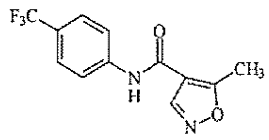
APOTEX INC.

Workplace Material Safety Data Sheet

NFPA

Canadian Classifications			
WHMIS	Apotex Haz. Class	Protective Clothing	TDG Air/Road/Rail
Covered by Food & Drug Act and therefore not regulated under WHMIS	2	< 1kg >1kg	

Section 1. Product Identification and Uses

Common/Trade name	**Leflunomide**	CI#	Not available.
Synonyms	Arava; 5-Methyl-N-(4-(trifluoromethyl)phenyl)-4-isoxazolecarbc 5-Methylisoxazole-4-carboxylic acid (4-trifluoromethyl)anilide;	DSL#	Not on the DSL list.
Chemical name	4-Isoxazolecarboxamide, 5-methyl-N-(4-(trifluoromethyl)phenyl)-	CAS#	75706-12-6
Chemical formula	$C_{12}H_9F_3N_2O_2$	Code	202328
Chemical family	Isoxazole derivative	Molecular weight	270.21 g/mole
Supplier	Hetero Drugs Limited S.No.s, 213, 214 & 255, Bontnapally Village, Jinnaram Mandal, Medak District Andhra Pradesh, India	Chemical structure	
Material uses	Pharmaceutical active ingredient. Therapeutic category: Immunosuppressant; anti-inflammatory; antirheumatic	Manufacturer	Not available
Emergency phone	**(416)-749-9300** ext. 5555 For general information call ext. 8483 (8 AM-4 PM)	DIN	Not applicable.

Section 2. Hazards Identification

Potential Acute Health Effects

Eye, skin, gastrointestinal and/or respiratory tract irritation.

Potential Chronic Health Effects

Possible hypersensitization.

WHMIS

CLASS D-1B: Material causing immediate and serious toxic effects (TOXIC).
CLASS D-2A: Material causing other toxic effects (VERY TOXIC).

Remark

Covered by Food & Drug Act and therefore not regulated under WHMIS

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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 immediate medical attention if irritation persists.
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	Flush out mouth with 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. Do not induce vomiting. If breathing has stopped, trained personnel should begin artificial respiration, or if the heart has stopped, cardiopulmonary resuscitation (CPR) immediately. Seek medical attention. Treatment of overdose should be symptomatic and supportive and may include the following: 1. Administer activated charcoal as a slurry. 2. Perform gastric lavage soon after ingestion. Protect airway by placement in Trendelenburg and left lateral decubitus position or by endotracheal intubation. Control any seizures first. 3. Monitor vital signs regularly. 4. For mild/moderate asymptomatic hypertension (no end organ damage), treatment is generally not necessary. For agitated patients with hypertension and tachycardia, sedate with benzodiazepines. For severe hypertension, administer nitroprusside. Labetalol, nitroglycerin, and phentolamine are alternatives. 5. The main active metabolite of leflunomide, M1, is not dialyzable. (Meditext 2007)

Section 4. Hazardous Ingredients

Name	CAS #	% (w/w)
Leflunomide	75706-12-6	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	These products are carbon oxides (CO, CO2), nitrogen oxides (NO, NO2...), halogenated compounds, hydrogen fluoride.
Flash points	Not applicable.
Flammable limits	Not applicable.
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.

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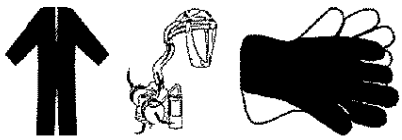
Risks of explosion	Risks of explosion of the product in presence of mechanical impact: No. Risks of explosion of the product in presence of static discharge: Fine airborne dust can be ignited by static discharge.
	Remark No additional remark.

