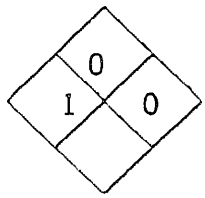
NOVARTIS




# MATERIAL SAFETY DATA SHEET

**NOVARTIS PHARMACEUTICALS CORPORATION**
59 State Hwy No. 10
East Hanover, NJ 07936

**24-Hour Emergency Telephone Number:** 1-973-781-7000
**Customer Response (MSDS requests):** 1-800-742-2422
**For Technical Information:** 1-973-781-3833 (9:00 AM - 5:00 PM E.S.T)

## SECTION 1. PRODUCT IDENTIFICATION

| | |
|---|---|
| PRODUCT NAME: | **DHE® Injection** |
| PRODUCT CODE(S): | NDC 0078-0041-01 |
| SYNONYMS: | Dihydergot®, Orstanorm®. |
| THERAPEUTIC CATEGORY: | Acute treatment of migraine headaches with or without aura. |
| GENERIC NAME: | Dihydroergotamine mesylate USP |
| CHEMICAL NAME: | Ergotaman-3',6',18-trione,9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-(5'α)-, monomethanesulfonate |
| CHEMICAL FORMULA: | $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$ |
| MOLECULAR WEIGHT: | 679.79 |

## SECTION 2. COMPOSITION/INFORMATION ON INGREDIENTS

| COMPOSITION | CAS# | CONCENTRATION |
|---|---|---|
| Dihydroergotamine mesylate, USP | 6190-39-2 | 1 mg/mL |
| Ethyl Alcohol, USP | 64-17-5 | 6.1% by vol. |
| Glycerin, USP | 56-81-5 | 15.0% by wt. |

## SECTION 3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

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**FINISHED PHARMACEUTICAL PRODUCT**
**REFER TO PHYSICIANS' DESK REFERENCE**
**AFFECTS VASCULAR SMOOTH MUSCLE**
**MAY ADVERSELY AFFECT THE DEVELOPING FETUS**

**********

| | |
|---|---|
| PRIMARY ROUTE(S) OF ENTRY: | Intravenous |
| EFFECTS OF OVEREXPOSURE: | Finished pharmaceutical product. Potential for exposure is reduced in this form. |
| Skin: | No hazard is expected from normal clinical use. |
| Eye: | No hazard is expected from normal clinical use. |
| Inhalation: | No hazard is expected from normal clinical use. |
| Ingestion: | No hazard is expected from normal clinical use. |
| THERAPEUTIC SIDE EFFECTS: | Nasal congestion or irritation, irritation of the nose and throat, taste disturbances, nausea, vomiting, dizziness, fatigue runny and stuffy nose, and flushing. Less frequent side effects include numbness and tingling of fingers and toes, muscle pain in the extremities,and elevation in blood pressure and temporary heart rate changes, swelling or iching. |
| TARGET ORGAN EFFECTS: | Direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels. |
| REPRODUCTIVE HAZARDS: | There are no adequate studies of dihydroergotamine in human pregnancy, but developmental toxicity has been demonstrated in experimental animals. It is known that ergotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse and unstable blood pressure in nursing infants. Therefore, nursing should not be undertaken during the use of D.H.E. 45®. |
| CARCINOGENICITY: | Studies of D.H.E. 45® to determine carcinogenic potential are ongoing. |
| MUTAGENICITY: | Dihydroergotamine mesylate was clastogenic in two in vitro assays, and non-mutagenic in three assays (see Section 11). |

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Known hypersensitivity to ergot alkaloids or any other components of the formulation; pregnancy and breast-feeding; conditions predisposing to vasospastic reactions: coronary heart disease, septic conditions, shock, obliterative vascular disease; inadequately controlled hypertension; severe hepatic (liver) impairment or renal function.

