

MATERIAL SAFETY DATA SHEET

Version No: MSDS/Pem-AUS/DP-003

Effective Date: 17th April 2020

Pemetrexed Disodium Powder for Injection, 100 mg/vial, 500 mg/vial and 1000 mg/vial

SECTION 1 – PRODUCT AND COMPANY IDENTIFICATION

Product Name: Pemetrexed Disodium Powder for Injection, 100 mg/vial, 500 mg/vial and 1000 mg/vial

Details of the Supplier of the Safety Data Sheet

Manufacturer:

Intas Pharmaceuticals Ltd.
Plot No. 5, 6 and 7, Pharmez,
Near Matoda Village,
Ahmedabad-382 213, Gujarat, India

Sponsor:

Accord Healthcare Pty Ltd
Level 24, 570 Bourke Street,
Melbourne, VIC, 3000,
Australia

SECTION 2 – COMPOSITION, INFORMATION ON INGREDIENTS

Mixtures:

Chemical name	Common name and synonyms.	%
Pemetrexed disodium hemipentahydrate	N-{4-[2-(2-Amino-4-oxo-4,7-dihydro-1H-pyrrolo [2,3-d]pyrimidin-5-yl)ethyl]phenyl} carbonyl}-Lglutamic acid disodium, Hemipentahydrate.	50

Composition comments: Remaining components of this product are non-hazardous and/or are present at concentrations below reportable levels.

SECTION 3 - HAZARDS IDENTIFICATION

Physical hazards : Not classified

Health hazards

Skin corrosion/irritation: : Category 2
Germ cell mutagenicity : Category 2
Reproductive toxicity : Category 1A
Specific target organ toxicity, repeated exposure : Category 1
OSHA defined hazards : Not classified

Label elements



Signal word : Danger

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Hazard statement: **H315-** Causes skin irritation.
H341- Suspected of causing genetic defects.
H360- May damage fertility or the unborn child.
H372- Causes damage to organs (Blood) through prolonged or repeated exposure

Precaution statement:

Prevention: **P201:** Obtain special instructions before use
P260: Do not breathe dust.
P264: Wash thoroughly after handling
P281: Use personal protective equipment as required.
Response: **P308 + P313:** IF exposed or concerned: Get medical advice/attention.

Storage : Not available.

Disposal : Not available.

Hazard(s) not otherwise classified (HNOC) : None known

Supplemental information: : None

SECTION 4 - FIRST AID MEASURES

Inhalation: Remove to fresh air. If breathing stops, provide artificial respiration. Get medical attention immediately.

Skin Contact: Wash off immediately with plenty of water. Continue to rinse for at least 15 minutes. Immediately take off all contaminated clothing. Get medical attention if irritation develops and persists. Wash contaminated clothing before reuse.

Eye Contact: In case of eye contact, remove contact lens and rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Get medical attention.

Ingestion: If conscious, give the victim plenty of water to drink. Never give anything by mouth to a victim who is unconscious or is having convulsions. Call a physician immediately.

Most important symptoms/effects, acute and delayed: Causes skin irritation. May cause redness and pain. Decreased fetal weight and viability have been reported in animal studies with pemetrexed disodium. The active ingredient, pemetrexed, is a folic acid antimetabolite, this class of compounds is known to cause developmental effects. Dilute solutions of pemetrexed disodium are not expected to be irritating to the eyes or skin. 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.

Indication of Immediate medical attention and special treatment needed: If overdose occurs, general supportive measures should be instituted as deemed necessary by the treating

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physician. Management of pemetrexed overdose should include consideration of the use of leucovorin or thymidine rescue.

SECTION 5 - FIRE FIGHTING MEASURES

Suitable Extinguishing Media: Carbon dioxide, dry chemical or water.

Unsuitable Extinguishing Media: None known.

Specific hazards arising from the chemical: Hazardous decomposition products formed under fire conditions.

Special protective equipment and precautions for firefighters: Wear self-contained breathing apparatus and protective clothing.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures: Wear suitable protective clothing, gloves and eye/face protection. See Section 8 of the SDS for Personal Protective Equipment.

Methods and materials for containment and cleaning up: 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.

Environmental precautions: Avoid discharge into drains, water courses or onto the ground.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling: Provide adequate ventilation. Avoid contact with eyes, skin, and clothing. Wash hands thoroughly after handling. See Section 8 of the SDS for Personal Protective Equipment.

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Conditions for safe storage, including any incompatibilities: Storage temperature: between 20 and 25 °C (68 to 77 °F). Excursions permitted from 15 to 30 C (59 to 86 F). [see USP]. Pemetrexed is not light sensitive. Keep in original container.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Occupational exposure limits:

Components	Type	Value	Form
Pemetrexed disodium hemipentahydrate	Excursion Limit	3.6 µg/m ³	30 minutes
	TWA (12hrs)	0.3 µg/m ³	
	TWA (8hrs)	0.3 µg/m ³	

Biological limit values: No biological exposure limits noted for the ingredient(s).

Exposure guidelines: For appropriate handling precautions in specific laboratory or manufacturing operations, consultation with an occupational health and safety or technical services representative is recommended. 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 and ELIMINATE hand-to-eye contact. Avoid skin contact, wear gloves, and take other appropriate precautions.

