

# SAFETY DATA SHEET

---

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

---

### Contact information

#### General



Leucadia Pharmaceuticals  
2325 Camino Vida Roble, Suite A  
Carlsbad, CA 92011  
Main: +1 (844) 538-2231 (Mon-Fri 8:00 AM - 6:00 PM Central)  
Email: info.sds@leucadiapharma.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

Dihydroergotamine mesylate, Nasal Spray

#### Synonyms

Ergotaman-3',6',18-trione,9,10-dihydro-12'-hydroxy-2'-methyl-5'(phenylmethyl-)(5'alpha)-,monomethanesulfonate

#### Trade names

None identified

#### Chemical family

Mixture - contains an ergot derivative

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

Formulated pharmaceutical product packaged in final form for patient use; used for the treatment of migraine headaches.

#### Note

This SDS is written to address potential worker health and safety issues associated with the handling of the formulated product. Workers manufacturing this 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****GHS signal word**

Warning

**GHS hazard statements**

H361d - Suspected of damaging the unborn child. H362 - May cause harm to breastfed children.

**GHS precautionary statements**

P201 - Obtain special instructions before use. P260 - Do not breathe mist/vapors/spray. P263 - Avoid contact during pregnancy/while nursing. P280 - Wear protective gloves/eye protection/face protection. 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**

Dihydroergotamine mesylate is a semi-synthetic ergotamine derivative. It binds to serotonin and noradrenaline alpha receptors. The therapeutic activity in migraine is generally attributed to the agonist effect at specific serotonin receptors. The most commonly reported adverse effects associated with therapeutic use include nasal irritation, gastrointestinal disturbances, throat inflammation, and dizziness.

Ergot drugs, including dihydroergotamine mesylate, are known to stimulate uterine contractions and should be avoided during pregnancy. Further, ergotamine is secreted in breast milk and may cause vomiting, diarrhea, weak pulse, and blood pressure instability in nursing infants. Based on this information and its mechanism of action, it is reasonable to predict that dihydroergotamine mesylate may adversely affect pregnancy and breastfed infants.

**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**

---

<u>Ingredient</u>	<u>CAS #</u>	<u>EINECS/ ELINCS#</u>	<u>Amount</u>	<u>GHS Classification</u>
Dihydroergotamine mesylate	6190-39-2	228-235-6	0.3-0.5%	RT2: H361d, H362
Caffeine, anhydrous	58-08-2	95789-13-2	1-2%	ATO3: H301, AA3: H402

**Note**

The substance(s) listed above are considered hazardous. The remaining components are not hazardous and/or are present at amounts below reportable limits.

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

<b>Immediate Medical Attention Needed</b>	Yes
<b>Eye Contact</b>	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.
<b>Skin Contact</b>	Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.
<b>Inhalation</b>	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.
<b>Ingestion</b>	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.
<b>Protection of first aid responders</b>	See Section 8 for Exposure Controls/Personal Protection recommendations.
<b>Most important symptoms and effects, both acute and delayed</b>	See Sections 2 and 11.
<b>Indication of immediate medical attention and special treatment needed, if necessary</b>	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

---

<b>Extinguishing media</b>	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
<b>Specific hazards arising from the substance or mixture</b>	No information identified. May emit carbon monoxide, carbon dioxide, oxides of nitrogen, sulfur, and nitrogen- and sulfur-containing compounds.
<b>Flammability/Explosivity</b>	As product is an aqueous solution, it is not expected to be flammable or explosive.
<b>Advice for firefighters</b>	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

---

<b>Personal precautions, protective equipment and emergency procedures</b>	If vials 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 mist/vapors/spray.
<b>Environmental precautions</b>	Do not empty into drains. Avoid release to the environment.
<b>Methods and material for containment and cleaning up</b>	If vials 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.
<b>Reference to other sections</b>	See Sections 8 and 13 for more information.

---

## SECTION 7 - HANDLING AND STORAGE

---

<b>Precautions for safe handling</b>	If vials are crushed or broken, mist/vapor/spray containing drug substance may be released. Minimize mist/aerosol/spray generation and accumulation. Avoid breathing mist/vapor/spray.
<b>Conditions for safe storage including any incompatibilities</b>	Store at room temperature (~15°C to 25°C). Avoid extreme temperatures.
<b>Specific end use(s)</b>	Pharmaceutical.

