SAFETY DATA SHEET

1. IDENTIFICATION

Product identifier: NINLARO Capsules 2.3, 3.0, 4.0mg

Compound Number/ Synonyms: ML00701203; MLN9708; MLN2238 citrate ester; Ixazomib citrate
Ixazomib

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

2. HAZARD(S) IDENTIFICATION

GHS Hazard Classification:

Physical	Health	Environment
Not Hazardous	Acute Oral Toxicity Category 2 (H300) Reproductive Toxicity Category 2 (H361) Specific Target Organ Toxicity Repeat Dose Category 1 (H372)	Not Hazardous

Label Elements:

Signal Word: DANGER

Pictograms:

Hazard Statements:
H300 Fatal if swallowed.
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.
P301 + P310 IF SWALLOWED: Immediately call a POISON CENTER or doctor.
P330 Rinse mouth.
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	2.2-6.6%
Microcrystalline Cellulose	9004-34-6	Proprietary
Talc	14807-96-6	Proprietary
Magnesium Stearate	557-04-0	Proprietary

The exact percentage is a trade secret.

4. FIRST-AID MEASURES

Inhalation: If capsules are damaged and contents are 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 after handling. 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 unintentionally 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: No adverse effects are expected from handling intact capsules. Fatal if swallowed in amounts above therapeutic doses. 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.

Specific hazards arising from the chemical: Capsules are not a fire hazard but may burn under fire conditions.

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.

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 if capsules are damaged (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 damage to capsules (carefully scoop up). If capsules are damaged, avoid the generation of airborne dusts. Collect by scooping up intact capsules. Carefully wipe up with a damp cloth. 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.

7. HANDLING AND STORAGE

Precautions for safe handling: Ixazomib Citrate is an anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling Ixazomib Capsules. 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.

Conditions for safe storage, including any incompatibilities: Store in a secure area as directed on product packaging.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Exposure guidelines:

Chemical Name	Exposure Limit/Source
Ixazomib Citrate	None Established
Microcrystalline Cellulose	10 mg/m3 TWA ACGIH TLV 5 mg/m3 (respirable), 15 mg/m3 (total dust) OSHA PEL
Talc	2 mg/m2 (respirable) TWA ACGIH TLV 20 mppcf TWA OSHA PEL
Magnesium Stearate	10 mg/m3 TWA ACGIH TLV (as stearates)

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.

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 hard capsules
Odor: None

Odor threshold: Not established	**pH:** Not applicable
Melting/freezing point: Not established	**Initial boiling/boiling range:** Not applicable
Flash point: None	**Evaporation rate:** Not applicable
Flammability (solid, gas): Not a flammable solid	
Flammable limits: LEL: Not determined	**UEL:** Not determined
Vapor pressure: Not applicable	**Vapor density:** Not applicable
Relative density: Not determined	**Solubility(ies):** Water: Not determined
Partition coefficient (n-octanol/water): Not established	**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.
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, magnesium, boron, and nitrogen and hydrogen chloride.

11. TOXICOLOGICAL INFORMATION

Acute effects of occupational exposure:
Inhalation: Inhalation of dust from damaged capsules 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: No adverse effects expected from contact with intact skin.
Eye contact: Dust from damaged capsules may be irritating to eyes.

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 for Ixazomib Citrate
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. 0.25, 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.

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.

Toxicity Data for Excipients:
Acute toxicity:
Microcrystalline Cellulose: LD50 oral rat >5000 mg/kg
Talc: No data available – not acutely toxic.
Magnesium Stearate: LD50 oral rat >2500 mg/kg

Repeat Dose Toxicity:
Magnesium stearate was fed to rats at levels of 0, 5, 10 and 20% in a semisynthetic diet for 3 months. Effects were observed in the kidneys and liver. The no-effect-level is estimated to be 5% magnesium stearate in the diet, corresponding to 2,500 mg/kg bw/day.

Carcinogenicity Status: None of the excipients are classified as carcinogens under the GHS or listed as carcinogens by IARC, NTP or OSHA.

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

Non Regulated for Transport when shipped according to US DOT 49 CFR 173.4b De minimis exceptions and/or IATA 2.6.10 De minimis quantities.

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: New SDS.
Date of preparation: September 13. 2015
Date of previous revision: New SDS

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.