## SECTION 4. EMERGENCY AND FIRST AID MEASURES

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|---|---|
| **Skin Contact:** | Wash contaminated area with soap and water. |
| **Eye Contact:** | Flush with running water for 15 minutes holding eyelids open. |
| **Inhalation:** | Remove patient to fresh air. Support breathing as needed. |
| **Ingestion:** | Get medical attention immediately. |

## SECTION 5. FIRE FIGHTING MEASURES

**Flash Point:** >200°F **Method Used:** closed cup

**Flammable Limits (% in air)**
Lower: not applicable Upper: not applicable

| | |
|---|---|
| **Autoignition Temperature:** | Not available |
| **Extinguishing Media:** | Use media suitable for fire in surrounding area. |
| **Special Fire Fighting Procedures and Precautions:** | Evacuate area and fight fire from safe distance. |
| **Fire and Explosion Hazards:** | None |
| **Fire-Fighting Equipment:** | Wear full protective clothing and positive pressure self-contained breathing apparatus. |
| **Combustion Products:** | Thermal decomposition may result in the emission of carbon monoxide, carbon dioxide and nitrogen oxides. |

NFPA Ratings: Health = 1 Flammability = 0 Reactivity = 0 Special Hazard = None
Hazard Rating Scales: 0 = Minimal 1 = Slight 2 = Moderate 3 = Serious 4 = Severe U = Unknown

## SECTION 6. ACCIDENTAL RELEASE MEASURES

**Steps to be taken if Material is Released or Spilled:** Using appropriate protective equipment, sweep up and containerize spilled material. Avoid contamination of sewers and waterways.

## SECTION 7. HANDLING AND STORAGE

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|---|---|
| **Storage Temperature:** | Store below 77°F (25°C). |
| **Shelf Life:** | 3 years |
| **Special Sensitivity:** | None. |
| **Handling and Storage Precautions:** | Do not use if solution is discolored. Do not refrigerate or freeze. |

## SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

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|---|---|
| **Eye Protection:** | Not required under normal conditions of therapeutic administration and use. |
| **Skin Protection:** | Not required under normal conditions of therapeutic administration and use. |
| **Respiratory Protection:** | Not required under normal conditions of therapeutic administration and use. |
| **Ventilation Requirements:** | Not required under normal conditions of therapeutic administration and use. |

**Exposure Limits (Definition of terms):**

| | |
|---|---|
| ACGIH: | American Conference of Governmental Industrial Hygienists |
| NPIEL: | Novartis Pharma Internal Exposure Limit |
| OSHA: | Occupational Safety and Health Administration |
| PEL: | Permissible Exposure Limit |
| TLV: | Threshold Limit Values |
| TWA: | Time-Weighted Average |
| ppm: | parts per million |

| Component | Exposure Limit |
|---|---|
| Dihydroergotamine mesylate | NPIEL = 0.001 mg/m³ TWA |
| Ethyl Alcohol | OSHA PEL = 1000 ppm, TWA<br>ACGIH TLV = 1000 ppm, TWA |

| | |
|---|---|
| Glycerin | OSHA PEL = 10 mg/m$^3$, TWA<br>ACGIH TLV = 10 mg/m$^3$, TWA |

## SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

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|---|---|---|---|
| **Appearance:** | Clear solution in ampuls | **Odor Threshold:** | Not available |
| **Color:** | Colorless to faint yellow | **Odor Characteristics:** | Not available |
| **pH:** | Not available | **Vapor Pressure (mm Hg):** | Not available |
| **Boiling Point:** | Not available | **Vapor Density:** | Not available |
| **Melting Point/Range:** | Not applicable | **Specific Gravity:** | Not available |
| **Freezing Point:** | Not available | **% Volatile by Wt:** | Not available |
| **Soluble In:** | Water, alcohol | **Viscosity:** | Not applicable |

## SECTION 10. STABILITY AND REACTIVITY

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|---|---|
| **Stable (yes/no):** | Yes |
| **Hazardous Polymerization:** | Will not occur. |
| **Conditions and Materials to Avoid:** | Protect from temperatures exceeding 77°F (25°C). Do not refrigerate or freeze. |
| **Incompatibility:** | Not available |
| **Hazardous Decomposition Products:** | None known. |

## SECTION 11. TOXICOLOGICAL INFORMATION

**Eye Irritation:** In an eye irritation study in New Zealand white rabbits, D.H.E. 45® Nasal Spray was found to have a transient weak irritant potential. Draize score of 4.17.

