SAFETY DATA SHEET

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

Contact information

General

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Product identifier

Halaven® (eribulin mesylate) Injection (0.5 mg/mL; 2- and 3-mL vials)

Synonyms

For eribulin mesylate: 11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one, 2-[(2*S*)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-,(2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-, methanesulfonate (salt); E7389; NSC-707389; ER-086526-13; BOLD

Trade names

Halaven®

Chemical family

Mixture - contains a sulfonate derivative

Relevant identified uses of the substance or mixture and uses advised against

Bulk formulated pharmaceutical product/Formulated pharmaceutical product intended for the final user; indicated for the treatment of metastatic breast cancer.

Note

This SDS is written to address potential worker health and safety issues associated with the handling of the formulated drug product. The physical, chemical, and ecological properties of this mixture have not been fully characterized. This SDS will be revisited as more data become available.

Issue Date

10 March 2015

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 labelling in the US, EU or Canada.** Please consult the prescribing/packaging information. **The classification and labelling listed below is for bulk drug product.**
Regulation (EC) 1272/ 2008 [GHS]	Mixture not yet fully tested
Directive 67/548/EEC or 1999/45/EC	Mixture not yet fully tested
Label elements	
CLP/GHS hazard pictogram	None required
CLP/GHS signal word	None required
CLP/GHS hazard statements	None required
CLP/GHS precautionary statements	None required
EU symbol/indication of danger	None required
Risk (R) Phrase(s)	None required
Safety Advice	None required
Other hazards	Halaven® Injection contains eribulin mesylate ("eribulin") - a potent microtubule inhibitor that blocks cell division, subsequently leading to cell death. Common adverse effects reported in patients receiving eribulin include neutropenia (decreased immune neutrophils), anemia, weakness, fatigue, hair loss, peripheral neuropathy, nausea, and constipation. QT prolongation (a heart irregularity) has also been reported. Neutropenia may be severe and accompanied by fever. Neuropathy may be delayed in onset, or take a longer time to resolve in comparison to mechanistically-similar. Based on its mechanism of action and effects noted in non-clinical studies, at potential for eribulin to adversely affect fertility and fetal development, or to be mutagenic/carcinogenic, cannot be excluded in the absence of definitive data.
US Signal word	Caution
US Hazard overview	Mixture not yet fully tested.

Note This mixture does not meet criteria for classification according to directive 1999/45/EC and Regulation EC No 1272/2008 (EU CLP). Nevertheless, it should be regarded as hazardous because it has not yet been full tested and it contains a pharmacologically active ingredient. See Section 16 for full text of EU and GHS classifications. The GHS classifications are based on Regulation (EC) 1272/2008. The EU symbol/indicator of danger, R Phrases and Safety Advice are based on Directive 1999/45/EC.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	EU Classification	GHS Classification
Ethanol	64-17-5	200-578-6	2-4 %	Highly flammable - F: R11	FL2: H225
Eribulin mesylate	441045-17-6	N/A	0.03-0.05%	Toxic - T: R61, R62, R40, R46; Dang. for Env. - N: R50/53.	STOT-S1: H370; STOT-R1: H372; RT1B: H360Df; GCM1B: H340; Carc2: H351; AA1: H410

Note The ingredient(s) listed above are considered dangerous/hazardous. The remaining components are non-dangerous/not hazardous and/or present at amounts below reportable limits. The balance of the mixture is water for injection. See Section 16 for full text of EU and EU-CLP/GHS classifications. The EU classification is based on Directive 67/548/EEC and the GHS classification is based on Regulation (EC) 1272/2008.

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 and carbon dioxide, oxides of nitrogen, oxides of sulfur, and other nitrogen- 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 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 with an appropriate solvent (*i.e.*, isopropyl alcohol) (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 potent pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Avoid breathing mist/spray. Wash thoroughly after handling.

Conditions for safe storage including any incompatibilities

Store at controlled room temperature (25°C); excursions permitted to 15-30°C. Store away from incompatible materials, protected from light. 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

Compound	Issuer	Type	OEL
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

Control Parameters/ Occupational Exposure Limit Values …continued

Compound	Issuer	Type	OEL
	Estonia, Germany, Lithuania, Netherlands, Slovak Republic, Sweden	TWA-8 HR	500 ppm
	Finland	STEL	1300 ppm
	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
Eribulin mesylate	Eisai	8-HR TWA	0.08 µg/m³
	Eisai	ASL	40 ng/cm²

Exposure/Engineering controls

None required for normal handling of packaged product. If vials are crushed/ broken: Control exposures to below the OEL for the active ingredient. Otherwise, selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Open handling should not be performed when handling potent substances, or substances of unknown toxicity. Material should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for aerosols.

