1. Product and Company Identification

PRODUCT NAME: Leflunomide Tablets, 10 mg, 20 mg

Supplier:
Winthrop U.S.
A business of Sanofi U.S.
55 Corporate Drive
Bridgewater, NJ 08807

24-Hour Transport Emergency, US (Chemtrec):	**(800) 424-9300**
24-Hour Transport Emergency, outside US (Chemtrec):	**(703) 527-3887**
US Customer Service	**(800) 207-8049**
24-Hour Emergency, sanofi-aventis US:	**(908) 981-5550**

Product use: Pharmaceutical product.

2. Hazards Identification

2.1 Classification in accordance with 29 CFR 1910.1200

Classification of the finished drug product is not required according to OSHA 29 CFR 1910.1200. The following information is provided for the drug substance, leflunomide:

Classification:
Acute toxicity, Category 3
Reproductive toxicity, Category 1B

2.2 Label elements in accordance with 29 CFR 1910.1200

Labeling of the finished drug product is not required according to OSHA 29 CFR 1910.1200. The following information is provided for the drug substance, leflunomide:

Signal Word: Danger

Hazard Statement(s): Toxic if swallowed. May damage the unborn child.

Symbol(s): Skull and crossbones; Health hazard

Precautionary Statement(s):

- Prevention: Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Wear protective gloves. Wash hands thoroughly after handling. Do not eat. Drink or smoke when using this product.

- Response: If swallowed: Immediately call a poison center. Rinse mouth. If exposed or concerned: Get medical advice.

- Storage: Store locked up.

- Disposal: Dispose of in accordance with applicable regional, national and local laws and regulations.

2.3 Hazards Not Otherwise Classified (HNOC)

Not classified.

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3. Composition/Information on Ingredients

Chemical Name:	**Common Name:**	**CAS #:**	**Percentage or concentration range**
N-(4-Trifluoromethylphenyl)-5-methyl-isoxazol-4-carbonamide	Leflunomide	75706-12-6	10 or 20 mg per tablet

Inactive Ingredients: Colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, starch, talc, titanium dioxide, and yellow ferric oxide (20 mg tablet only).

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4. First Aid Measures

4.1 First aid procedures

Eye contact: In case of contact with dust from broken tablets or capsules, immediately flush eyes with plenty of water for at least 15 minutes. If easy to do, remove contact lenses if worn. Get medical attention.

Skin contact: In case of contact with broken tablets or capsules, immediately flush skin with plenty of water. Remove contaminated clothing and shoes. Get medical attention if irritation develops and persists.

Ingestion: If swallowed: Immediately call a poison center. Rinse mouth. Do NOT induce vomiting unless directed to do so by a physician. Never give anything by mouth to an unconscious person.

Inhalation: If dust from broken tablets or capsules is inhaled, remove to fresh air. If breathing is difficult, trained personnel should give oxygen. Get medical attention.

4.2 Most important symptoms and effects, both acute and delayed

Fetal harm. Hepatotoxicity. Elevated liver enzymes (ALT and AST), alopecia and rash.

4.3 Indication of any immediate medical attention and special treatment needed

Treat symptomatically and supportively.

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5. Fire Fighting Measures

5.1 Extinguishing media

Suitable extinguishing media: All means: water, carbon dioxide, foam or dry chemical.

Unsuitable extinguishing media: Strong water jet.

5.2 Specific hazards arising from the chemical

Hazardous combustion products: Carbon monoxide, carbon dioxide, oxides of nitrogen.

5.3 Special Protective Equipment and Precautions for Fire-fighters

In case of fire, use full firefighting turnout (bunker) gear and self-contained breathing apparatus (SCBA). Keep personnel upwind and away from fire. Move container from fire area if you can do it without risk. Do not scatter spilled material with high-pressure water streams. Dike fire-control water for later disposal.

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6. Accidental Release Measures

6.1 Personal precautions and Protective Equipment:

Eye protection, respiratory protective equipment, and suitable protective clothing should be worn if significant dust emissions are generated from broken or crushed tablets or capsules.

6.2 Emergency Procedures:

Follow local workplace procedures. Prevent the product from entering the environment. Avoid discharges to sewers, drains, waterways, or onto the ground.

6.3 Methods for containment:

Vacuum or scoop up, moisten any dust with water before collection with a shovel or broom.

6.4 Methods for clean-up:

Place material in suitable container for disposal. Wash the floor with plenty of water, absorb or retain the cleaning water for disposal.