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

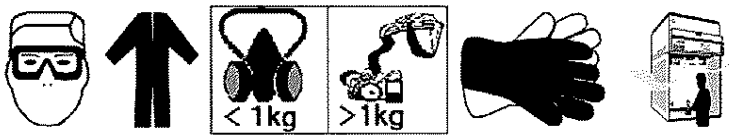
Protective clothing in case of large spill	Hooded Full suit -Tyvek coveralls or equivalent. Powered Air Purifying Respirator with combination particulate/organic vapour cartridge. Gloves.



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). Rubber 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.

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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: Safety goggles.
SKIN PROTECTION:
Impervious gloves (eg. natural or butyl rubber, nitrile, neoprene or PVC). Apotex standards require that all latex gloves should be medical grade hypoallergenic gloves. For those who have Type I hypersensitive reaction to latex, nitrile gloves are recommended. Hooded full impervious suit and boots (eg. Shield 2 or Tyvek brands and/or equivalent resistant protective clothing). Have a safety shower/eye-wash fountain readily available in the immediate work area.
RESISTANCE OF MATERIALS FOR PROTECTIVE CLOTHING:
Guidelines : GOOD: Natural, butyl or styrene-butadiene rubber (SBR), neoprene, nitrile, polyvinyl chloride (PVC), polyurethane, nitrile+PVC, neoprene+SBR, neoprene+natural rubber, SBR/neoprene NOTE: Resistance of specific materials can vary from product to product. Evaluate resistance under conditions of use and maintain clothing carefully.
EXPOSURE CONTROLS/PERSONAL PROTECTION COMMENTS:
Remove contaminated clothing promptly. Launder before rewearing. 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 housekeeping.

Section 9. Physical and Chemical Properties

Physical state and appearance	Solid. (Powder.)	Odor	Odorless.
pH	Not available.	Taste	Not available.
Odor threshold	Not available.	Color	White.
Volatility	Not applicable.		
Melting point/ Freezing point	163° - 168°C		
Boiling point	Decomposes.		
Specific gravity	Not available.		
Vapor density	Not available.		
Vapor pressure	Not available.		
Partition Coefficient:	n-octanol/water: 2.43		
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 ethanol, in diethyl ether, in chloroform, in methanol, in isopropanol, and in ethyl acetate.		

Section 10. Stability and Reactivity

Stability	Normally stable.
Hazardous decomp. products	When heated to decomposition material emits toxic fumes o NOx and HF. Emits toxic fumes under fire conditions.
Degradability	Not available.
Corrosivity	Not available.

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	Remark No additional remark.
Reactivity/ Incompatibility	Strong oxidizing agents. Avoid exposure to light and heat.
	Remark No additional remark.