---

## SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

---

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

### Control Parameters/ Occupational Exposure Limit Values

<u>Compound</u>	<u>Issuer</u>	<u>Type</u>	<u>OEL</u>
Dihydroergotamine mesylate	--	--	--
Caffeine, anhydrous	Latvia	8-HR TWA	0.5 mg/m <sup>3</sup>
	Russia	STEL (15 min)	0.5 mg/m <sup>3</sup>

---

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

---

<b>Exposure/Engineering controls</b>	None required for normal handling of packaged product. If handling bulk product and/or vials are open/crushed/broken: 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.
<b>Respiratory protection</b>	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.
<b>Hand protection</b>	None required for the normal handling of packaged product. Wear nitrile or other impervious gloves if skin contact with formulated material is possible.
<b>Skin protection</b>	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.
<b>Eye/face protection</b>	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.
<b>Environmental Exposure Controls</b>	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.
<b>Other protective measures</b>	Wash hands in the event of contact with formulated product, 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**

<b>Appearance</b>	Vials with clear solution.
<b>Color</b>	Colorless to faint yellow.
<b>Odor</b>	Odorless
<b>Odor threshold</b>	No information identified.
<b>pH</b>	No information identified.

---

**SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ...continued**

---

<b>Melting point/ freezing point</b>	No information identified.
<b>Initial boiling point and boiling range</b>	No information identified.
<b>Flash point</b>	No information identified.
<b>Evaporation rate</b>	No information identified.
<b>Flammability (solid, gas)</b>	Not applicable.
<b>Upper/lower flammability or explosive limits</b>	Not applicable.
<b>Vapor pressure</b>	No information identified
<b>Vapor density</b>	No information identified.
<b>Relative density</b>	No information identified.
<b>Water solubility</b>	Soluble.
<b>Solvent solubility</b>	No information identified.
<b>Partition coefficient (<i>n</i>-octanol/water)</b>	No information identified.
<b>Auto-ignition temperature</b>	Not applicable.
<b>Decomposition temperature</b>	Not applicable.
<b>Viscosity</b>	Not applicable.
<b>Explosive properties</b>	Not applicable.
<b>Oxidizing properties</b>	Not applicable.
<b>Other information</b>	
<b>Molecular formula</b>	Not applicable (Mixture)
<b>Molecular weight</b>	Not applicable (Mixture)

---

**SECTION 10 - STABILITY AND REACTIVITY**

---

<b>Reactivity</b>	No information identified.
<b>Chemical stability</b>	Stable under normal handling and storage conditions.
<b>Possibility of hazardous reactions</b>	No information identified.
<b>Conditions to avoid</b>	No information identified.

---

**SECTION 10 - STABILITY AND REACTIVITY ...continued**

---

**Incompatible materials** No information identified.

**Hazardous decomposition products** No information identified.

---

**SECTION 11 - TOXICOLOGICAL INFORMATION**

---

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

**Information on toxicological effects**

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

**Acute toxicity**

<u>Compound</u>	<u>Type</u>	<u>Route</u>	<u>Species</u>	<u>Dose</u>
Dihydroergotamine mesylate	LD <sub>50</sub>	Oral	Rat	>40 mg/kg
	LD <sub>50</sub>	Oral	Mice	>100 mg/kg
Caffeine, anhydrous	LD <sub>50</sub>	Oral	Dog	140 mg/kg
	LD <sub>50</sub>	Oral	Guinea Pig	230 mg/kg
	LD <sub>50</sub>	Oral	Mouse	127 mg/kg
	LD <sub>50</sub>	Oral	Rabbit	224 mg/kg
	LD <sub>50</sub>	Oral	Rat	192 mg/kg

**Irritation/Corrosion** Dihydroergotamine mesylate was slightly irritating to rabbit eye. Caffeine was not irritating to rabbit eye and skin.

**Sensitization** No studies with dihydroergotamine mesylate were identified. Caffeine was not sensitizing in mice.

**STOT-single exposure** Following oral or intravenous administration of a single dose of dihydroergotamine mesylate in rats and mice, drooping of the upper eyelid and clonic/tonic convulsions were observed. No macroscopic abnormalities were observed in principal organs examined (no further details were identified).

