SAFETY DATA SHEET

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

Contact information

General

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Product identifier	Valrubicin 40 mg/mL (200 mg/5mL)
Synonyms	N-trifluoroacetyladriamycin-14-valerate
Trade names	None identified
Chemical family	Mixture - contains anthracycline doxorubicin
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 certain types of bladder cancer.
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]	Flammable liquid - Category 2. Germ Cell Mutagenicity - Category 2. Reproductive Toxicity - Category 2. Specific Target Organ Toxicity (repeated exposure) - Category 2.

Label elements

SECTION 2 - HAZARDS IDENTIFICATION …continued

GHS hazard pictogram	This is an empty field.
GHS signal word	Danger
GHS hazard statements	H225 - Highly flammable liquid and vapor.
GHS precautionary statements	P201 - Obtain special instructions before use. P202 - Do not handle until all safety precautions have been read and understood. 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. P260 - Do not breathe dust/mist/vapors/spray. P281 - Use personal protective equipment as required. P303 + P361 + P353 - IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower. P308 + P313 - IF exposed or concerned: get medical advice/attention. P314 - Get medical advice/attention if you feel unwell. 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. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/ international regulations.
Other hazards	Valrubicin is a chemotherapeutic drug that causes chromosomal damage and stops cell division. The most common adverse effects reported with clinical use include urinary tract infection, abdominal pain, nausea, lack of energy, headache, and diarrhea. One individual with a perforated bladder received 800 mg of valrubicin intravesically, which caused a severe drop in white blood cells two weeks after dosing.
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
Valrubicin	56124-62-0	--	4.4	ATO3:H301; GC2:H341; RT2:H361fd; STOT-R1:H372
Ethanol	64-17-5	200-578-6	43.2	FL2: H225

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS …continued

Note	The ingredient(s) listed above are considered hazardous and/or because they are pharmacologically active and not yet been fully tested. Classifications for ethanol are described in EU CLP Annex VI - Table 3.1. Remaining ingredients are either not hazardous or present at or below reportable limits. See Section 16 for full text of GHS classifications.

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	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 and other fluorine compounds.

SECTION 5 - FIREFIGHTING MEASURES …continued

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	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 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. Do not breathe mist/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.
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	If vials are crushed or broken, drug substance may be released into the air. Minimize generation and accumulation of airborne material. Follow recommendations for handling bulk product or packaged pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Ground and bond all bulk transfer equipment. Avoid contact with eyes, skin and other mucous membranes. Wash thoroughly after handling. Use only with adequate local exhaust ventilation. Avoid breathing vapor, spray or mist.
Conditions for safe storage including any incompatibilities	Keep only in the original container in a cool (2-8°C), well ventilated place away from: heat and ignition sources, direct sunlight, incompatible materials (strong oxidizing agents). Keep in fireproof place. Keep container tightly closed. Do not freeze. Electrically ground all containers, pumps and piping to avoid static electrical discharge.
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.

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Valrubicin	--	--	--
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

Control Parameters/ Occupational Exposure Limit Values

…continued

Compound	Issuer	Type	OEL
	France, Romania	STEL	5000 ppm
	Germany, Lithuania	Ceiling	1000 ppm
	Hungary	STEL	7600 mg/m³
	Hungary, Poland	TWA-8 HR	1900 mg/m³
	Slovak Republic	Ceiling	1920 mg/m³
	Slovenia	STEL	4000 ppm
	United Kingdom	STEL	3000 ppm
	Brazil	TWA-8 HR	780 ppm

Exposure/Engineering controls

None required for normal handling of packaged product. If handling bulk product and/or vials 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. Utilize closed and sealed systems whenever possible. Solutions used for procedures where aerosolization may occur (e.g., spraying, pumping, open transfers,) must be handled using an engineered local exhaust ventilation (LEV) and/or enclosure or isolator system. Control the potential for spills and leaks by securing all connections. Use clean-in-place systems.

Respiratory protection

None required for normal handling of packaged product. If handling bulk product and/or vials are open/crushed/broken: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. A powered air-purifying respirator (PAPR) with HEPA filters and head cover is required when performing aerosol generating operations. An airline respirator or self-contained breathing apparatus (SCBA) and disposable outerwear 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 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.

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	Liquid. Clear solution. Free of visible particulates.
Color	Red solution.
Odor	No information identified.
Odor threshold	No information identified.
pH	4.0 to 7.0
Melting point/ freezing point	-114 °C (ethanol)
Initial boiling point and boiling range	~78°C (100% ethanol)
Flash point	12-14°C (100% ethanol)
Evaporation rate	No information identified.
Flammability (solid, gas)	Not applicable.
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.

