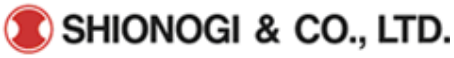
SAFETY DATA SHEET

SECTION 1 - IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/ UNDERTAKING

Contact information

General



Shionogi & Co., Ltd.
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Emergency telephone number

+1 (800) 849-9707 (toll-free; USA and Canada)
(24-hour Availability; 7 days/week)

Product identifier	Naldemedine Tosylate Tablets
Synonyms	S-297995B Tablets
Trade names	Symproic
Chemical family	Mixture. Contains an active pharmaceutical ingredient.
Relevant identified uses of the substance or mixture and uses advised against	Bulk formulated pharmaceutical mixture/Formulated pharmaceutical product/ mixture packaged in final form for patient use.
Note	This SDS is written to address potential worker health and safety issues associated with the handling of the formulated drug product.

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture	**Drugs in the finished state and intended for the final user are not subject to labeling in the US, EU or Canada.** Consult prescribing/packaging information. **The classification and labeling listed below is for bulk drug product.**
Globally Harmonized System [GHS]	Not classified

Label elements

GHS hazard pictogram	None required
GHS signal word	None required
GHS hazard statements	None required

SECTION 2 - HAZARDS IDENTIFICATION …continued

GHS precautionary statements

None required

Other hazards

Naldemedine is a peripheral opioid receptor blocker that doesn't readily cross the blood-brain barrier. It is indicated to treat opioid-induced constipation in adults. The recommended dose is 0.2 mg/day. The most common adverse effects reported in clinical trials of healthy subjects were gastrointestinal effects (abdominal pain, diarrhea, nausea, vomiting, and gastroenteritis). Symptoms consistent with opioid withdrawal were reported in some patients taking opioid pain medications. Naldemedine crosses the placenta and may be excreted in breast milk.

Note

This mixture does not meet criteria for classification under GHS as implemented by Regulation EC No 1272/2008 (EU CLP), WHMIS 2015 (Health Canada), and Hazard Communication Standard No. 1910.1200 (US OSHA). Nevertheless, it should be handled with caution as it contains an active pharmaceutical ingredient. .

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	GHS Classification
Naldemedine Tosylate	1345728-04-2	N/A	<0.2%	RT2: H361d, H362; EI2B: H319
Talc	14807-96-6	238-877-9	<2%	STOT-S3: H335
Magnesium Stearate	557-04-0	209-150-3	<1%	Not classified

Note

The ingredient(s) listed above are considered hazardous or are the active pharmaceutical ingredient. The remaining components are non-hazardous and/or present at amounts below reportable limits. Magnesium stearate and talc are included because OELs were identified. See Section 16 for full text of GHS classifications. Amounts are listed as ranges; the exact percentage of composition is withheld as a trade secret.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures

Immediate Medical Attention Needed

No. If exposed or concerned: Get medical advice/attention.

Eye Contact

If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.

Skin Contact

Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.

SECTION 4 - FIRST AID MEASURES …continued

Inhalation	Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.
Ingestion	Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.
Protection of first aid responders	See Section 8 for Exposure Controls/Personal Protection recommendations.
Most important symptoms and effects, both acute and delayed	See Sections 2 and 11.
Indication of immediate medical attention and special treatment needed, if necessary	Treat symptomatically and supportively. If accidental exposure occurs to an individual who is also taking one or more concomitant medications, consult the respective package or prescribing information for potential drug interactions.

SECTION 5 - FIREFIGHTING MEASURES

Extinguishing media	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
Specific hazards arising from the substance or mixture	No information identified. May emit carbon monoxide, carbon dioxides, oxides of nitrogen or sulphur.
Flammability/ Explosivity	No information identified.
Advice for firefighters	Wear full protective clothing and an approved, positive pressure, self-contained breathing apparatus. Wash all equipment thoroughly after use.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Do not crush, break or chip tablets.
Environmental precautions	Do not empty into drains. Avoid release to the environment.

