



SAFETY DATA SHEET

1. IDENTIFICATION

Product identifier: Ixazomib Citrate

Compound Number/ : ML00701203; MLN9708

Synonyms

Recommended use: Active Pharmaceutical Ingredient

Restrictions on use: All other uses

Manufacturer: Takeda Pharmaceuticals International Company

Address: 40 Landsdowne Street
Cambridge, MA 02139

Telephone number: 617-679-7000

Emergency phone number: For Chemical Emergency

- o Spill, Leak, Fire, Exposure, or Accident
- o Call CHEMTREC Day or Night
- o Within USA and Canada: 1-800-424-9300
- o Outside USA and Canada: +1 703-527-3887 (collect calls accepted)

2. HAZARD(S) IDENTIFICATION

GHS Hazard Classification:

Physical	Health	Environment
Combustible Dust	Acute Oral Toxicity Category 1 (H300) Skin Irritation Category 2 (H315) Eye Irritation Category 2A (H319) Reproductive Toxicity Category 2 (H361) Specific Target Organ Toxicity Repeat Dose Category 1 (H372)	Not Hazardous

Label Elements:

Signal Word: DANGER

Pictograms:



Hazard Statements:

May form combustible dust concentrations in air.

H300 Fatal if swallowed.

H315 Causes skin irritation.

H319 Causes serious eye irritation.

H361 Suspected of damaging fertility or the unborn child.

H372 Causes damage to lymphoid tissue, bone marrow, gastrointestinal tract and nervous system through prolonged or repeated exposure.

Precautionary Statements:

P201 Obtain special instructions before use.

P202 Do not handle until all safety precautions have been read and understood.

P260 Do not breathe dust

P264 Wash exposed skin thoroughly after handling.

P270 Do not eat, drink or smoke when using this product.

P280 Wear protective gloves, protective clothing and eye protection.

P301 + P310 IF SWALLOWED: Immediately call a POISON CENTER or doctor.

P330 Rinse mouth.

P302 + P352 IF ON SKIN: Wash with plenty of soap and water.

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P332 + P313 If skin irritation occurs: Get medical attention.

P362 + P364 Take off contaminated clothing and wash it before reuse.

P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

P337 + P313 If eye irritation persists: Get medical attention.

P308 + P313 IF exposed or concerned: Get medical advice/attention.

P405 Store locked up.

P501 Dispose of contents and container in accordance with local and national regulations.

3. COMPOSITION / INFORMATION ON INGREDIENTS

Chemical name	CAS No.	Concentration
Ixazomib Citrate	1239908-20-3	>99%

4. FIRST-AID MEASURES

Inhalation: If product is inhaled, move to fresh air and seek immediate medical attention. If breathing is difficult, have qualified person administer oxygen.

Skin contact: Wash hands thoroughly with soap and water. Seek medical attention if irritation or other symptoms develop.

Eye contact: In case of contact with eyes, flush with water for at least 15 minutes while holding eyelids open. Seek medical attention if irritation develops.

Ingestion: If swallowed, rinse mouth with water and seek immediate medical attention. Never give anything by mouth to anyone who is unconscious or not alert.

Most important symptoms/effects, acute and delayed: Fatal if swallowed. Severe eye and skin irritant. May cause adverse effects on reproduction, lymphoid tissue, bone marrow, gastrointestinal tract and nervous system based on animal studies.

Indication of immediate medical attention and special treatment, if necessary: Seek immediate medical attention if swallowed or inhaled. If skin or eye irritation develop, seek medical attention.

5. FIRE-FIGHTING MEASURES

Suitable (and unsuitable) extinguishing media: Use water spray, carbon dioxide, dry chemical or foam to extinguish a fire. Do not use straight water stream as this may raise a dust cloud.

Specific hazards arising from the chemical: Airborne dust may present a potential fire and explosion hazard if suspended in air at high concentrations. Settled dust presents a fire hazard. Resuspension of the dust into the air by vibration, traffic, material handling, etc. in high concentrations in the presence of an ignition source could result in a dust explosion. Minimize the generation and accumulation of dust. Combustion will generate oxides of carbon, boron, and nitrogen and hydrogen chloride.

Special protective equipment and precautions for fire-fighters: Firefighters should wear positive pressure self-contained breathing apparatus and full protective clothing for all fires involving chemicals. Cool fire exposed containers with water.

6. ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment, and emergency procedures: Evacuate the area in accordance with your internal procedures. Wear appropriate eye protection, protective gloves, clothing and respiratory protection (see Section 8). If dust is present, eliminate all ignition sources.