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

Individual protection measures, such as personal protective equipment:

Eye/face protection: Wear goggles/face shield.

Skin protection:

Hand protection: Chemical-resistant gloves and impermeable body covering to minimize skin contact.

Other: 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.

Respiratory protection: When the exposure guidelines may be exceeded, use an approved HEPA-filtered or supplied-air respirator. Select respirator with appropriate protection factor. Select appropriate respirator for physical characteristics of material. Respirator selection must

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be based on known or anticipated exposure levels, the hazards of the product and the safe working limits of the respirator.

Thermal hazards: Not available.

General hygiene considerations: 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:

Physical State:	: Solid
Form	: Solid. (Lyophilized).
Color	: White.
Odor	: Odorless
Odor threshold	: No data available.
pH	: No data available.
Melting point/freezing point	: No data available.
Initial boiling point and boiling Range	: No data available.
Flash point	: Not applicable.
Evaporation rate	: No data available.
Flammability (solid, gas)	: No test data available.

Upper/lower flammability or explosive limits:

Flammability limit – lower (%)	: No data available.
Flammability limit – upper (%)	: No data available.
Explosive limit - lower (%)	: No data available.
Explosive limit - upper (%)	: No data available.
Vapor pressure	: No data available.
Vapor density	: No data available.
Relative density	: No data available.

Solubility(ies)

Solubility (water)	: 89.4 g/l , (pH 9), (as free acid) 101.5 g/l , (pH 7), (as free acid)
Partition coefficient (n-octanol/water)	: < 1.000
Auto-ignition temperature	: No data available.
Decomposition temperature	: No data available.
Viscosity	: Not applicable.

Other information

Density	: No data available.
Explosive properties	: Not explosive
Oxidizing properties	: The substance or mixture is not classified as oxidizing.

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Percent volatile : No data available.
VOC : No data available.

SECTION 10 - STABILITY AND REACTIVITY

Reactivity: Not water reactive.
Chemical Stability: Material is stable under normal conditions.
Possibility of hazardous reactions: Hazardous polymerization does not occur.
Conditions To Avoid: None known.
Incompatibility Materials: Strong oxidizing agents.
Hazardous Decomposition products: Hazardous decomposition products formed under fire conditions.

SECTION 11 - TOXICOLOGY INFORMATION

Information on toxicological effects

Pemetrexed disodium hemipentahydrate

Acute toxicity:

Acute:

Components	Species	Test Results
Dermal		
LD	Rabbit	> 1000 mg/kg
Oral		
LD	Rat	> 500 mg/kg , (as free base)
Other		
LD50	Rat	> 1574 mg/kg, Intravenous (female), Convulsions. Mortality. 1332 mg/kg, Intravenous (male), Convulsions.

Skin corrosion/irritation: Rabbit: Irritating to skin.

Serious eye damage/eye Irritation: Rabbit: Mild eye irritation. (cleared within 7 days)
Based on available data, the classification criteria are not met.

Respiratory or skin sensitization:

Respiratory sensitization: Due to lack of data the classification is not possible.

Skin sensitization: No test data available. Skin rash has been reported in patients not pretreated with a corticosteroid (dexamethasone). Based on available data, the classification criteria are not met.

Germ cell mutagenicity: Clastogenic in the in vivo micronucleus assay in the mouse.
Results in genetic toxicity assays (in vitro): Negative

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Carcinogenicity: Not listed by IARC, NTP, ACGIH or OSHA. Due to lack of data the classification is not possible.

IARC Monographs. Overall Evaluation of Carcinogenicity: Not listed.

OSHA Specifically Regulated Substances (29 CFR 1910.1001-1050): Not regulated.

US. National Toxicology Program (NTP) Report on Carcinogens: Not listed.

Reproductive toxicity: 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.

Specific target organ toxicity - single exposure: Due to lack of data the classification is not possible.

Specific target organ toxicity - repeated exposure: Causes damage to organs (Blood) through prolonged or repeated exposure. 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.

Aspiration hazard: Not applicable.

Further information: Patients are instructed to take folic acid and vitamin B12 to reduce treatment related toxicity.

SECTION 12 - ENVIRONMENTAL IMPACT INFORMATION

Ecotoxicity: Harmful to aquatic life.

Pemetrexed disodium hemipentahydrate:

Components	Species	Test Results
EC50	Respiration inhibition of activated sludge	> 1000 mg/l, 3 h (highest concentration tested) (as free acid) (OECD 209)
LOEC	Midge (Chironomus riparius)	> 100 mg/kg, 28 d (highest concentration tested) (free acid) (OECD 218)
NOEC	Midge (Chironomus riparius)	100 mg/kg, 28 d (highest concentration tested) (free acid) (OECD 218)
Aquatic		
Algae		
EbC50	Algae (Pseudokirchneriella subcapitata)	17 mg/l, 72 h (as free acid) (OECD 201)
ErC50	Algae (Pseudokirchneriella)	63 mg/l, 72 h (as free acid) (OECD 201)

