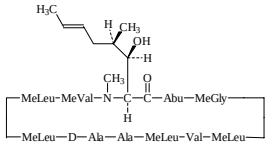
APOTEX
ADVANCING GENERICS

Material Safety Data Sheet

Section 1. Product Identification and Uses

Common/Trade name	**Cyclosporine**	**DSL#**	On the DSL list.
Synonyms	Antibiotic S 7481F1; Cyclosporin; Cyclosporine A; Ramihyphin A; Sandimmun; Sandimmune	**CAS#**	59865-13-3
Chemical name	Cyclosporin A	**Molecular weight**	1048.45 g/mole
Chemical family	Cyclic polypeptide	**Chemical formula**	$C_{62}H_{111}N_{11}O_{12}$
Supplier	Reddy-Cheminor 66 South Maple Ave. Ridgewood, N.J. 07450 tel.# (416)444-4424	**Chemical structure**	
Material uses	Pharmaceutical active ingredient. Therapeutic category: Immunosuppressant.	**Manufacturer**	North China Pharmaceutical Corporation 4, Heping Road (C), Shijazhuang China
Emergency phone	1- (416)-749-9300 ext. 5555 For general information call ext. 8483 (8 A.M.- 4 P.M.)	**DIN**	Not applicable.

Section 2. Hazards Identification

Potential Acute Health Effects	Possible eye, skin, gastrointestinal and/or respiratory tract irritation.
Potential Chronic Health Effects	Possible hypersensitization, immunosuppression, kidney toxicity and cancer.
WHMIS	WHMIS CLASS D-2A: Material causing other toxic effects (VERY TOXIC).

Remark

Not regulated under WHMIS: Covered by Food & Drug Act.

Apotex Hazard Classification (For Apotex internal practices only)	This material has been assigned hazard class: **2**

Section 3. First Aid Measures

Eye contact	IMMEDIATELY flush eyes with running water for at least 15 minutes, keeping eyelids open. Take care not to rinse contaminated water into the non-affected eye. Always seek medical attention for accidents involving the eyes.
Skin contact	Flush the contact area with lukewarm running water for at least 15 minutes. Remove contaminated clothing, taking care not to spread the chemical. Seek medical attention if irritation persists.
Hazardous skin contact	If contamination is extensive, remove clothing under running water. Discard or decontaminate clothing under running water. Discard or decontaminate clothing before reuse. Unless contact has been slight, seek medical attention. Seek medical attention if irritation persists.
Slight inhalation	Allow the victim to rest in a well ventilated area. Seek medical attention, if irritation persists.

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Hazardous inhalation	Take proper precautions to ensure your own safety before attempting rescue. Remove source of contamination or move victim to fresh air. If breathing has stopped, trained personnel should begin artificial respiration (use protective mask with one-way valve), or if the heart has stopped, cardiopulmonary resuscitation (CPR) immediately. Seek medical attention.
Slight ingestion	NEVER give an unconscious person anything to ingest. Rinse mouth thoroughly with water. Have conscious person drink several glasses of water. Seek medical attention if irritation persists.
Hazardous ingestion	Never give anything by mouth if victim is rapidly losing consciousness, or is unconscious or convulsing. Rinse mouth thoroughly with water. If breathing has stopped, trained personnel should begin artificial respiration (use protective mask with one -way valve), or if the heart has stopped, cardiopulmonary resuscitation (CPR) immediately. Seek medical attention. 1. Support respiratory and cardiovascular function. 2. Induced vomiting is not recommended. Consider activated charcoal or gastric lavage after a potentially toxic ingestion. 3. Control seizures with a benzodiazepine; if seizures persist or recur administer phenobarbital. 4. Correct magnesium deficits. 5. Calcium channel blockers may be the preferred agent for treatment of cyclosporine-induced hypertension, as they may prevent nephrotoxicity. 6. Low-dose dopamine is effective for treatment of nephrotoxicity. 7. Azithromycin or metronidazole has been used to treat gingival hyperplasia. 8. Monitor cyclosporine plasma levels, kidney and liver function, and serum electrolytes. 9. Hemodialysis does not appear to be effective in increasing clearance of cyclosporine. (Poisindex 2002; Poisoning & Toxicity 2005)

Section 4. Hazardous Ingredients

Name	CAS #	% (w/w)
Cyclosporine	59865-13-3	100

Toxicity values of the hazardous ingredients

Refer to Sec. 11.

