicable information found

Vapor Pressure: No applicable information found

Section 10 - Stability and Reactivity

Stability: Stable at normal temperatures and pressures.

Incompatibility: May react with strong oxidizing agents (e.g., peroxides, permanganates, nitric acid, etc.).

Hazardous Decomposition: May emit toxic fumes when heated to decomposition.

Hazardous Polymerization: Will not occur.

Section 11 - Toxicological Information

Acute Exposure

No data available for mixture or formulation. Data for ingredient(s) or related material(s) are presented.

Oral:

Pemetrexed - Rat, 500 mg/kg, no deaths or toxicity.

Skin:

Pemetrexed disodium - Rabbit, 1000 mg/kg, no deaths.

Inhalation: No applicable information found.

Intravenous:

Pemetrexed disodium - Rat (male), median lethal dose 1332 mg/kg, convulsions.

Rat (female), median lethal dose greater than 1574 mg/kg, mortality, convulsions.

Skin Contact:

Pemetrexed disodium - Rabbit, irritant

Eye Contact:

Pemetrexed disodium - Rabbit, mild irritant

Chronic Exposure

No data available for mixture or formulation. Data for ingredient(s) or related material(s) are presented.

Target Organ Effects:

Pemetrexed disodium - Decreased testes weights with decreased sperm production and decreased red blood cells were reported in mice with intraperitoneal exposure for 6 weeks. Intravenous exposure in dogs for up to 6 months resulted in mortality, decreased white blood cell counts, mild anemia, and intestinal lesions.

Reproduction:

Pemetrexed disodium - Administration to pregnant mice resulted in decreased fetal weight, incomplete ossification of some skeletal structures, and cleft palate. Male reproductive toxicity characterized by reduced fertility, hypospermia, and testicular atrophy was observed when given to male mice.

Sensitization: No applicable information found.

Mutagenicity:

Pemetrexed disodium - Clastogenic in the in vivo micronucleus assay in the mouse, but was negative in the in vitro chromosome aberration test in Chinese hamster ovary cells. Negative in the Ames test.

Section 12 - Ecological Information

No environmental data for the mixture or formulation. The environmental information for ingredient(s) or related material(s) are presented.

Ecotoxicity Data:

Pemetrexed disodium

Rainbow trout 96-hour median effective concentration: >1212.7 mg/L

Daphnia magna 48-hour median effective concentration: 509.5 mg/L

Green algae (*S. capricornutum*) 72-hour median effective concentration (average specific growth rate): 210 mg/L

Activated sludge respiration inhibition 3-hour median effective concentration: >122 mg/L

Environmental Fate:

Pemetrexed disodium

Log Kow: <1

Bioconcentration factor: <4.6

Dissociation constants in 66% DMF/water (pKa): <3.5, 6.24, 7.61, and >13.5

Biodegradation half-life (1.5 g solids/L): <3.9 hours

Biodegradation half-life (0.15 g solids/L): >24 hours

Amount associated with municipal sludge solids: none

Environmental Summary:

Pemetrexed disodium - Practically non-toxic to fish, aquatic invertebrates, green algae, and activated sludge microorganisms. No volatility expected. Low potential to bioconcentrate in aquatic organisms. Persistence in the environment not expected due to biodegradation.

Lilly Aquatic Exposure Guideline (LAEG):

Pemetrexed disodium

LAEG for Drinking Water: 0.045 micrograms/L

LAEG for Chronic Exposure: 1 micrograms/L

LAEG for Acute Exposure of Aquatic Organisms: 16 mg/L

Section 13 - Disposal Considerations

Waste Disposal: Dispose of any cleanup materials and waste residue according to all applicable laws and regulations. To avoid accidental exposure due to waste handling, place waste residue in a segregated, sealed plastic container.