Environmental precautions: Avoid release to the environment. Notify authorities of releases as required by local and federal regulations.

Methods and materials for containment and cleaning up: Carefully collect in a manner to minimize the generation of airborne dusts or vacuum with a high efficiency vacuum cleaner. If a vacuum is used, explosion proof equipment is required. Nonsparking tools should be used. Treat surface with a standard 5% bleach or 30% hydrogen peroxide solution with a one hour contact time. After one hour, rinse the area with water, add sorbent material, and clean up residue with a HEPA vacuum. Place in a suitable, closed container for disposal. Clean the spill area thoroughly.

Dust deposits should not be allowed to accumulate on surfaces, as these may form an explosive mixture if they are released into the atmosphere in sufficient concentrations. Avoid dispersal of dust in the air (i.e., clearing dust surfaces with compressed air.)

7. HANDLING AND STORAGE

Precautions for safe handling: Ixazomib Citrate API is an anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling Ixazomib Citrate. Please refer to published guidelines regarding the proper handling and disposal of anticancer agents. Prevent contact with the eyes, skin and clothing. Do not generate airborne dust. Wash hands thoroughly with soap and water after handling. Wear suitable personal protective clothing. Minimize the generation and accumulation of dust. Keep dust away from open flames, hot surfaces and sources of ignition. Follow good housekeeping practices to keep surfaces, including areas overhead such as piping, drop ceilings, ductwork, etc. free from settled dust. Dry powders can build static electricity charges when subjected to friction of transfer and in mixing operations. Provide adequate precautions, such as electrical grounding and bonding, or inert atmospheres.

Conditions for safe storage, including any incompatibilities: Store in a secure area away from heat and sources of ignition.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Exposure guidelines:

Chemical Name	Exposure Limit/Source
Ixazomib Citrate	None Established

Appropriate engineering controls: Engineering controls should be used as the primary means to control exposures. Use local exhaust ventilation, lab hoods or other engineering controls to minimize exposures. It is recommended that all dust control equipment such as local exhaust ventilation and material transport systems involved in handling this product contain explosion relief vents or an explosion suppression system or an oxygen deficient environment. Ensure that dust handling systems (such as exhaust ducts, dust collectors, vessels and processing equipment) are designed in a manner to prevent the escape of dust into the work area (i.e., there is no leakage from the equipment). Use only appropriately classified electrical equipment and powered industrial trucks.

Protective equipment

Respiratory protection: If needed, use an approved respirator in accordance with OSHA 1910.134 and good industrial hygiene practice.

Skin protection: Wear impervious gloves if contact with the drug substance is possible.

Eye protection: Wear safety goggles if contact with the drug substance is possible.

Other: Suitable eye flushing and washing facilities should be available in the work area.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance (physical state, color, etc.): White to off-white crystalline solid

Odor: None

Odor threshold: Not established	pH: 3.1
Melting/freezing point: 220°C	Initial boiling/boiling range: Not applicable
Flash point: None	Evaporation rate: Not applicable
Flammability (solid, gas): Dust may be explosive in	

air	
Flammable limits: LEL: Not determined	UEL: Not determined
Vapor pressure: Not applicable	Vapor density: Not applicable
Relative density: Not determined	Solubility(ies): Water: 15 mg/L@ pH 7.8
Partition coefficient (n-octanol/water): 2.0	Auto-ignition temperature: Not determined
Decomposition temperature: Not determined	Viscosity: Not applicable

10. STABILITY AND REACTIVITY

Reactivity: Not reactive

Chemical stability: Stable under normal use and storage conditions. Oxidizes when in solution.

Possibility of hazardous reactions: None known

Conditions to avoid: None known.

Incompatible materials: Strong oxidizing agents.

Hazardous decomposition products: Thermal decomposition may generate oxides of carbon, boron, and nitrogen and hydrogen chloride.

11. TOXICOLOGICAL INFORMATION

Acute effects of occupational exposure:

Inhalation: Inhalation of dust may be very hazardous. Inhalation data not identified. Based on the high acute toxicity reported in non-clinical IV studies, a potential for toxicity via the inhaled route cannot be excluded. May cause irritation.

Ingestion: Very toxic if swallowed. Based on animal studies lymphoid, bone marrow, peripheral nervous system and gastrointestinal effects would be expected from ingestion of amounts over therapeutic doses.

Skin contact: Causes severe irritation.

Eye contact: Causes severe irritation.