SECTION 6 - ACCIDENTAL RELEASE MEASURES…continued

Methods and material for containment and cleaning up	If tablets are spilled, scoop up and dispose of in a manner that is compliant with federal, state or local laws. If tablets are crushed/broken, DO NOT RAISE DUST. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize entry of powder into the air. Scoop up broken pieces. Add excess liquid to allow the material to enter into solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container for disposal in accordance with applicable waste disposal regulations (see section 13). Decontaminate the area twice.
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	If tablets/capsules are crushed or broken, dust containing drug substance may be released. Minimize dust generation and accumulation.
Conditions for safe storage including any incompatibilities	Store at 15°C to 30°C. Protect from light. PE bags, silica gel, nylon foil bag, HDPE drum.
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Naldemedine Tosylate	--	--	--
Talc	ACGIH, Austria, NIOSH, Portugal, Spain	TWA-8 HR	2 mg/m³ (respirable fraction; containing no asbestos and <1% crystalline silica)
	Australia	TWA-8 HR	2.5 mg/m³ (containing no asbestos)
	Belgium, Greece, Hungary	TWA-8 HR	2 mg/m³ (respirable fraction)
	Ireland	TWA-8 HR	0.8 mg/m³ (respirable dust)
	Netherlands	TWA-8 HR	0.25 mg/m³
	Poland	TWA-8 HR	1 mg/m³ (respirable dust)
	Romania	TWA-8 HR	2 mg/m³ (total dust)
	United Kingdom	TWA-8 HR/STEL	1 mg/m³/3 mg/m³ (respirable dust)
Magnesium Stearate	ACGIH	TWA-8 HR	10 mg/m³ (stearates)
	Lithuania	TWA-8 HR	3 mg/m³

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION…continued

Control Parameters/ Occupational Exposure Limit Values …continued

Compound	Issuer	Type	OEL
	Sweden	TWA-8 HR	5 mg/m³

Exposure/Engineering controls

None required for normal handling of packaged product. If tablets are crushed or broken: Control exposures to below the OEL (if available). Otherwise, selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Use local exhaust and/or enclosure at dust-generating points. Emphasis is to be placed on closed material transfer systems and process containment, with limited open handling of powders. High-energy operations such as milling, particle sizing, spraying or fluidizing should be done within an approved emission control or containment system.

Respiratory protection

None required for normal handling of packaged product. If tablets are crushed or broken, or if handling bulk formulation: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine powder handling tasks, an approved and properly fitted air-purifying respirator with HEPA filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use a powered air-purifying respirator equipped with HEPA filters or combination filters or a positive-pressure air-supplied respirator if there is any potential for an uncontrolled release, when exposure levels are not known, or in any other circumstances where a lower level of respiratory protection may not provide adequate protection.

Hand protection

None required for normal handling of packaged product. Wear nitrile or other impervious gloves if skin contact with tablets is possible.

Skin protection

Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.

Eye/face protection

Wear safety glasses with side shields, chemical splash goggles, or full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available.

Environmental Exposure Controls

Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel.

Other protective measures

Wash hands in the event of contact with this substance, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors).

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Round, film-coated tablet
Color	Yellow
Odor	No information identified.
Odor threshold	No information identified.
pH	Not applicable
Melting point/ freezing point	No information identified.
Initial boiling point and boiling range	No information identified.
Flash point	No information identified.
Evaporation rate	No information identified.
Flammability (solid, gas)	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Vapor pressure	No information identified.
Vapor density	No information identified.
Relative density	No information identified.
Water solubility	No information identified.
Solvent solubility	No information identified.
Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.

Other information

Molecular formula	Mixture.
Molecular weight	Mixture.

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	Stable
Possibility of hazardous reactions	Not expected to occur.
Conditions to avoid	No information identified.
Incompatible materials	No information identified.
Hazardous decomposition products	No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note No data on product formulation. The following information is for the constituent ingredients.

Information on toxicological effects

Route of entry May be absorbed by inhalation, skin contact, eye contact, and ingestion.

Acute toxicity

Compound	Type	Route	Species	Dose
Naldemedine Tosylate	LD_{50}	Oral	Rat	>2000 mg/kg
Talc	--	--	--	--
Magnesium Stearate	LC_{50}	Inhalation	Rat	>2000 mg/m³

Irritation/Corrosion For naldemedine, no dermal irritation and slight eye irritation (reversible) was reported in rabbits. Additional details were not identified.

Sensitization No data available.

STOT-single exposure In rats exposed to naldemedine, decreases in body weight gain were seen at single oral doses of ≥500 mg/kg in males and 2000 mg/kg in females. In dogs, vomiting occurred after oral doses of of ≥200 mg/kg. Transient chemistry changes indicating liver effects were also noted.

STOT-repeated exposure/Repeat-dose toxicity In a 6-month oral rat study with naldemedine, a decrease in body weight gain directly associated with changes in food consumption was noted at 1000 mg/kg/day; a NOAEL of 100 mg/kg/day was identified. In a 9-month oral dog study, reversible liver effects, including slight single cell necrosis and clinical chemistry changes, were noted at 20 mg/kg/day; a NOAEL of 4 mg/kg/day was identified.