TLV Not established.

Section 5. Fire Fighting Measures

The product is:	May be combustible.
Autoignition temperature	Not available.
Fire degradation products	Decomposition products may include the following materials: carbon oxides (CO, CO_2), nitrogen oxides (NO, NO_2 etc.).
Flash points	Not applicable.
Flammable limits	Not available.
Fire extinguishing procedures	Extinguisher media: water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials. Special fire fighting procedures: As with all fires, evacuate personnel to safe area. Firefighters should use self-contained breathing equipment and protective clothing.
Flammability	This material is assumed to be combustible. As with all dry powders it is advisable to ground mechanical equipment in contact with dry material to dissipate the potential buildup of static electricity.
	Remark No additional remark.
Risks of explosion	Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Fine airborne dust can be ignited by static discharge.
	Remark No additional remark.

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Section 6. Accidental Release Measures

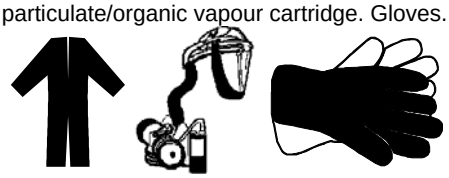
Spill and leak

Vacuum or sweep up spillage. Avoid dust. Place spillage into an appropriate labeled waste disposal container. Wash contaminated clothing before reuse. Ventilate area and wash spill site. Follow appropriate Safe Work Practices.

Protective Clothing Pictograms in case of large spill and/or high exposure levels

Protective clothing in case of large spill

Hooded Full suit -Tyvek coveralls or equivalent. Powered Air Purifying Respirator with combination particulate/organic vapour cartridge. Gloves.



Section 7. Handling and Storage

Precautions

Use with adequate dust control. In case of insufficient ventilation, wear suitable respiratory equipment. Avoid inhalation, skin and eye contact. Wash thoroughly after handling.

Storage

Store in suitable labelled containers. Keep containers tightly closed when not in use and when empty. Protect from damage. Store in a cool, dry, well-ventilated area, out of direct sunlight.

Section 8. Exposure Controls/Personal Protection

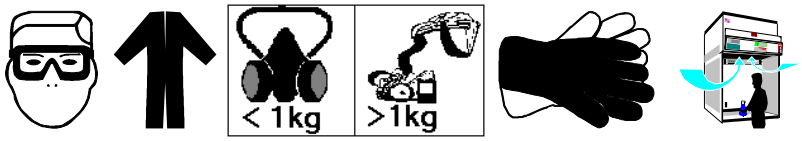
Engineering Controls

Exposure to this material can be controlled in many ways. The measures appropriate for a particular worksite depend on how this material is used and on the extent of exposure. This general information can be used to help develop specific control measures. Ensure that control systems are properly designed and maintained. Comply with occupational, environmental, fire, and other applicable regulations.
Engineering methods to control hazardous conditions are preferred. Methods include mechanical (local exhaust) ventilation, process or personnel enclosure and control of process conditions. Administrative controls and personal protective equipment may also be required. Supply sufficient replacement air to make up for air removed by exhaust system.

Personal Protection

Splash goggles. Full suit with hood, or disposable/washable coveralls. Half facepiece Air Purifying Respirator with combination particulate/organic vapour cartridge (less then 1 kg). Powered Air Purifying Respirator (PAPR) with combination particulate/organic vapour cartridge (greater then 1 kg). Nitrile gloves (impervious). Chemical fume hood.

