

SAFETY DATA SHEET

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

Contact information

General



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Product identifier	Argatroban Injection, 100 mg/ml
Synonyms	1-[5-[(aminoiminomethyl)amino]-1-oxo-2[[[(1,2,3,4-tetrahydro-3-methyl-8-quinoliny)lsulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate
Trade names	Not applicable
Chemical family	Mixture containing L-arginine derivative in ethanol solution.
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; indicated for the treatment and prophylaxis of thromboembolism.
Note	This SDS is written to address potential worker health and safety issues associated with the handling of the formulated product. Workers manufacturing this product should consult the SDSs of each hazardous ingredient for hazard information and handling recommendations.
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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. Please consult the prescribing/packaging information. **The classification and labeling listed below is for bulk drug product.**

Regulation (EC) 1272/2008 [GHS]

Flammable liquid - Category 2.

Label elements

CLP/GHS hazard pictogram



CLP/GHS signal word

Danger

CLP/GHS hazard statements

H225 - Highly flammable liquid and vapor.

CLP/GHS precautionary statements

P210 - Keep away from heat/sparks/open flames/hot surfaces. - No smoking.
P233 - Keep container tightly closed. P240 - Ground/bond container and receiving equipment. P241 - Use explosion-proof electrical/ventilating/lighting equipment. P242 - Use only non-sparking tools. P243 - Take precautionary measures against static discharge. P303 + P361 + P353 - If on skin or hair: Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower. P370 + P378 - In case of fire: Use water spray (fog), foam, dry powder or carbon dioxide for extinction. P403 + P235 - Store in a well-ventilated place. Keep cool. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Other hazards

Argatroban is an anti-coagulant, indicated for the treatment and prophylaxis of thromboembolism in patients with heparin-induced thrombocytopenia, and as an adjunct in patients undergoing coronary angioplasty. The recommended intravenous (IV) dose ranges from 2 to 25 µg/kg/min. Commonly reported adverse effects associated with therapeutic use include bleeding, diarrhea, nausea, vomiting, shortness of breath, apnea, dizziness, sepsis, fever, back pain, headache, low blood pressure, rapid/irregular heart-rate, and chest pain.

Note

This mixture is classified as hazardous according to Regulation EC No 1272/2008 (EU CLP) and Hazard Communication Standard No. 1910.1200 (US OSHA). The pharmacological, toxicological and ecological properties of this mixture have not been fully characterized. See Section 16 for full GHS classifications.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

<u>Ingredient</u>	<u>CAS #</u>	<u>EINECS/ ELINCS#</u>	<u>Amount</u>	<u>GHS Classification</u>
Ethanol	64-17-5	200-578-6	40-50%	FL2: H225
Argatroban	74863-84-6	N/A	10-15%	Not classified

Note The ingredient(s) listed above are considered dangerous/hazardous and/or are pharmacologically active. Ethanol, ethyl alcohol, and dehydrated alcohol are synonyms for the same chemical compound. The remaining components of the drug solution are non-dangerous/not hazardous. See Section 16 for full text of classifications. The GHS classification is based on Regulation (EC) 1272/2008 and Hazard Communication Standard No. 1910.1200.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures

Immediate Medical Attention Needed Yes

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.

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 Mixture contains argatroban - anticoagulant. Medical conditions aggravated by exposure: Bleeding disorders. 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 and carbon dioxide, oxides of nitrogen, and sulfur-containing compounds.
Flammability/Explosivity	Flammable. Keep away from heat, sparks and flame. Vapors are heavier than air and may flow along surfaces to remote ignition sources and flashback.
Advice for firefighters	In case of a fire, keep containers cool with water and remove from fire area. 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	Remove ignition sources. If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Keep away from heat, sparks, and flame. Do not breathe mist/vapors/spray.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	DO NOT CAUSE MATERIAL TO BECOME AIRBORNE. For small spills, soak up material with absorbent, e.g., paper towels. For large spills, cordon off spill area and minimize the spreading of spilled material. Soak up material with absorbent. Collect spilled material, absorbent, and rinse water into suitable containers for proper disposal in accordance with applicable waste disposal regulations (see Section 13). Decontaminate the area twice with an appropriate solvent (see Section 9).
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	Follow recommendations for handling pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Avoid breathing vapor/mist/spray. Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Store at controlled room temperatures (20-25°C) away from incompatible materials. Keep container upright and tightly closed. Keep away from heat, sparks or open flames. Keep out of reach of children.
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note Wash hands, face and other potentially exposed areas immediately in the event of physical contact. Dispose of broken vials/syringes in a sharps container.

