SAFETY DATA SHEET

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

Contact information

General

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Product identifier	Icatibant Acetate
Synonyms	Icatibant
Trade names	None identified
Chemical family	Mixture - contains a synthetic peptide
Relevant identified uses of the substance or mixture and uses advised against	Formulated pharmaceutical product/mixture packaged in final form for patient use; used for the treatment of hereditary angioedema, which is a disorder characterized by recurrent swelling episodes.
Note	This SDS is written to address potential worker health and safety issues associated with the handling of the formulated product/mixture. Workers manufacturing this product/mixture should consult the SDS of each hazardous ingredient for hazard information and handling recommendations.

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]	Reproductive Toxicity - Category 2.

Label elements

SECTION 2 - HAZARDS IDENTIFICATION …continued

GHS hazard pictogram
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GHS signal word
Warning

GHS hazard statements
H361fd - Suspected of damaging fertility. Suspected of damaging the unborn child.

GHS precautionary statements
P201 - Obtain special instructions before use. P202 - Do not handle until all safety precautions have been read and understood. P281 - Use personal protective equipment as required. P308 + P313 - IF exposed or concerned: get medical advice/ attention. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Other hazards
Icatibant blocks the hormone bradykinin (B2) receptor; thereby preventing the typical symptoms of inflammation caused by trauma. The most common adverse effects reported with clinical use include injection site reactions, dizziness, headache, nausea, fever, and increased liver enzymes (ALT and AST).

In a clinical setting, healthy adult men and women treated with a single SC 30 mg injection every 6 hours for 3 doses every 3 days for a total of 9 doses did not exhibit any changes in concentration of reproductive hormones.

Note
This mixture is classified as hazardous 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).

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	GHS Classification
Icatibant acetate	138614-30-9	N/A	1-5%	RT2:H361fd
Sodium chloride	7647-14-5	231-598-3	0-1%	Not classified
Acetic acid (glacial)	64-19-7	200-580-7	0.1-1%	FL3: H226; SC1A: H314

Note
The substance(s) listed above are considered hazardous. The primary ingredient in this mixture is sterile water (>97%) and the remaining components are not hazardous and/or present at amounts below reportable limits. Sodium chloride and acetic acid (glacial) are included because they have OELs and are present at or above 1%.

Amounts are listed as ranges; the exact percentage of composition is withheld as a trade secret. See Section 16 for full text of GHS classifications.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures

SECTION 4 - FIRST AID MEASURES …continued

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	Medical conditions aggravated by exposure: None known or reported. 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 dioxide, oxides of nitrogen, sulfur, and sulfur-containing compounds.
Flammability/ Explosivity	No explosivity or flammability data identified. As product is an aqueous solution, it is not expected to be flammable or explosive.
Advice for firefighters	Wear full protective clothing and a self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode. Decontaminate all equipment after use.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	If prefilled glass syringes are opened, crushed or broken, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe dust/mist/vapors/ spray.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	If prefilled glass syringes are crushed or broken, 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.
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	If prefilled glass syringes are crushed or broken, drug substance may be released into the air. Minimize generation and accumulation of airborne material. Follow recommendations for handling bulk formulated/packaged cytotoxic pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Store at 2-25°C (36-77°F). Do not freeze. Keep away from ignition sources including electrostatic charge, heat, sparks, and open flame. If aerosols are generated and insufficient ventilation is present, wear suitable respiratory protection.
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

Compound	Issuer	Type	OEL
Sodium chloride	Latvia, Lithuania, Russia	TWA-8 HR	5 mg/m³
Acetic acid (glacial)	ACGIH	TLV-TWA	10 ppm

Control Parameters/ Occupational Exposure Limit Values

…continued

Compound	Issuer	Type	OEL
	Austria, Belgium, Cyprus, Denmark, Estonia, Germany, Greece, Ireland, Italy, Malta, Latvia, Lithuania, Luxembourg	TWA-8 HR	10 ppm
	Finland, Sweden	TWA-8 HR	5 ppm
	Belgium, Greece, Ireland, Italy	STEL	15 ppm
	ACGIH	TLV-STEL	15 ppm
	Austria	STEL	20 ppm
	Estonia, Finland, France, Sweden	STEL	10 ppm
	Czech Republic	Ceiling	35 mg/m³
	Germany	Ceiling	20 ppm
	Bulgaria	STEL	37 mg/m³
	Hungary	STEL	25 mg/m³
	Bulgaria, Czech Republic, Hungary	TWA-8 HR	25 mg/m³
	Poland	TWA-8 HR	15 mg/m³
	Poland	STEL	30 mg/m³
	Portugal, Romania, Slovak Republic, Slovenia, Spain	TWA-8 HR	10 ppm
	Portugal, Spain	STEL	15 ppm

Control Parameters/ Occupational Exposure Limit Values
…continued

Compound	Issuer	Type	OEL
	U.S. OSHA	PEL-TWA 8-Hr	10 ppm

Exposure/Engineering controls

None required for normal handling of packaged product. If handling bulk product and/or prefilled glass syringes are open/crushed/broken: Control exposures to below the OEL (for the active ingredient(s) if available). 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. Use specifically designed and engineered local exhaust ventilation (LEV) and/or enclosure at dust-generating points and for high dust-generating operations. Limited open handling allowable for low dust-generating operations. Emphasis is placed on closed material transfer through direct connections, dust control and containment using LEV, certified downflow booths, glove bags, process containment via intermediate bulk containers (IBCs) with split butterfly valves (SBVs) and/or isolator technology.