Section 14 - Transport Information

Regulatory Organizations:

DOT: Not Regulated

ICAO/IATA: Not Regulated

IMO: Not Regulated

Section 15 - Regulatory Information

Below is selected regulatory information chosen primarily for possible Eli Lilly and Company usage. This section is not a complete analysis or reference to all applicable regulatory information. Please consider all applicable laws and regulations for your country/state.

U.S. Regulations

Pemetrexed disodium

TSCA - No

CERCLA - Not on this list

SARA 302 - Not on this list

SARA 313 - Not on this list

OSHA Substance Specific - No

Mannitol

TSCA - Yes

CERCLA - Not on this list

SARA 302 - Not on this list

SARA 313 - Not on this list

OSHA Substance Specific - No

EU Regulations

EC Classification

Contains pemetrexed disodium (C = 50%)

T (Toxic)

Xi (Irritant)

Mutagen Category 3

Reproductive Category 1

Risk Phrases

R 36/38 - Irritating to eyes and skin.

R 60 - May impair fertility.

R 61 - May cause harm to the unborn child.

R 68 - Possible risk of irreversible effects.

Safety Phrases

S 36/37/39 - Wear suitable protective clothing, gloves and eye/face protection.

S 53 - Avoid exposure -- obtain special instructions before use.

Section 16 - Other Information

MSDS Sections Revised: Section 7.

As of the date of issuance, we are providing available information relevant to the handling of this

material in the workplace. All information contained herein is offered with the good faith belief that it is accurate. THIS MATERIAL SAFETY DATA SHEET SHALL NOT BE DEEMED TO CREATE ANY WARRANTY OF ANY KIND (INCLUDING WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE). In the event of an adverse incident associated with this material, this safety data sheet is not intended to be a substitute for consultation with appropriately trained personnel. Nor is this safety data sheet intended to be a substitute for product literature which may accompany the finished product.

For additional information contact:

Eli Lilly and Company
Hazard Communication
317-277-6029

GLOSSARY:

ACGIH = American Conference of Governmental Industrial Hygienists
AIHA = American Industrial Hygiene Association
BEI = Biological Exposure Index
CAS Number = Chemical Abstract Service Registry Number
CERCLA = Comprehensive Environmental Response Compensation and Liability Act (of 1980)
CHAN = Chemical Hazard Alert Notice
CHEMTREC = Chemical Transportation Emergency Center
DOT = Department of Transportation
EC = European Community
EINECS = European Inventory of Existing Chemical Substances
ELINCS = European List of New Chemical Substances
EPA = Environmental Protection Agency
HEPA = High Efficiency Particulate Air (Filter)
IARC = International Agency for Research on Cancer
ICAO/IATA = International Civil Aviation Organization/International Air Transport Association
IEG = Lilly Interim Exposure Guideline
IMO = International Maritime Organization
Kow = Octanol/Water Partition Coefficient
LEG = Lilly Exposure Guideline
LEL = Lower Explosive Limit
MSDS = Material Safety Data Sheet
MSHA = Mine Safety and Health Administration
NA = Not Applicable, except in Section 14 where NA = North America
NADA = New Animal Drug Application
NAIF = No Applicable Information Found
NCI = National Cancer Institute
NIOSH = National Institute for Occupational Safety and Health
NOS = Not Otherwise Specified
NTP = National Toxicology Program
OSHA = Occupational Safety and Health Administration
PEL = Permissible Exposure Limit (OSHA)
RCRA = Resource Conservation and Recovery Act
RQ = Reportable Quantity
RTECS = Registry of Toxic Effects of Chemical Substances
SARA = Superfund Amendments and Reauthorization Act

STEG = Lilly Short Term Exposure Guideline

STEL = Short Term Exposure Limit

TLV = Threshold Limit Value (ACGIH)

TPQ = Threshold Planning Quantity

TSCA = Toxic Substances Control Act

TWA = Time Weighted Average/8 Hours Unless Otherwise Noted

UEL = Upper Explosive Limit

UN = United Nations

WEEL = Workplace Environmental Exposure Level (AIHA)