Section 11. Toxicological Information

Routes of entry	Ingestion. Eye contact. Skin contact. Inhalation
Toxicity data	RTECS#: NY2354200 LD50: 235 mg/kg (oral-rat) LD50: 445 mg/kg (oral-mouse)
	Remark No additional remark.
Long-term effects	Possible hypersensitization. Carcinogenicity: Not listed by IARC, NTP, ACGIH, or OSHA. The risk of malignancy, especially lymphoproliferative disorders, is increased with use of some immunosuppression, though no apparent increase in the incidence of malignancies or lymphoproliferative disorders were reported in clinical trials. There was no evidence of carcinogenicity in a 2-year study in rats given oral leflunomide at doses up to 6 mg/kg. Male mice administered 15 mg/kg for two years exhibited an increased incidence of lymphoma, and female mice, in the same study, exhibited a dose-related increased incidence of bronchoalveolar adenomas and carcinomas combined beginning at 1.5 mg/kg. Reproductive Toxicity: Leflunomide had no effect on fertility in either male or female rats at oral doses up to 4.0 mg/kg (approximately 1/30 the human M1 exposure based on AUC). Teratogenicity: Pregnancy Category X. Leflunomide has caused death, growth retardation, and malformations in rats and rabbits. The no-effect level for both species was 1 mg/kg. Therapeutic use of leflunomide is considered contraindicated in pregnancy. In a study of leflunomide-exposed pregnancies, out of 63 pregnancies there were six miscarriages (9.7 %). Of the 54 reported live births, two babies were born with structural defects (3.7%) and two with microcephaly (3.7%). The rate of babies with structural defects in a disease-matched comparison group was 4.2% and in a non-diseased comparison group was 3.7%. In 14 reported live births from another leflunomaide-exposed group, there were no structural defects and one report of hearing loss in the infants. (Organization of Teratology Information Specialists, 2006). Mutagenicity: Leflunomide was not mutagenic in the Ames test, the unscheduled DNA synthesis assay, or in the HGPRT gene mutation assay. A minor metabolite of leflunomide, 4-trifluoromethylamine (TFMA), was mutagenic in the Ames test and the HGPRT gene mutation assay. There was no evidence of clastogenicity with leflunomide or TFMA in the in vivo mouse micronucleus assay or in the cytogenic test in Chinese hamster bone marrow cells. There was no evidence of clastogenic activity with TFMA in the in vitro assay for chromosome aberration in the Chinese hamster cells.
	Remark Medical conditions aggravated by exposure: Hypersensitivity to material, bone marrow dysplasia, severe immunodeficiency, severe or uncontrolled infections, impaired liver or kidney function including hepatitis B or C, and history of blood abnormalities.
Short-term effects and Signs & Symptoms of overexposure	Eye, skin, gastrointestinal and/or respiratory tract irritation. The recommended adult oral dose of Leflunomide is 10 to 20 mg/day. Adverse effects may include congestion; difficulty breathing; loss of appetite; nausea or vomiting; yellow eyes or skin; dizziness; headache; cough; fever; sneezing; sore throat; bloody or cloudy urine; difficult, burning, or painful urination; frequent urge to urinate; unusual tiredness or weakness; chest pain; stomach or abdominal pain; indigestion; fast or pounding heartbeat; burning, prickling, or tingling sensations in fingers and/or toes; joint or muscle pain; hair loss; back pain; heartburn; skin rash; red or irritated eyes; dry mouth; itching skin, and runny nose. Possible allergic reaction to material if inhaled, ingested or in contact with skin.
	Remark The above adverse effects are based on clinical studies.

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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

CLASS 6.1: Toxic material.

UN	Shipping name: Toxic solid, organic, n.o.s (Leflunomide) UN: 2811 PG: III
Special Provisions for Transport	Not applicable.

Section 15. Other Regulatory Information and Pictograms

USA Classifications

NATIONAL FIRE PROTECTION ASSOCIATION (NFPA) HAZARD INDEX

NFPA-HEALTH-blue :2-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.)

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

Health Hazard	* 2
Fire Hazard	1
Reactivity	0
Personal Protection	X

* - Chronic hazard indicator
X - See Section 8

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

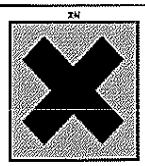
HCS CLASS: Harmful.

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

CLASS 6.1: Poisonous material.

European Classifications

DSCL (Dangerous Substances Classifications) (Europe) (Pictograms)



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DSCL Risk (R) and Safety (S) Phrases	R22- Harmful if ingested. R63- Possible risk of harm to the unborn child. R48- Danger of serious damage to health by prolonged exposure. R36/37/38- Irritating to eyes, respiratory system and skin. (Apotex) S36/37/39- Wear suitable protective clothing, gloves and eye/face protection.
ADR (European Agreement of Dangerous goods by Road) (Pictograms)	CLASS 6.1: Toxic substance. 
Other Regulations	Not available.

Section 16. Other Information

References The Merck Index
HSBD & RTECS Database
PDR Electronic Library

MSDS: **Validation date: (year.month)**

United States Pharmacopeial Convention, Inc. 04/20/2007
12601 Twinbrook Parkway
Rockville, MD 20852 USA
(301) 881-0666

Other Special Considerations SAMPLING AND ANALYSIS :
Use appropriate instrumentation and sampling strategy (location, timing, duration, frequency, and number of samples). Interpretation of the sampling results is related to these variables and the analytical method.

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