**Control Parameters/
Occupational Exposure
Limit Values**

<u>Compound</u>	<u>Issuer</u>	<u>Type</u>	<u>OEL</u>
Ethanol	ACGIH, NIOSH	TWA-8 HR	1000 ppm
	NIOSH	IDLH (Immediately dangerous to life or health)	3300 ppm
	Austria, Belgium, Denmark, Estonia, Finland, France, Greece, Ireland, Portugal, Romania, Slovenia, Spain, United Kingdom, Mexico, Singapore	TWA-8 HR	1000 ppm
	Austria	STEL (3 x 60 min)	2000 ppm
	Bulgaria, Czech Republic, Latvia	TWA-8 HR	1000 mg/m ³
	Czech Republic	Ceiling	3000 mg/m ³
	Estonia, Lithuania, Sweden	STEL	1000 ppm
	Estonia, Germany, Lithuania, Netherlands, Slovak Republic, Sweden	TWA-8 HR	500 ppm
	Finland	STEL	1300 ppm
	France, Romania	STEL	5000 ppm

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION ...continued

**Control Parameters/
Occupational Exposure****Limit Values**

...continued

<u>Compound</u>	<u>Issuer</u>	<u>Type</u>	<u>OEL</u>
	Germany, Lithuania	Ceiling	1000 ppm
	Hungary	STEL	7600 mg/m ³
	Hungary, Poland	TWA-8 HR	1900 mg/m ³
	Slovak Republic	Ceiling	1920 mg/m ³
	Slovenia	STEL	4000 ppm
	United Kingdom	STEL	3000 ppm
	Brazil	TWA-8 HR	780 ppm
Argatroban	--	--	--

**Exposure/Engineering
controls**

None required for normal handling of packaged product. If handling bulk mixture or syringes are opened/broken: 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 aerosol-generating points. Emphasis is to be placed on closed material transfer systems and process containment, with limited open handling. High-energy operations such as spraying should be done within an approved emission control or containment system.

**Respiratory
protection**

None required for normal handling of packaged product. If handling bulk mixture or syringes are opened/broken: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine handling tasks, an approved and properly worn powered air-purifying respirator equipped with appropriate HEPA filters or combination filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use 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 air purifying respirators may not provide adequate protection.

Hand protection

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

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION ...continued

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	Clear, colorless to pale yellow solution
Color	Clear, colorless to slightly yellow
Odor	Odorless
Odor threshold	No information identified.
pH	No information identified.
Melting point/freezing point	No information identified.
Initial boiling point and boiling range	No information identified.
Flash point	12-14°C (100% ethanol)
Evaporation rate	No information identified.
Flammability (solid, gas)	Not applicable.
Upper/lower flammability or explosive limits	LEL - 3.3%; UEL - 19% (100% ethanol)
Vapor pressure	No information identified.
Vapor density	No information identified.
Relative density	No information identified.
Water solubility	Insoluble in water.
Solvent solubility	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ...continued

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 weight Not applicable (Mixture)

Molecular formula Not applicable (Mixture)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity No information identified.

Chemical stability Stable under normal handling and storage conditions.

Possibility of hazardous reactions Not expected to occur.

Conditions to avoid Avoid flames, sparks, and other sources of ignition.

Incompatible materials No information identified.

Hazardous decomposition products No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note No data for this product/mixture were identified. The following data describe the active ingredient and/or the individual ingredients where applicable.

