SAFETY DATA SHEET

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

Contact information

General

Celgene Corporation
556 Morris Avenue, Summit, NJ 07901
Main: +1 (908) 673-9000
E-mail: MSDScoordinator@Celgene.com

Emergency telephone number

Chemtrec *(24-hour availability)*:
+1 (800) 424-9300 (USA and Canada)
+1 (703) 527-3887 (International; collect calls accepted)

Product identifier

Istodax® (Romidepsin) for Injection Lyophilized Powder, Bulk Formulation and Packaged Product (Vial #1 of 2)

Synonyms

Romidepsin for Injection, Istodax Lyophilized Powder

Trade names

Istodax® (Romidepsin) for Injection

Chemical family

Mixture

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

Bulk formulated pharmaceutical mixture/Formulated pharmaceutical product which is a mixture that contains romidepsin, packaged in final form and intended for the final user; indicated for the treatment of certain types of cancer.

Note

The ecological properties of this product/mixture and/or its ingredients have not been fully characterized. This SDS will be revisited as more data become available. There is a parallel diluent vial in the packaged product (Vial #2). Consult parallel SDS for Istodax® for Injection Vial #2 for additional hazard information.

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]

Acute Toxicity - Oral - Category 3. Skin Sensitizer - Category 1B. Reproductive Toxicity - Category 2. Specific Target Organ Toxicity (repeated exposure) - Category 1.

Label elements

GHS hazard pictogram

GHS signal word

Danger

GHS hazard statements

H301 - Toxic if swallowed. H317 - May cause allergic skin reaction. H361fd - Suspected of damaging fertility. Suspected of damaging the unborn child. H372 - Causes damage to hematological, reproductive, and gastrointestinal systems through prolonged or repeated exposure.

GHS precautionary statements

P201 - Obtain special instructions before use. P260 - Do not breathe dust. P264 - Wash hands thoroughly after handling. P270 - Do not eat, drink or smoke when using this product. P272 - Contaminated work clothing should not be allowed out of the workplace. P280 - Wear protective gloves/eye protection/face protection. P301+P310: IF SWALLOWED: Immediately call a Poison Center or doctor/ physician. P302 + P352 - IF ON SKIN: Wash with plenty of soap and water. P308 + P313 - IF exposed or concerned: get medical advice/attention. P333 + P313 - If skin irritation or rash occurs: 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

Contains an antiproliferative agent used for treatment of cancer. The most commonly observed adverse effects in clinical trials with romidespsin were hematotoxicity (anemia, neutropenia, thrombocytopenia), gastrointestinal disturbances (nausea, vomiting, constipation, diarrhea), infection, fatigue, lethargy, asthenia, and transient liver enzyme abnormalities. Other frequent effects included anorexia, clinical chemistry abnormalities, fever, taste alteration, and ECG abnormalities without clinically significant sequelae. Serious and sometimes fatal infections,and reactivation of latent viruses, have been reported. May cause skin sensitization (based on animal data).

There are no adequate and well-controlled studies of romidepsin in pregnancy. However, based on its mechanism of action and the embryocidal/developmental effects seen in rats, it is reasonable to predict that romidepsin may cause fetal harm when administered to pregnant women.

There are scientific studies suggesting that personnel (*e.g.*, nurses, pharmacists) who prepare and administer parenteral antineoplastics may be at some risk due to potential mutagenicity, adverse effects on reproduction and/or carcinogenicity if these materials in the workplace if exposures are not properly controlled. The actual risk in the workplace is not known.

SECTION 2 - HAZARDS IDENTIFICATION …continued

Note This product component (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
Romidepsin	128517-07-7	N/A	33%	ATO3: H301; RT2: H361fd; STOT-R1: H372; SS1B: H317
Polyvinylpyrrolidone	9003-39-8	618-363-4	67%	Not classified

Note The first ingredient listed above is considered hazardous. The second component is not considered dangerous/hazardous. 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.