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

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	Stable under recommended handling and storage conditions.
Possibility of hazardous reactions	No information identified.
Conditions to avoid	Sources of ignition. Direct sunlight. Heat sources.
Incompatible materials	Strong oxidizing agents.
Hazardous decomposition products	No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Information on toxicological effects

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

Acute toxicity

Compound	Type	Route	Species	Dose
Valrubicin	LD_{50}	Oral	Rat	>200 mg/kg
	LD_{50}	Intraperitoneal (IP)	Rat	109 mg/kg
Ethanol	LD_{50}	Oral	Rat	7060 mg/kg
	LD_{50}	Oral	Mouse	3400 mg/kg
	LC_{50}	Inhalation	Rat	20000 ppm/10 hours

Acute toxicity

…continued

Compound	Type	Route	Species	Dose
	LC_{50}	Inhalation	Mouse	39 g/m^3/4 hours

Irritation/Corrosion Valrubicin produced no dermal irritation and only mild ocular irritation in rabbits. Ethanol is a moderate eye irritant, but not a skin irritant, in animals.

Sensitization Ethanol is not a sensitizer.

STOT-single exposure No studies identified.

STOT-repeated exposure/Repeat-dose toxicity In rats, 3 repeat intrathoracic dosings of valrubicin (50 mg/kg) caused mortality in 14 out of 20 animals and surviving rats had toxicity in the heart (e.g., pericarditis), bone marrow (e.g., lymphopenia), liver and spleen. Rabbits IV dosed with valrubicin (2 mg/kg/week) for up to 12 weeks exhibited toxicity in the heart (e.g., edema, vacuolization), bone marrow (e.g., hypoplasia), and changes in the spleen and liver.

For ethanol, in a 2-year oral rat study, the lowest reported NOAEL was 2400 mg/kg/day (minor biochemistry changes at higher doses; liver effects at ≥3600 mg/kg/day).

Reproductive toxicity IV administration of valrubicin during organogenesis caused fetal resorptions and fetal malformations in rats at greater or equal to 6 and greater than 12 mg/kg/day, respectively. In repeated exposure studies, weekly intravesical administration of valrubicin in male dogs for 6 weeks caused mild to moderate prostate damage and testicular degeneration. The ethanol oral NOAEL in rats is 2000 mg/kg/day (fertility).

Developmental toxicity Daily IV administration of valrubicin (12 mg/kg) to rats during fetal development caused fetal malformations. A dose of 24 mg/kg caused an increase in fetal resorptions and a decrease in viable fetuses, as well as numerous, severe alterations in the skull and skeleton of the developing fetuses.

For ethanol, NOAELs determined from collective oral animal studies are 6400 mg/kg/day for developmental effects and 3600 mg/kg/day for maternal effects.

Genotoxicity Valrubicin was genotoxic *in vitro* (Ames test, chromosomal aberration assay in Chinese Hamster Ovary cells) and *in vivo* (micronucleus assay in male rats). Ethanol was negative in a battery of *in vitro* and *in vivo* assays.

Carcinogenicity The carcinogenic potential of valrubicin has not been evaluated, but the drug does cause damage to DNA *in vitro*. Doxorubicin, valrubicin's semisynthetic analogue, is listed by both NTP and IARC as a carcinogen. Consumption of alcohol is listed as a group I IARC carcinogen (carcinogenic to humans). Ethanol is considered a confirmed animal carcinogen with unknown relevance to humans by ACGIH.

Aspiration hazard No studies identified

Human health data See "Section 2 - Other Hazards"

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Additional information The toxicological properties of this substance have not been fully characterized.

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Valrubicin	--	--	--
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

Persistence and Degradability Ethanol is readily biodegradable under aerobic and anaerobic conditions.

Bioaccumulative potential Ethyl alcohol: Log K_{ow} -0.32

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

Adsorption coefficient (Koc) 2.75 (ethanol)

Results of PBT and vPvB assessment No data available.

Other adverse effects No data available.

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 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 regulated as a hazardous material/dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG.

SECTION 14 - TRANSPORT INFORMATION …continued

UN number	UN1170
UN proper shipping name	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	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	Ethanol is listed under SARA 313.
California proposition 65	Ethyl alcohol (ethanol) 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. ATO3 - Acute Toxicity (Oral) Category 3. H301 - Toxic if swallowed. GCM2 - Germ Cell Mutagenicity Category 2. H341 - Suspected of causing genetic defects. RT2 - Reproductive toxicity Category 2. H361fd - Suspected of damaging fertility. Suspected of damaging the unborn child. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. H372 - Causes damage to organs through prolonged or repeated exposure.

SECTION 16 - OTHER INFORMATION …continued

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	13 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 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.