Chronic effects of occupational exposure: May cause adverse effects on reproduction, lymphoid tissue, bone marrow, gastrointestinal tract and nervous system based on animal studies.

Known clinical effects: The most common effects observed in clinical trials were nausea, diarrhea, vomiting, constipation, anemia, fatigue, swelling, rash, dizziness and peripheral neuropathy.

Toxicity Data

Acute toxicity:

No acute studies have been conducted. However, in oral 2 and 5 cycle studies, administration of ≥ 1 mg/kg cause mortality in rats. The acute oral LD50 in rats is assumed to be < 5 mg/kg.

Irritation: Severe irritant in a dermal irritation study; presumes to be a severe eye irritant.

Repeat Dose Toxicity:

Rat, 5 cycle (BIW dosing for 2 weeks separated by a 10-day non-dosing observation period), 0.2, 0.4, or 0.6/0/8 mg/kg, oral, LOAEL = 0.2 mg/kg (target organs: lymphoid tissue, bone marrow, gastrointestinal tissues)

Dog, 5 cycle (BIW dosing for 2 weeks separated by a 10-day non-dosing observation period), 0.05, 0.1, or 0.15 mg/kg, oral, LOAEL = 0.15 mg/kg (target organs: nervous system)

Reproductive Toxicity: A study was conducted to evaluate the embryo-fetal developmental toxicity of ixazomib citrate by oral gavage QD (0, 0.1, and 0.3 mg/kg) or once every 3 days (0.4, 0.6, and 0.8 mg/kg) to rats. At a dose of 0.6 mg/kg possible embryo-fetal effects were observed that included a trend toward reduced fetal weight and viability, and a possible increase in postimplantation loss. In a second study to evaluate the embryo-fetal developmental toxicity of ixazomib citrate (0.025, 0.5, 1.0 and 1.2 mg/kg) when administered by oral gavage on GD 7, 10, 13, 16, and 19 to pregnant New Zealand white rabbits. Embryo-fetal effects were observed at 1.0 mg/kg and included postimplantation loss and reduced fetal viability.

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Germ Cell Mutagenicity: Ixazomib citrate was negative in the bacterial reverse mutation test and the bone marrow micronucleus assay in mice. Ixazomib citrate was positive in an in vitro clastogenicity test in HPBLs. It is not considered to present a genotoxic risk.

Carcinogenicity: Carcinogenicity studies have not been conducted.

Carcinogenicity Status: Ixazomib citrate is not listed as a carcinogen by IARC, NTP or OSHA

Other Toxicological Information: Ixazomib citrate API is a cytotoxic antineoplastic compound that exerts its biological effects by inhibiting the activity of the proteasome, a macromolecular complex found in all cells that plays a critical role in protein homeostasis.

12. ECOLOGICAL INFORMATION

Ecotoxicity: No data available

Persistence and degradability: No data available

Bioaccumulative potential: No data available

Mobility in soil: No data available

Other adverse effects: No data available

13. DISPOSAL CONSIDERATIONS

Dispose of as a pharmaceutical biological/medical waste according to local, state and federal guidelines.

14. TRANSPORT INFORMATION

UN number: UN2811

UN proper shipping name: Toxic solid, organic, n.o.s. (1,3,2-Dioxaborolane-4,4-diacetic acid, 2-[(1*R*)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]-5-oxo)

Transport hazard classes(es): 6.1

Packing group, if applicable: I

Environmental hazards: None

Transport in bulk (according to Annex II of MARPOL 73/78 and the IBC Code): Not applicable, transported in packaged form only.

Special precautions: None

15. REGULATORY INFORMATION

Safety, health, and environmental regulations specific for the product in question.

CERCLA: This product is not subject to CERCLA reporting. Many states have more stringent release reporting requirements. Report releases in accordance with federal, state and local regulations.

SARA Hazard Category (311/312): Acute Health, Chronic Health

SARA 313: Not applicable.

EPA TSCA Inventory: Drugs are not subject to TSCA.

CANADA:

Canadian CEPA: Drugs are not subject to CEPA.

Canadian WHMIS Classification: Drugs are not subject to WHMIS.

16. OTHER INFORMATION

SDS Revision History: Section 11 – added irritation data.

Ixazomib Citrate

Date of preparation: September 22, 2015

Date of previous revision: August 30, 2015

NOTICE

This above information is believed to be correct but does not propose to be all inclusive and shall be used only as a guide. Takeda Pharmaceuticals International Company shall not be held liable for any damage resulting from handling or from contact with the above product. This information relates only to the product designated herein and does not relate to its use in combination with any other material or process.