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	subcapitata)	
LOEC	Algae (Pseudokirchneriella subcapitata)	27 mg/l (growth rate) (as free acid) (OECD 201)
		11 mg/l (yield) (as free acid) (OECD 201)
NOEC	Algae (Pseudokirchneriella subcapitata)	11 mg/l (growth rate) (as free acid) (OECD 201)
		4 mg/l (yield) (as free acid) (OECD 201)
Crustacea		
EC50	Daphnia magna	462 mg/l, 48 h (as free acid) (OECD 202)
LOEC	Daphnia magna	2.1 mg/l, 21 d (reproduction) (as free acid) (OECD 211)
NOEC	Daphnia magna	1.2 mg/l, 21 d (reproduction) (as free acid) (OECD 211)
Fish		
LC50	Rainbow trout,donaldson trout (Oncorhynchus mykiss)	> 1099.6 mg/l, 96 h (highest concentration tested) (as free acid) (OECD 203)
LOEC	Fathead Minnow (Pimephales promelas)	> 13 mg/l (embryo + 28 days post hatch) (highest concentration tested) (as free acid) (OECD 210)
NOEC	Fathead Minnow (Pimephales promelas)	13 mg/l (embryo + 28 days post hatch) (highest concentration tested) (as free acid) (OECD 210)

Persistence and degradability: Stable in water: less than 10% hydrolysis in pH 4, 7, 9 buffers at 50C (OECD 105) Not ready biodegradable: only 20% of theoretical released as CO₂ over 29 days (OECD 301) Degradable in sewage sludge: DT50 < 1 day; numerous degradation peaks observed (OECD 302) Degradable in water-sediment systems: DT50 < 0.5 days, major degradation products degraded over 100 day study (OECD 308).

Bioaccumulative potential: No data available on bioaccumulation. Potential to bioaccumulate is low.

Partition coefficient n-octanol / water (log Kow):

Pemetrexed disodium hemipentahydrate: < 1 (HPLC) (estimation) (OECD 117).

Mobility in soil: No data available.

Other adverse effects:Not available.

SECTION 13 - DISPOSAL INFORMATION

Disposal instructions: To avoid accidental exposure due to waste handling, place waste residue in a segregated, sealed plastic container. Used syringes, needles, and sharps should not be crushed, clipped, or recapped, but placed directly into an approved sharps container. Dispose of any cleanup materials and waste residue according to all applicable laws and regulations, e.g., secure chemical landfill disposal.

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Waste from residues / unused: Not available.

Contaminated packaging: Not available.

SECTION 14 - TRANSPORTATION INFORMATION

DOT: Not regulated as dangerous goods.

IATA: Not regulated as dangerous goods.

IMDG: Not regulated as dangerous goods.

Transport in bulk according to Annex II of
MARPOL 73/78 and the IBC Code: Not applicable.

SECTION 15 - REGULATORY INFORMATION

US federal regulations: This product is a "Hazardous Chemical" as defined by the OSHA Hazard Communication Standard, 29 CFR 1910.1200. One or more components are not listed on TSCA. CERCLA/SARA Hazardous Substances - Not applicable.

TSCA Section 12(b) Export Notification (40 CFR 707, Subpt. D): Not regulated.

CERCLA Hazardous Substance List (40 CFR 302.4): Not listed.

SARA 304 Emergency release notification: Not regulated.

OSHA Specifically Regulated Substances (29 CFR 1910.1001-1050): Not regulated.

Superfund Amendments and Reauthorization Act of 1986 (SARA)

Hazard categories: Immediate Hazard - Yes

Delayed Hazard - Yes

Fire Hazard - No

Pressure Hazard - No

Reactivity Hazard - No.

SARA 313 (TRI reporting) Not regulated.

Other federal regulations:

Clean Air Act (CAA) Section 112 Hazardous Air Pollutants (HAPs) List: Not regulated.

Clean Air Act (CAA) Section 112(r) Accidental Release Prevention (40 CFR 68.130):
Not regulated.

Safe Drinking Water Act (SDWA): Not regulated.

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US state regulations: California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65): This material is not known to contain any chemicals currently listed as carcinogens or reproductive toxins.

International Inventories

Country(s) or region	Inventory name	On inventory (yes/no)*
Canada	Domestic Substances List (DSL)	No
Canada	Non-Domestic Substances List (NDSL)	No
United States & Puerto Rico	Toxic Substances Control Act (TSCA) Inventory	No

*A "Yes" indicates that all components of this product comply with the inventory requirements administered by the governing country(s)

A "No" indicates that one or more components of the product are not listed or exempt from listing on the inventory administered by the governing country(s).

SECTION 16 - OTHER DATA

List of abbreviations:

LAEG: Lilly Aquatic Exposure Guideline.
LEG: Lilly Exposure Guideline
LOEC: Lowest Observed Effect Concentration
NOEC: No Observed Effect Concentration
TWA: Time Weighted Average

Revision information: Hazard(s) identification: Hazard statement
Exposure controls/personal protection: Exposure guidelines
Exposure controls/personal protection: General hygiene considerations
Physical & Chemical Properties: Multiple Properties
GHS: Classification

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