Respiratory protection

None required for normal handling of packaged product. If handling bulk product and/or prefilled glass syringes are open/crushed/broken: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. At a minimum, a tight-fitting full-face respirator with HEPA filters is required when performing aerosol generating operations. A powered air-purifying respirator (PAPR) with HEPA filters and head cover is required for spill cleanup.

Hand protection

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

None required for normal handling of packaged product. Wear safety glasses with side shields if eye contact is likely, e.g., during clean up of large spill. Base the choice of protection on the job activity and potential for contact with eyes and face.

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 solution, 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	Liquid, clear.
Color	Colorless
Odor	Odorless
Odor threshold	Faint odor of acetic acid.
pH	5.2-5.8
Melting point/ freezing point	220-270°C
Initial boiling point and boiling range	No information identified.
Flash point	No information identified.
Evaporation rate	No information identified.
Flammability (solid, gas)	Not applicable.
Upper/lower flammability or explosive limits	Not applicable.
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

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Molecular formula	Not applicable (Mixture)
Molecular weight	Not applicable (Mixture)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	Stable under normal conditions.
Chemical stability	Stable under normal handling and storage conditions.
Possibility of hazardous reactions	Not expected to occur.
Conditions to avoid	No information identified.
Incompatible materials	No information identified.
Hazardous decomposition products	See Section 5 - Hazardous combustion products.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note **No data on product formulation. The following information is for XXX (the active ingredient) and other ingredients, where applicable.**

Information on toxicological effects

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

Acute toxicity

Compound	Type	Route	Species	Dose
Sodium chloride	LD_{50}	Oral	Rat	3000 mg/kg
	LD_{50}	Dermal	Rabbit	>10,000 mg/kg
	LC_{50}	Inhalation	Rat	>42 g/m³ (1-hr)
	LD_{50}	Oral	Mouse	4000 mg/kg
Acetic acid (glacial)	LD_{50}	Oral	Mouse	4960 mg/kg
	LD_{50}	Oral	Rat	3310 mg/kg
	LD_{50}	Oral	Rabbit	1200 mg/kg

Irritation/Corrosion	No studies identified.
Sensitization	No studies identified.
STOT-single exposure	No studies identified.
STOT-repeated exposure/Repeat-dose toxicity	Effects on reproductive organs were seen in 6-month rat and 9-month dog studies, including altered structure, sperm changes, and decreased ovarian follicle development at doses ranging from 1 to 25 mg/kg/day. The dog study NOAEL was 1 mg/kg/day. The tissue findings appeared to be reversible in the treatment-free period.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Reproductive toxicity No effects on fertility or reproductive performance in male mice and rats treated daily with icatibant at IV doses up 81 mg/kg or SC doses up to 10 mg/kg, respectively. However, decreased fertility was noted when untreated female rats mated with males treated with SC doses of 25 mg/kg/day.

Developmental toxicity Icatibant was not teratogenic in rats and rabbits treated with SC doses up to 25 and 10 mg/kg/day, respectively. In rats, delayed parturition and fetal death occurred following maternal doses of 1 and 3 mg/kg, respectively, while increased pre-implantation loss occurred at 10 mg/kg/day. No effects in rat pups after a single SC dose of 1 mg/kg to pregnant rats. Rabbits had pre-implantation loss and increased fetal loss at maternal doses of 10 mg/kg/day.

Genotoxicity Icatibant was not genotoxic *in vitro* (Ames test, Chinese hamster bone marrow chromosome aberration assay) or *in vivo* (mouse micronucleus test).

Carcinogenicity No evidence of tumorigenicity was observed in rats treated SC with icatibant at doses up to 6 mg/kg/day for 2 years. None of the other components of this 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
Sodium chloride	EC_{50}/48h	Daphnia magna	340-1000 mg/L
	EC_{50}/96h	Fish (various species)	>4,700 mg/L
Acetic acid (glacial)	LC_{50}/96h	Pimephales promelas	79 mg/L [static]
	LC_{50}/96h	Lepomis macrochirus	75 mg/L [static]
	EC_{50}/24h	Daphnia magna	47 mg/L
	EC_{50}/48h	Daphnia magna	65 mg/L [static]

Persistence and Degradability No data available.

Bioaccumulative potential No data available.

Mobility in soil No data available.

Results of PBT and vPvB assessment Not performed.

Other adverse effects No data available.

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

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

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	This product/mixture is not regulated as an environmental hazard or a marine pollutant.
Special precautions for users	Due to lack of data, 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.

SECTION 15 - REGULATORY INFORMATION …continued

Additional information No other information identified.

SECTION 16 - OTHER INFORMATION

Full text of H phrases and GHS classifications This is an empty field.

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; PBT - Persistent, Bioaccumulative, and Toxic; 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; vPvB - Very Persistent and Very Bioaccumulative; WHMIS - Workplace Hazardous Materials Information System

Issue Date 15 February 2019

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 pharmaceutical product. The above information is offered in good faith and with the belief that it is

Disclaimer …continued

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.