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7. Handling and Storage

7.1 Precautions for Safe Handling

Use with adequate ventilation. Avoid breathing dust if tablets are crushed or spilled. Do not get dust in eyes or on skin. Wash thoroughly after handling.

7.2 Conditions for Safe Storage

Keep container tightly closed. Protect from light. Store in a cool, well-ventilated area.

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8. Exposure Controls/Personal Protection

8.1 Exposure Limits

Sanofi occupational exposure limit, leflunomide: 0.005 mg/m^3, 8-hour TWA.

8.2 Appropriate Engineering Controls

Provide adequate ventilation. No other specific controls are needed under normal handling conditions. If the integrity of the tablets is compromised (cutting, crushing, or unintended

breakage), then handling within a ventilated control device is recommended. If handled outside of a ventilated control device, appropriate respiratory protection should be used.

8.3 Individual Protection Measures

Eye/face protection: None normally required. Safety glasses or safety goggles should be worn if there is a potential for dust exposure from broken or crushed tablets.

Skin protection: Suitable protective gloves should be worn for routine handling. If the integrity of the tablets is compromised (cutting, crushing, or unintended breakage), then double gloves are recommended.

Respiratory protection: None normally required. If the integrity of the tablets is compromised (cutting, crushing, or unintended breakage), then handling within a ventilated control device is recommended. If handled outside of a ventilated control device, appropriate approved respiratory protection should be used.

General hygiene considerations: Suitable work clothes. If the integrity of the tablets is compromised (cutting, crushing, or unintended breakage), then a protective gown is recommended. Wash hands before breaks and at the end of the work shift.

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9. Physical and Chemical Properties

Appearance: White or yellow solid tablets.
Odor: No data available.
Odor threshold: No data available.
pH: No data available.
Melting point/ Freezing point: Not applicable.
Initial boiling point/boiling point range: Not applicable.
Flash point: Not applicable.
Evaporation rate: Not applicable.
Flammability: No data available.
Upper/lower flammability or explosive limits: No data available.
Vapor pressure: Not applicable.
Vapor density: Not applicable.
Relative density: No data available.
Solubility: No data available.
Partition coefficient: n-octanol/water (leflunomide): Log Kow = 2.43 (calculated)
Auto-ignition temperature: No data available.
Decomposition temperature: No data available.
Viscosity: No data available.

10. Stability and Reactivity

10.1 Reactivity

Not a reactive material under normal handling conditions.

10.2 Chemical Stability

Stable under normal handling conditions.

10.3 Possibility of hazardous reactions

None known.

10.4 Conditions to Avoid

Keep away from heat, sparks and flames.

10.5 Incompatible materials

Strong oxidizing and reducing agents.

10.6 Hazardous decomposition products

Carbon monoxide, carbon dioxide, oxides of nitrogen.

11. Toxicological Information

The following information is for the active ingredient leflunomide unless otherwise noted:

Information on likely routes of exposure: Exposure not expected under normal use. Dust from broken or crushed tablets could result in exposure to eyes, skin and respiratory tract.

Symptoms related to the physical, chemical and toxicological characteristics: Elevated liver enzymes (ALT and AST), alopecia and rash.

Effects of short-term (acute) exposure: Elevated liver enzymes (ALT and AST), alopecia and rash.

Effects of long-term (chronic) exposure: Hepatotoxicity. May cause fetal harm.

Acute toxicity (LD50):
Oral route, rat: 100 – 250 mg/kg.
Oral route, mouse: 250 – 500 mg/kg.

Skin corrosion/irritation: Non-irritant. Method: OECD 404.

Serious eye damage/irritation: Slight irritant effect - does not require labeling.

Sensitization: Non-sensitizing.

Specific target organ toxicity – single exposure (STOT-SE): No data.

Specific target organ toxicity – repeated exposure (STOT-RE): Liver.

Carcinogenicity: No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of leflunomide up to the maximally tolerated dose of 6 mg /kg.

Not listed by NTP, not found to be a potential carcinogen by IARC or OSHA.

Titanium dioxide has been classified by IARC as 2B: Possibly carcinogenic to humans. Tumors were observed at high dose in animal studies by inhalation and intratracheal administration. Tumors were not observed by other routes.