SECTION 4 - FIRST AID MEASURES …continued

Indication of immediate medical attention and special treatment needed, if necessary	Contains romidepsin, a cytotoxic agent. Medical conditions aggravated by exposure: Immunosuppression, anemia. 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	May emit toxic fumes of carbon monoxide, carbon dioxide, oxides of nitrogen, sulfur oxides and other sulfur-containing compounds.
Flammability/ Explosivity	No information identified. High concentrations of finely divided organic particles can explode if ignited.
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	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 dust.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	If vials are opened, crushed, or broken, or when handling bulk product: 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. Add excess liquid to allow the material to enter solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container suitable 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 vials are opened, crushed or broken, drug substance may be released. Keep container closed. Use only with adequate ventilation.

SECTION 7 - HANDLING AND STORAGE …continued

Conditions for safe storage including any incompatibilities

Store at controlled room temperature (20-25°C) away from incompatible materials. Excursions are permitted between 15 and 30°C. Keep away from children. Keep vials in carton, upright and tightly closed. Store locked up.

Specific end use(s)

No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note

Dispose of broken vials in a sharps container.

**See below - A dermal sensitizer notation is appended to this OEL.*

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Romidepsin	Celgene	OEL TWA	0.1 µg/m³, DSEN*
Polyvinylpyrrolidone	--	--	--

Exposure/Engineering controls

If handling bulk product or vials are opened/crushed/broken: Control exposures to below the OEL (for the active ingredient). Selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. No open handling. Use specifically designed and engineered local exhaust ventilation (LEV) and/or enclosure at dust-generating points and for dust-generating operations unless process is contained. Isolation and closed containment technologies are strongly recommended (enclosed process - a barrier between the equipment and worker) with use of glove bags/continuous liners, isolator systems, direct connections and closed systems. Use clean-in-place systems.

Respiratory protection

If handling bulk product or vials are opened/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 dust-generating operations. An airline respirator or self-contained breathing apparatus (SCBA) and disposable outerwear is required for spill cleanup.

Hand protection

Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered. When the material is dissolved or suspended in an organic solvent, wear gloves that provide protection against the solvent.

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	Solid, white cake or powder; may be packaged in glass vial
Color	White
Odor	No information identified.
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	Not applicable.
Evaporation rate	Not applicable.
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.

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 (N/A); Mixture
Molecular weight	Not applicable (N/A); Mixture

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	Chemically stable for at least 36 months at 25°C and 60% RH; for 6 months at 40°C and 75% RH; and for 3 months at either 50°C or at 25°C and 83% RH. The reconstituted stock solution (5 mg/mL) is chemically stable for up at least 8 hours at room temperature. the diluted injection solution (0.016-0.2 mg/mL) is chemically stable for at least 24 hours at room temperature
Possibility of hazardous reactions	No information identified.
Conditions to avoid	No information identified. Avoid extreme temperatures.
Incompatible materials	Strong oxidizers, acids, bases.
Hazardous decomposition products	During thermal decomposition, it may be possible to generate irritating vapors and/ or toxic fumes of carbon oxide, nitrogen oxides, and sulfur oxides.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note	**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
Romidepsin	LD_{50}	Oral	Rat	55 mg/kg
	LD_{50}	Intravenous	Rat	2.6-3.6 mg/kg [M], 3.6-5.1 mg/kg [F]
	LD_{50}	Intravenous	Dog	>1 mg/kg
Polyvinylpyrrolidone	LD_{50}	Oral	Rat	100,000 mg/kg
	LD_{50}	Oral	Mouse	>40,000 mg/kg
	LD_{50}	Oral	Guinea Pig	100,000 mg/kg

Irritation/Corrosion Romidepsin was not irritating to rabbit skin.

Sensitization Romidepsin was positive for dermal sensitization in a murine Local Lymph Node Assay.

STOT-single exposure No data available.