Protective Clothing (Pictograms)



PERSONAL PROTECTIVE EQUIPMENT:
If engineering controls and work practices are not effective in controlling exposure to this material, then wear suitable personal protective equipment, including approved respiratory protection. Have appropriate equipment available for use in emergencies such as spills or fire. If respiratory protection is required, institute a complete respiratory protection program, including selection, fit testing, training, maintenance and inspection. Refer to the CSA Standard Z94, "Selection, Care, and Use of Respirators".
RESPIRATORY PROTECTION GUIDELINES:
Where Local Exhaust Ventilation (LEV) at dust generating process points exists, respiratory protection may not be required.
When working with quantities less than 1 kg and in the absence of appropriate Local Exhaust Ventilation (LEV) with dusty processes, a half facepiece Air Purifying Respirator with combination particulate/organic vapour cartridge and goggles is recommended.
When working with quantities greater than 1 kg and in the absence of Local Exhaust Ventilation (LEV) with dusty processes, a Powered Air Purifying Respirator (PAPR) with combination particulate/organic vapour cartridge and helmet/hood or Supplied Air Respirator (SAR) is recommended.
The specific respirator selected must be based on contamination levels found in the work place, the specific operation and not exceed the working limits of the respirator.
When performing cleaning activities refer to appropriate cleaning solution MSDS.
EYE/FACE PROTECTION: Splash goggles/safety glasses.
PROTECTIVE CLOTHING/SKIN PROTECTION: Glove selection must take into account any solvents and other hazards present. The selection of gloves for a specific activity must be based on the material's properties and on possible permeation and degradation that may occur under the circumstances of use. Potential allergic reactions can occur with certain glove materials (e.g. Latex) and therefore these should be avoided. Full environmental suit with hood. and/or other resistant protective clothing when working in dusty areas. Have a safety shower/eye-wash fountain readily available in the immediate work area.
EXPOSURE CONTROLS/PERSONAL PROTECTION COMMENTS: In the event clothing becomes contaminated, remove promptly. Launder before use. Inform laundry personnel of contaminant's hazards. Do not eat, drink or smoke in work areas. Wash hands thoroughly after handling this material. Maintain good

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housekeeping.

Section 9. Physical and Chemical Properties

Physical state and appearance	Solid. (Crystalline powder or prismatic needles)	**Odor**	Not available.
pH	6.5-8.0	**Taste**	Not available.
Odor threshold	Not available.	**Color**	White or almost white
Volatility	Not available.		
Melting point/ Freezing point	148-151°C		
Boiling point	Not available.		
Specific gravity	Not available.		
Vapor density	Not available.		
Vapor pressure	Not available.		
Partition Coefficient:	n-octanol/water: 2.92		
Ionicity (surface active agent)	Not available.		
Critical temperature	Not available.		
Instability temperature	Not available.		
Conditions of instability	No additional remark.		
Dispersion properties	See solubility.		
Evaporation rate	Not available.		
Solubility	Practically insoluble in water. Soluble in alcohol, in acetone, in chloroform, in dichloromethane, in ether, and in methyl alcohol. Slightly soluble in saturated hydrocarbons.		

Section 10. Stability and Reactivity

Stability	The product is stable.
Hazardous decomp. products	When heated to decomposition material emits toxic fumes of NOx. Emits toxic fumes under fire conditions.
Degradability	Not available.
Corrosivity	Not corrosive
	Remark No additional remark.
Reactivity/ Incompatibility	Oxidizing agents. Avoid exposure to light and heat.
	Remark No additional remark.

Section 11. Toxicological Information

Routes of entry	Ingestion. Inhalation. Eye contact. Skin contact.
Toxicity data	RTECS#: GZ4120000 TDLo: 12 mg/kg (oral-human) LD50: 1480 mg/kg (oral-rat) LD50: 2329 mg/kg (oral-mouse)