Reproductive toxicity and teratogenicity: Can cause fetal harm when administered to a pregnant woman. Leflunomide, when administered orally to rats during organogenesis at a dose of 15 mg/kg, was teratogenic. The systemic exposure of rats at this dose was approximately 1/10 the human exposure level based on AUC. Under these exposure conditions, leflunomide also caused a decrease in the maternal body weight and an increase in embryolethality with a decrease in fetal body weight for surviving fetuses. In rabbits, oral treatment with 10 mg /kg of leflunomide during organogenesis resulted in fused, dysplastic sternebrae. The expo sure level at this dose was essentially equivalent to the maximum human expo sure level based on AUC. At a 1 mg /kg dose, leflunomide was not teratogenic in rats and rabbits.

Mutagenicity: Leflunomide was not mutagenic in the Ames Assay, the Unscheduled DNA Synthesis Assay, or in the HGPRT Gene Mutation Assay. In addition, leflunomide was not clastogenic in the in vivo Mouse Micronucleus Assay or in the in vivo Cytogenetic Test in Chinese Hamster Bone Marrow Cells.

Aspiration hazard: Not applicable.

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12. Ecological Information

The following information is for the active ingredient leflunomide unless otherwise noted:

12.1. Ecotoxicity

Fish toxicity (LC50): 3.74 mg/l
Species: zebra fish
Exposure duration: 48 h
Method: OECD 203

Fish toxicity (LC50): 2.64 mg/l
Species: zebra fish
Exposure duration: 96 h
Method: OECD 203

Chronic aquatic toxicity: not determined.

Toxicity on invertebrates (EC50): 17 mg/l
Species: Daphnia magna
Exposure duration: 48 h

Toxicity on invertebrates (Chronic toxicity): not determined.

Algae toxicity (EC50): 22.42 mg/l
Species: Desmodesmus subspicatus
Exposure duration: 72 h
Endpoint: Growth rate
Method: OECD 201

Algae toxicity (NOEC): 6.25 mg/l
Species: Desmodesmus subspicatus
Exposure duration: 72 h
Endpoint: Growth rate
Method: OECD 201

Bacteria toxicity (EC50): > 1,000 mg/l
Species: Activated sludge.
Exposure duration: 3 h
Method: OECD 209

12.2. Persistence and degradability

Biological degradability : < 20 %; Not readily biodegradable.
Testing period: 28 day
Method of analysis: CO2 formation in % of theoretical value
Method: modified Sturm test

12.3. Bioaccumulative potential

Unlikely to be bioaccumulable in living organisms (Log Kow < 4).

12.4 Mobility in soil

No data available.

12.5 Other adverse effects

No data available.

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13. Disposal Considerations

13.1 Disposal of product waste

Disposal should be in accordance with applicable regional, national and local laws and regulations. Local regulations may be more stringent than regional or national requirements.

13.2 Disposal of packaging waste

Dispose of in a safe manner in accordance with federal, state and local environmental regulations. Empty packages, containers or liners may contain product residue.

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14. Transport Information

14.1 Basic shipping information, finished product

U.S. DOT	Not a regulated material.
ICAO/IATA	Not a regulated material.
IMDG	Not a regulated material.

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15. Regulatory Information

US Regulations

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

Clean Water Act Section 311 Hazardous Substances (40 CFR 117.3): Not listed.

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

SARA Title III:

Section 302 Extremely Hazardous Substance (40 CFR 355, Appendix A): Not listed.

Section 313 Toxic Release Inventory (40 CFR 372): Not listed.

State Regulations

California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65): Titanium dioxide (airborne, unbound particles of respirable size).

Massachusetts Right-To-Know List: Titanium dioxide.
New Jersey Right-To-Know List: Titanium dioxide.
Pennsylvania Right-To-Know List: Titanium dioxide.

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16. Other Information

Leflunomide is included in in the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016.

Other Information: The information contained herein is based upon data considered true and accurate. Winthrop U.S. makes no warranties, express or implied, as to the adequacy of the information contained herein. This information is offered solely for the user's consideration, investigation and verification. Report to the manufacturer any allegations of health effects resulting from handling or accidental contact with this material.

Abbreviations and Acronyms
CAS: Chemical Abstracts Service
DOT: U.S. Department of Transportation
EST: Eastern standard time (U.S.)
IATA: International Air Transport Association
IMDG: International Maritime Dangerous Goods Code
LC50: Lethal concentration, 50%
LD50: Lethal dose, 50%
OEL: Occupational Exposure Limit
PPE: Personal Protection Equipment
SDS: Safety Data Sheet
STEL: Short-term exposure limit
TWA: Time-weighted average

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