STOT-repeated exposure/Repeat-dose toxicity Repeat intermittent-dose IV toxicity studies of up to 26 weeks' duration, and repeat daily-dose studies of 4 weeks' duration, have been conducted in rats and dogs. Primary findings across species included injection-site inflammation, lymphoid tissue atrophy, reversible changes in hematology and clinical chemistry parameters, as well as toxicity to the lymph nodes and bone marrow, spleen and thymus, reproductive system/organs, pituitary gland (rats only), and gastrointestinal tract (dogs only). Effects were mostly reversible after cessation of dosing, and there were no signs of cumulative toxicity. The severity of the response was independent of study length. Continuous or intermittent infusion was better tolerated than bolus or daily dosing. In rats, bone marrow toxicity was dose-limiting at 1 mg/kg/day or greater.

Maximum Tolerated IV Dose, dog: 1 mg/kg twice weekly
NOAEL, rat IV: 0.0032 mg/kg/day
LOAEL, dog IV: 0.0032 mg/kg/day

Reproductive toxicity Definitive fertility studies with romidepsin were not identified. However, adverse effects on reproductive organs were noted in rats, dogs, and mice in repeat IV dose toxicity studies. In rats, testicular atrophy was noted at ≥0.33 mg/kg/week, while atrophy in female sex organs (*e.g.*, ovary, uterus, mammary gland) occurred at ≥0.1 mg/kg/week. Testicular degeneration was noted in male mice treated with 8 mg/kg, twice weekly for 50 days. In dogs, doses >1 mg/kg/day caused hypospermia in the testes and epididymides as well as degeneration of seminiferous tubules.

Developmental toxicity Developmental effects, in the presence of maternal toxicity, was observed in embryo-fetal developmental toxicity studies with rats administered IV romidepsin doses ≥0.2 mg/kg/day during organogenesis. Adverse findings included early resorptions, reduced fetal body weights, increased incidences of rotated hindlimbs and folded retina, delayed ossifications and supernumerary thoracic ribs at doses. While 0.1 mg/kg/day was considered the NOAEL for developmental toxicity, it was the LOAEL for maternal toxicity.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Genotoxicity Romidepsin was negative in the Ames bacterial mutagenicity assay and an *in vivo* rat micronucleus test. It was very weakly positive in a mouse lymphoma forward mutation assay. The data suggest that romidepsin is not genotoxic in standard short-term screening assays.

Carcinogenicity Long-term carcinogenicity studies with romidepsin have not been conducted. 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

Compound	Type	Species	Concentration
Romidepsin	--	--	--
Polyvinylpyrrolidone	--	--	--

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 romidepsin have not been fully investigated. Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods Dispose of wastes by appropriately permitted chemical waste incinerator in accordance to prescribed federal, state, and local guidelines. 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 onsite 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. May be eligible for shipment as a consumer commodity (ID8000, Class 9); refer to instruction Y963.
Transport	Packaged product contains two components (vials) which may be regulated for transportation as a hazardous material/dangerous good. **Transport information for bulk romidepsin is as per Vial #1; transport information for packaged product is as per Vials #1 and #2.**
UN number	Vial #1: UN2811 Vial #2: UN1170
UN proper shipping name	Vial #1: Toxic solid, organic, n.o.s. (contains romidepsin) Vial #2: Ethyl alcohol solution
Transport hazard classes and packing group	Vial #1: Hazard Class - 6.1; Packing Group III Vial #2: Hazard Class - 3; Packing Group III
Environmental hazards	Based on the available data, this product 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	ATO3 - Acute Toxicity (Oral) Category 3. H301 - Toxic if swallowed. SS1B - Skin sensitizer Category 1B. H317 - May cause an allergic skin reaction. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. H372 - Causes damage to hematological, reproductive, and gastrointestinal systems through prolonged or repeated exposure. RT2 - Reproductive toxicity Category 2. H361fd - Suspected of damaging fertility. Suspected of damaging the unborn child.
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	27 June 2018
Revisions	Reviewed new internal data (no changes necessary); Updated handling in Section 8.
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

Disclaimer …continued

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.