


Material Safety Data Sheet

Section 1. Product Identification and Uses

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|--------------------------|--|---------------------------|---|
| Common/Trade name | Leflunomide Tablets | DSL# | Not on the DSL list. |
| Synonyms | Brand Name: Arava | CAS# | Mixture. |
| Chemical name | Not applicable. | Molecular weight | Not applicable. |
| Chemical family | Isoxazole derivative | Chemical formula | Not applicable. |
| Supplier | Apotex Corp. Weston, Florida 33326 | Chemical structure | Not applicable. |
| Material uses | Pharmaceutical industry: Dosage form Therapeutic category: Immunosuppressant; anti-inflammatory; antirheumatic | Manufacturer | Apotex Inc. 150 Signet Drive Weston, Ontario M9L 1T9 416-749-9300 |
| Emergency phone | (416)-749-9300 ext. 5555 For general information call ext. 8483 (8 AM-4 PM) | DIN | Not available. |

Section 2. Hazards Identification

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| Potential Acute Health Effects | Not expected to be hazardous under normal handling conditions. |
| Potential Chronic Health Effects | Possible hypersensitization. |
| WHMIS | Class D-2A: Material causing other toxic effects (Very toxic). |
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| Remark | Covered by Food & Drug Act and therefore not regulated under WHMIS |
| Apotex Hazard Classification (For Apotex internal practices only) | This material has been assigned hazard class: 2 |

Section 3. First Aid Measures

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| Eye contact | Flush with copious quantities of water. If irritation persists, obtain medical advice. |
| Skin contact | Not expected to result in hazardous effects. |
| Hazardous skin contact | Flush with copious amounts of water. Seek medical attention if irritation persist. |
| Slight inhalation | Not expected to result in hazardous effects. |
| Hazardous inhalation | Remove from exposure. Persons developing serious hypersensitivity reactions must receive immediate medical attention. If not breathing give artificial respiration (use protective mask with one-way valve). If breathing is difficult give oxygen. |
| Slight ingestion | Flush out mouth with water. Seek medical attention if irritation persists. |

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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 | 10 - 30 |
| Crospovidone | 9003-39-8 | 30 - 50 |

Toxicity values of the hazardous ingredients

Refer to Sec. 11.

TLV Not established.

Section 5. Fire Fighting Measures

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| The product is: | May be combustible at high temperature. |
| 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.), halogenated compounds, hydrogen fluoride. |
| Flash points | Not available. |
| 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 | Not available. |
| | 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: Not available. |
| | 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 Full facepiece Air Purifying Respirator with particulate cartridge P100 (HEPA). Gloves. Covering uniform.



Section 7. Handling and Storage

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| Precautions | In case of insufficient ventilation, wear suitable respiratory equipment. Avoid breathing dust. Wash thoroughly after handling. Women with childbearing potential should avoid exposure to this product. |
| Storage | Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F). Protect from light. |

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 When handling small quantity of the product with adequate ventilation, gloves are sufficient. Where a packaging process involves limited containment of open product, a half facepiece Air Purifying Respirator with combination particulate/organic vapour cartridges, covering uniform and safety glasses are required.
PREGNANCY PRECAUTION:
Women with childbearing potential should avoid exposure to this product unless:
 True Barrier Technology or appropriate engineering controls exists or PPE as specified.

Protective Clothing (Pictograms)



PERSONAL PROTECTIVE EQUIPMENT/RESPIRATORY PROTECTION GUIDELINES: Respiratory protection may not be required in areas where a high degree of process containment exists.

The respirator use limitations specified by the approving agency and the manufacturer must be observed. Refer to the CSA Standard Z94, "Selection, Care, and Use of Respirators". Have appropriate equipment available for use in emergencies such as spills or fire.

EYE/FACE PROTECTION : Safety glasses when working in dusty area.

SKIN PROTECTION : The use of nitrile gloves is required for Good Manufacturing Practices (GMP) compliance.

RESISTANCE OF MATERIALS FOR PROTECTIVE CLOTHING :

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: 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 housekeeping.

Section 9. Physical and Chemical Properties

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| Physical state and appearance | 10 mg: white, round, tablets engraved "LE" over "10" on one side and engraved "APO" on the other. 20 mg: white, triangular-shaped tablets engraved "LE" over "20" on one side and engraved "APO" on the other. | |
| pH | Not available. | Taste Not available. |
| Odor threshold | Not available. | Odor Not available. |
| Volatility | Not available. | |
| Melting point/Freezing point | Not available. | |
| Boiling point | Not available. | |
| Specific gravity | Not available. | |
| Vapor density | Not available. | |
| Vapor pressure | Not available. | |
| Partition Coefficient: | Not available. | |
| Ionicity (surface active agent) | Not available. | |
| Critical temperature | Not available. | |

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| Instability temperature | Not available. |
| Conditions of instability | No additional remark. |
| Dispersion properties | See solubility. |
| Evaporation rate | Not available. |
| Solubility | Not available. |

Section 10. Stability and Reactivity

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| Stability | Normally stable. |
| Hazardous decomp. products | Decomposition products may include the following materials: halogenated compounds, hydrogen fluoride. |
| Degradability | Not available. |
| Corrosivity | Not available. |
| | Remark No additional remark. |
| Reactivity/Incompatibility | Protect from light. |
| | Remark No additional remark. |

Section 11. Toxicological Information

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| Routes of entry | As the product is a solid dosage form, the major route of entry is ingestion. Other routes of entry, including inhalation, skin and eye contact may occur only under certain circumstances. |
| Toxicity data | Leflunomide: RTECS#: NY2354200 LD50: 235 mg/kg (oral-rat) LD50: 445 mg/kg (oral-mouse) |
| Long-term effects | <p>Possible hypersensitization.</p> <p>Carcinogenicity: Not listed by IARC, NTP, ACGIH, or OSHA.</p> <p>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.</p> <p>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).</p> <p>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 leflunomide-exposed group, there were no structural defects and one report of hearing loss in the infants. (Organization of Teratology Information Specialists, 2006).</p> <p>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.</p> |
| | 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

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.

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.

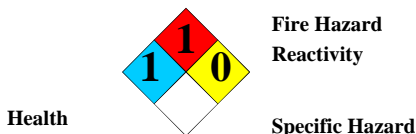
Special Provisions for Transport Not applicable.

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.)



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

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

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

Not an HCS controlled material in USA.

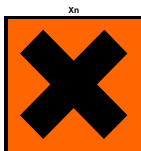
* - Chronic hazard indicator
 X - See Section 8

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

Not a DOT controlled material (United States).

EU Classification and Labelling

Exempt from requirements of EU Dangerous Preparations directive - product regulated as a medicinal product, cosmetic product or medical device. R63- Possible risk of harm to the unborn child. R40-Limited evidence of a carcinogenic effect. R48- Danger of serious damage to health by prolonged exposure.



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**The Merck Index
HSBD & RTECS Database
PDR Electronic Library**MSDS:**

U. S. Pharmacopeia

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(year.month)

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