Information on toxicological effects

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

SECTION 11 - TOXICOLOGICAL INFORMATION ...continued

Acute toxicity

<u>Compound</u>	<u>Type</u>	<u>Route</u>	<u>Species</u>	<u>Dose</u>
Ethanol	LD ₅₀	Oral	Rat	7060 mg/kg
	LD ₅₀	Oral	Mouse	3400 mg/kg
	LC ₅₀	Inhalation	Rat	20000 ppm/10 hours
	LC ₅₀	Inhalation	Mouse	39 g/m ³ /4 hours
Argatroban	LD ₅₀	Oral	Rat	>15,000 mg/kg
	LD ₅₀	Oral	Mouse	6,200 mg/kg
	LD ₅₀	Oral	Dog	>1,000 mg/kg
	LD ₅₀	IV	Rat	138 mg/kg
	LD ₅₀	IV	Mouse	211 mg/kg
	LD ₅₀	IV	Dog	>66 mg/kg

Irritation/Corrosion Ethanol is a moderate eye irritant in animals.

Sensitization No data available.

STOT-single exposure No data available.

STOT-repeated exposure/Repeat-dose toxicity Minimal effects consistent with the pharmacological response were seen in repeat-dose studies in dogs and rats given argatroban. In 1 month continuous IV studies in dogs and rats, no over toxicity was reported at the highest doses tested. The NOELs were reported as 60 and 30 mg/kg/day, respectively.

Reproductive toxicity Fertility or reproductive function was not affected in male and female rats were treated IV doses up to 27 mg/kg/day argatroban.

Developmental toxicity IV administration of up to 27 and 11 mg/kg/day argatroban did not induce malformations or fetal toxicity in pregnant rats and rabbits, respectively, treated during organogenesis.

Genotoxicity Argatroban was not genotoxic *in vitro* (e.g., Ames bacterial mutagenicity assay, Chinese hamster ovary cell mutation test, Chinese hamster lung fibroblast chromosome aberration test) and *in vivo* (mouse micronucleus test).

Carcinogenicity Consumption of alcohol is listed as a Group 1 IARC carcinogen (carcinogenic to humans). Ethanol is considered a confirmed animal carcinogen with unknown relevance to humans by ACGIH. None of the 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

<u>Compound</u>	<u>Type</u>	<u>Species</u>	<u>Concentration</u>
Ethanol	LC ₅₀ /96h	Rainbow trout	12900 mg/L (flow through)
	LC ₅₀ /96h	Fathead minnow	15000 mg/L
	EC ₅₀ /48h	Daphnia magna	9268 mg/L
	EC ₅₀ /5-30 min	Photobacterium phosphoreum	~35000 mg/L
Argatroban	--	--	--

Additional toxicity information Ethanol is readily biodegradable under aerobic and anaerobic conditions.

Persistence and Degradability No data available.

Bioaccumulative potential No data available.

Mobility in soil Ethanol would move quickly through soil, if released.

Results of PBT and vPvB assessment Not performed.

Other adverse effects No data available.

Note Avoid release to the environment.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Do not send down the drain or flush down the toilet. All wastes containing the material should be properly labeled. 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

Note The following applies to product packaged for distribution in shipping containers (combination packaging) weighing 30 kg or less. May be eligible for shipment as an excepted quantity.

Transport Based on the available data, this product/mixture is regulated as a hazardous material/dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG.

UN number UN1170

SECTION 14 - TRANSPORT INFORMATION ...continued

UN proper shipping name	Flammable liquid, n.o.s. Ethyl alcohol solution
Transport hazard classes and packing group	Hazard Class 3 - Packing Group II
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.
WHMIS classification	Class B - Flammable Liquid
TSCA status	Drugs are exempt from TSCA.
SARA section 313	Not listed.
California proposition 65	Ethyl alcohol as contained in alcoholic beverages (and consumed) is listed as a reproductive toxicant, but this is not applicable with normal use of this product
Additional information	No other information identified.

SECTION 16 - OTHER INFORMATION

Full text of H phrases and GHS classifications	FL2 - Flammable Liquid Category 2. H225 - Highly flammable liquid and vapor.
Sources of data	Information from published literature and internal company data.

SECTION 16 - OTHER INFORMATION ...continued

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; 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

Revisions

This is the first 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.