Reproductive toxicity In a rat reproductive study with naldemedine, no effects were noted in males given oral doses of up to 1000 mg/kg/day. Delayed estrous was noted in females at 10 mg/kg/day, but this effect was due to a rat-specific mechanism that is not relevant to humans.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Developmental toxicity

No malformations occurred in the offspring of female rats given oral doses of up to 1000 mg/kg/day naldemedine during pregnancy, continuing through lactation (gestation day 7 through lactation day 20). Deaths during parturition were noted at the highest dose. At doses ≥30 mg/kg/day, reductions in maternal body weight gains and food consumption were accompanied by reduced pup weights, low birth index, and pup mortality due to poor nursing. Naldemedine was excreted in the milk of lactating rats. In rabbits, spontaneous abortions or premature delivery occurred at oral doses of 400 mg/kg/day, but were accompanied by marked decreases in maternal food consumption and a reduction in fetal body weights.

Genotoxicity

Naldemedine was negative in a battery of short-term *in vitro* and *in vivo* assays for genotoxicity.

Carcinogenicity

Naldemedine was non-carcinogenic in 2-year studies in rats and mice at oral doses of up to 100 mg/kg/day. None of the other components of the mixture present at levels greater than or equal to 0.1% are listed by NTP, IARC, ACGIH or OSHA as a carcinogen.

Aspiration hazard

No data available.

Human health data

See "Section 2 - Other Hazards".

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Naldemedine Tosylate	--	--	--
Talc	--	--	--
Magnesium Stearate	--	--	--

Persistence and Degradability

No data identified.

Bioaccumulative potential

No data identified.

Mobility in soil

No data identified.

Results of PBT and vPvB assessment

Not performed.

Other adverse effects

No data identified.

Note

The environmental characteristics of this mixture have not been fully investigated. Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods	Used product should be disposed of according to local, state, and federal regulations. Do not send down the drain or flush down the toilet. All wastes containing the material should be properly labeled. Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.

SECTION 14 - TRANSPORT INFORMATION

Transport	Based on the available data, this product/mixture is not regulated as a hazardous material/dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG.
UN number	None assigned.
UN proper shipping name	None assigned.
Transport hazard classes and packing group	None assigned.
Environmental hazards	Based on the available data, this product/mixture is not regulated as an environmental hazard or a marine pollutant.
Special precautions for users	Avoid release to the environment.
Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code	Not applicable.

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS generally complies with the requirements listed under current guidelines in the US, EU and Canada. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.
TSCA status	Drugs are exempt from TSCA.
SARA section 313	Not listed
California proposition 65	Not listed.
Additional information	No other information identified.

SECTION 16 - OTHER INFORMATION

Full text of H phrases and GHS classifications	RT2 - Reproductive toxicity Category 2. H361d - Suspected of damaging the unborn child. H362 - May cause harm to breast-fed children. EI2B - Eye irritant Category 2B. H319 - Causes serious eye irritation. STOT-S3 - Specific Target Organ Toxicity Following Single Exposure Category 3. H335 - May cause respiratory irritation.
Sources of data	Information from published literature and internal company data.
Abbreviations	ACGIH - American Conference of Governmental Industrial Hygienists; ADR/RID - European Agreement Concerning the International Carriage of Dangerous Goods by Road/Rail; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number; CLP - Classification, Labelling, and Packaging of Substances and Mixtures; DNEL - Derived No Effect Level; DOT - Department of Transportation; EINECS - European Inventory of New and Existing Chemical Substances; ELINCS - European List of Notified Chemical Substances; EU - European Union; GHS - Globally Harmonized System of Classification and Labeling of Chemicals; IARC - International Agency for Research on Cancer; IDLH - Immediately Dangerous to Life or Health; IATA - International Air Transport Association; IMDG - International Maritime Dangerous Goods; LOEL - Lowest Observed Effect Level; LOAEL - Lowest Observed Adverse Effect Level; NIOSH - The National Institute for Occupational Safety and Health; NOEL - No Observed Effect Level; NOAEL - No Observed Adverse Effect Level; NTP - National Toxicology Program; OEL - Occupational Exposure Limit; OSHA - Occupational Safety and Health Administration; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; STOT - Specific Target Organ Toxicity; STEL - Short Term Exposure Limit; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System;
Issue Date	29 Sep 2017
Revisions	This is the second version of this SDS.
Disclaimer	The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions. No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a potent pharmaceutical product. The above information is offered in good faith and with the belief that it is accurate. As of the date of issuance, we are providing all information relevant to the foreseeable handling of the material. However, in the event of an adverse incident associated with this product, this Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.