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Long-term effects

Target organs: liver, kidneys and immune system.
Possible hypersensitization, immunosuppression, kidney toxicity, and cancer.
Carcinogenicity: Known to be a human carciongen.
IARC Cancer Review:Group 1. Human Sufficient Evidence. Animal limited evidence.
NTP 96th Report on Carcinogens, 2000: Known to be human carcinogen.
Lymphomas and skin malignancies have developed in humans treated with cyclosporine. The risk of these malignancies is related to the intensity and duration of immunosuppression. (USP DI 2005)
Teratogenicity: Adequate and well-controlled pregnancy studies in humans have not been done. Premature birth and low birth weight have been observed in clinical use of cyclosporine. Studies in rats and rabbits have shown that cyclosporine is toxic to the fetus at doses 2 to 5 times the human dose. Pregnancy category C.
Reproductive Toxicity: No impairment in fertility was demonstrated in studies in male and female rats.
Mutagenicity: No evidence of mutagenicity/genotoxicity was found in the Ames test, the V79-HPRT test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. However, one study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes in vitro gave indication of a positive effect (i.e., induction of SCE) at high concentrations in this system.

Remark

Medical conditions aggravated by exposure: Hypersensitivity to material, current malignancy or premalignant skin lesions, chickenpox (including recent exposure), herpes zoster, impaired liver or kidney function, and infection.

Short-term effects and Signs & Symptoms of overexposure

Possible eye, skin, gastrointestinal and/or respiratory tract irritation.
The usual oral adult dose of cyclosporine is 12 to 15 mg per kilogram of body weight per day initially, then gradually reduced to 5 to 10 mg per kilogram of body weight per day.
Adverse effects may include kidney toxicity; high blood pressure; tender, bleeding, or swollen gums; increased hair growth; trembling hands; seizures; acne or oily skin; headache; leg cramps; nausea; vomiting; abdominal discomfort; fever or chills; lethargy; and frequent urge to urinate. Possible allergic reaction to material if inhaled, ingested or in contact with skin.
Symptoms of overdose may include flushing of face, gum soreness or bleeding, headache, tingling in hands or feet, nausea, vomiting, and tremor.

Remark

The above adverse effects are based on clinical studies.

Section 12. Ecological Information

Ecological Information Not available.

Section 13. Disposal Considerations

Waste Disposal

For internal Apotex waste disposal: Collect in sealed containers and place in appropriate labeled pharmaceutical solid waste class 261A.
For external waste disposal: Follow all appropriate safe work procedures and federal, provincial and local regulations for disposal. Use only licensed disposal and waste hauling companies.

Section 14. Transport Information TDG, IATA, IMDG

Not controlled under TDG (Canada).

UN Not applicable (PIN and PG).

Special Provisions for Transport Not applicable.

Section 15. Other Regulatory Information and Pictograms

NATIONAL FIRE PROTECTION ASSOCIATION (NFPA) HAZARD INDEX

NFPA-HEALTH-blue :1-Slightly hazardous to health.
NFPA-FLAMMABILITY-red :1-Materials that must be preheated before ignition can occur.
NFPA-REACTIVITY-yellow :0-Normally stable.

National Fire Protection Association (U.S.A.)

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Specific Hazard

Hazardous Material Information System (U.S.A.)

Health Hazard	*	1
Fire Hazard		1
Reactivity		0
Personal Protection		X

* - Chronic hazard indicator
X - See Section 8

HCS (Hazardous Communication System) (OHSA, U.S.A.)

HCS CLASS: May cause cancer.

DOT (Department of Transportation) (U.S.A) (Pictograms)

Not a DOT controlled material (United States).

EU Classification and Labelling

R36/37/38- Irritating to eyes, respiratory system and skin. R33- Danger of cumulative effects. R45- May cause cancer. R47- May cause birth defects. S53- Avoid exposure - obtain special insturction before use.

ADR (European Agreement of Dangerous goods by Road) (Pictograms)

Not controlled under ADR (Europe).

Other Regulations

This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations (CPR) and the MSDS contains all of the information required by the CPR.

Section 16. Other Information

References

HSBD & RTECS Database
The Merck Index
PDR Electronic Library

MSDS:

U.S. Pharmacopeia

Validation date: (year.month)

October 28, 2005

Revision date: 7/4/2012.

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Notice to Reader