**STOT-repeated exposure/Repeat-dose toxicity** In mice and rats, intranasal administration of dihydroergotamine mesylate in 1- and 3-month studies at doses 0.04-0.2 and 0.08-1.2 mg/day, respectively, resulted in mild rhinitis, eosinophilic inclusions and very mild goblet cell proliferation. In monkeys, 13-week intranasal study resulted in transient superficial mucosal ulceration. The NOAEL was 3.68 mg/day, the highest dose tested. Oral 6-month studies in rats and dogs established NOAELs of 11 and 1.5 mg/kg/day, respectively, based on diarrhea, blue-red discoloration of the tail-tip, increased liver enzymes, and decreased spleen weight observed at higher doses.

**Reproductive toxicity** No fertility impairment was observed in rats administered intranasal doses of dihydroergotamine mesylate up to 1.6 mg/day.

---

**SECTION 11 - TOXICOLOGICAL INFORMATION ...continued**

---

<b>Developmental toxicity</b>	Oral or intranasal administration of dihydroergotamine mesylate to pregnant rats, rabbits, and monkeys caused no fetal malformations. Minimal maternal toxicity was observed at intranasal doses of 1.2 mg/day in rats and 3.6 mg/day in rabbits. Reduced fetal body weights and/or delayed skeletal ossification occurred in rats and rabbits administered 0.16 and 3.6 mg/day, respectively; these doses were maternally toxic in rabbits, but not rats. The rabbit NOAEL was 1.2 mg/day; a rat NOAEL was not identified. Fetal growth retardation in animals treated with dihydroergotamine mesylate has been attributed to reduced utero-placental blood flow due to prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone.
<b>Genotoxicity</b>	Dihydroergotamine mesylate was not mutagenic in the Ames bacterial and <i>in vitro</i> mammalian cell assays. It was not genotoxic in a rat hepatocyte unscheduled DNA synthesis test and <i>in vivo</i> mouse and hamster micronucleus tests. It was clastogenic in chromosome aberration assays in mammalian cells and human peripheral blood lymphocyte assay, however only at one time point and with only the highest dose.
<b>Carcinogenicity</b>	No studies identified. None of the 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.
<b>Aspiration hazard</b>	No data available.
<b>Human health data</b>	See "Section 2 - Other Hazards"

---

**SECTION 12 - ECOLOGICAL INFORMATION**

---

**Toxicity**

<u>Compound</u>	<u>Type</u>	<u>Species</u>	<u>Concentration</u>
Dihydroergotamine mesylate	--	--	--
Caffeine, anhydrous	LC <sub>50</sub> (96h)	Fish	87 mg/L
	EC <sub>50</sub> (48h)	Invertebrates	182 mg/L
	EC <sub>50</sub> (72h)	Algae	>100 mg/L

**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. Trace amounts of dihydroergotamine mesylate and caffeine were measured in waste water treatment effluents and aquatic organisms, but removal process is shown to be fairly good.



---

## SECTION 13 - DISPOSAL CONSIDERATIONS

---

<b>Waste treatment methods</b>	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

---

<b>Transport</b>	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.
<b>UN number</b>	None assigned.
<b>UN proper shipping name</b>	None assigned.
<b>Transport hazard classes and packing group</b>	None assigned.
<b>Environmental hazards</b>	This product/mixture is not regulated as an environmental hazard or a marine pollutant.
<b>Special precautions for users</b>	Avoid release to the environment.
<b>Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code</b>	Not applicable.

---

## SECTION 15 - REGULATORY INFORMATION

---

<b>Safety, health and environmental regulations/legislation specific for the substance or mixture</b>	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.
<b>Chemical safety assessment</b>	Not conducted.
<b>TSCA status</b>	Drugs are exempt from TSCA.
<b>SARA section 313</b>	Not listed.
<b>California proposition 65</b>	Not listed.
<b>Additional information</b>	No other information identified.

---

## SECTION 16 - OTHER INFORMATION

---

<b>Full text of H phrases and GHS classifications</b>	H361d - Suspected of damaging the unborn child. H362 - May cause harm to breastfed babies. RT2 - Reproductive toxicity Category 2. H301 - Toxic if swallowed. ATO3 - Acute Toxicity (Oral) Category 3. H402 - Harmful to aquatic life. AA3- Acute aquatic toxicity Category 3.
<b>Sources of data</b>	Information from published literature and internal company data.
<b>Abbreviations</b>	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
<b>Issue Date</b>	5 December 2018
<b>Revisions</b>	This is the first version of this SDS.
<b>Disclaimer</b>	<p>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.</p> <p>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 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.</p>