Respiratory protection

None required for normal handling of packaged product. If vials are crushed/ 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

Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION…continued

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 mixture, 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 (in vials)
Color	Clear; Colorless
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	No information identified.
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.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Relative density	No information identified.
Water solubility	Soluble in water.
Solvent solubility	Isopropyl alcohol is the preferred solvent for cleaning purposes.
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. Refer to prescribing information for further details.
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 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 and ingestion.

Acute toxicity

Compound	Type	Route	Species	Dose
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
Eribulin mesylate	LD_{50}	Intravenous	Rat/Mouse	0.5-0.75 mg/kg

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

Sensitization No data available.

STOT-single exposure Intravenous (IV) doses of 0.075 mg/kg/day eribulin for 2 days were lethal to dogs. Target organs of toxicity included the bone marrow and gastrointestinal (GI) tract (consistent with the pharmacological mechanism of action).

STOT-repeated exposure/Repeat-dose toxicity Repeat-dose IV toxicity studies with intermittent dosing regimens of eribulin were conducted in rats and dogs. In the longest studies, weekly injections were given for 3 weeks, followed by a 14-day recovery period, and repeated for 6 cycles. Target organs of toxicity were bone marrow and testes in both species, peripheral nerves in rats, and lymphoid tissues (*e.g.*, lymph nodes, Peyer's patches, and thymus) in dogs. Elevated liver enzymes and decreased reticulocytes were also noted in rats and dogs, respectively. All effects were reversible except for the peripheral nerve and testicular toxicity. NOAELs (IV) of 0.015 and 0.0045 mg/kg/dose were identified in rats and dogs, respectively.

Reproductive toxicity No data available.

Developmental toxicity Eribulin caused increased resorptions and decreased fetal body weights in the offspring of rats treated with an IV doses of 0.1 mg/kg on Gestation Days 8, 10, and 12. An IV dose of 0.15 mg/kg/day also caused external and/or soft tissue anomalies and malformations. Maternal toxicity (decreased body weight and food consumption) was also reported at these two doses (an IV NOAEL of 0.03 mg/kg/dose was identified for maternal and developmental toxicity)..

Genotoxicity Eribulin was negative in the Ames bacterial mutagenicity assay, but was weakly positive in a forward mutation study using mouse lymphoma cells.

Carcinogenicity Ethanol consumption 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 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
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
Eribulin mesylate	EC_{50}/48h	*Daphnia magna* (crustacea)	0.79 mg/L
	EC_{50}/24h	*Daphnia magna* (crustacea)	6.9 mg/L

Persistence and Degradability Eribulin is not significantly degraded. Ethanol is readily biodegradable.

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 Eisai has established an Acceptable Discharge Limit of 0.9 µg/L for eribulin.

Note The environmental characteristics of this mixture have not been fully investigated. The above data are for the active ingredient and/or any other ingredient(s) where applicable. 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. 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.

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.

SECTION 14 - TRANSPORT INFORMATION …continued

Special precautions for users	Mixture not fully tested - avoid exposure.
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 complies with the requirements under US, EU and GHS (EU CLP - Regulation EC No 1272/2008) guidelines. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.
OSHA Hazardous	No. Caution. Mixture not fully tested.
WHMIS classification	Not required. Drugs are not subject to WHMIS. This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations and the SDS contains all of the information required by those regulations.
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 R phrases and EU Classifications	F - Highly Flammable. T - Toxic. N - Dangerous for the Environment. R11 - Highly Flammable. R61 - May cause harm to the unborn child. Repr. Cat. 2 - Toxic for reproduction Category 2. R62 - Possible risk of impaired fertility. Repr. Cat. 3 - Toxic for Reproduction Category 3. R40 - Limited evidence of a carcinogenic effect. Carc. Cat. 3 - Carcinogenic Category 3. R46 - May cause heritable genetic damage. Muta. Cat. 2 - Mutagenic Category 2. R50/53 - Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Full text of H phrases, P phrases and GHS classification	FL2 - Flammable Liquid Category 2. H225 - Highly flammable liquid and vapor. STOT-S1 - Specific Target Organ Toxicity Following Single Exposure Category 1. H370 - Causes damage to the bone marrow and gastrointestinal tract. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. H372 - Causes damage to peripheral nerves, male reproductive organs, and lymphoid tissues through prolonged or repeated exposure. RT1B - Reproductive toxicity Category 1B. H360Df - May damage the unborn child. Suspected of damaging fertility. GCM1B - Germ Cell Mutagenicity Category 1B. H340 - May cause

SECTION 16 - OTHER INFORMATION …continued

Full text of H phrases, P phrases and GHS classification …continued	genetic defects. Carc2 - Carcinogenicity Category 2. H351 - Suspected of causing cancer. AA1- Acute aquatic toxicity Category 1. H410 - Very toxic to aquatic life with long lasting effects.
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; ASL - Acceptable Surface Limit; 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	Updated Section 1 to include additional vial volume.
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.