**Skin Irritation/Sensitization:** No data available.

**Oral Toxicity:** The maximum non-lethal doses (MNLD) after a single oral dose of D.H.E. 45® Nasal Spray solution were found to be > 100 mg/kg in mice and > 40 mg/kg in rats.

**Dermal Toxicity:** No data available.

**Parenteral Toxicity:** Following a single intravenous dose, the maximum non-lethal doses were 32 mg/kg in male mice, 28 mg/kg in female mice and male rats, and 20 mg/kg in female rats.

**Inhalation Toxicity:** No data available.

**Subchronic/Subchronic:** The intranasal toxicity of D.H.E. 45® Nasal Spray, given as microdroplets, was evaluated in 4- and 13-week toxicity studies at doses of up to 0.2 mg/day in mice and 1.6 mg/day in rats (both doses about 20 times human AUC or $C_{max}$). There were minor decreases in body weight gain and food consumption in both

species at the highest dose. Other treatment-related findings were confined to the nasal cavities which showed a dose-related minimal to moderate rhinitis in both species.

A 13-week study was also performed in cynomolgus monkeys at doses up to 3.7 mg/day given by nasal spray. There was no evidence of systemic toxicity. Treatment-related changes were noted only in high-dose animals and consisted of mild rhinitis with slight focal hyperplasia of the respiratory epithelium.

**Carcinogenicity:** No data available.

**Mutagenicity:** Dihydroergotamine mesylate is not considered mutagenic. It was clastogenic in two *in vitro* chromosomal aberration assays, the V79 Chinese hamster cell assay. Dihydroergotamine mesylate is not mutagenic when tested in the two gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster V79/HGPRT assay) and in an assay for DNA damage (the rat hepatocyte unscheduled DNA synthesis test). Dihydroergotamine was not clastogenic in the *in vivo* mouse and hamster micronucleus tests.

**Reproductive Effects:** **FDA Use-in-Pregnancy Category X: Contraindicated in pregnancy:** In embryo-fetal development studies intranasal administration of dihydroergotamine mesylate nasal spray to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses of 0.16 mg/day. Delayed skeletal ossification was also noted in rabbit fetuses following intranasal administration of 3.6 mg/day (maternal exposures approximately 7 times those in humans receiving the maximum recommended daily dose) during organogenesis. When dihydroergotamine mesylate nasal spray was administered intranasally to female rats during pregnancy and lactation, decreased body weights and impaired reproductive function (decreased mating indices) were observed in the offspring at doses of 0.16 mg/day or greater. Effects on development occurred at doses below those that produced evidence of significant maternal toxicity in these studies. Dihydroergotamine-induced intrauterine growth retardation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone.

Ergot drugs are also known to inhibit prolactin. It is known that ergotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse and unstable blood pressure in nursing infants. Therefore, nursing should not be undertaken during the use of D.H.E. 45®.

## SECTION 12: ECOLOGICAL INFORMATION

Biological elimination:

95 % (aerobic, DOC) Initial concentration: app. 20 mg DOC/l 28 d, well degradable in biol. waste water treatment plant. Method: OECD 301E * 1981 Mod. OECD screening test (ready)

Fish toxicity:

LC0: 100 mg/l, LC50: > 100 mg/l, LC100: > 100 mg/l (Species: rainbow trout (salmo gairdneri, oncorhynchus mykiss), Exp. time: 96 h) Method: OECD 203 * 1992 limit test.

Daphnia toxicity:

EC0: 9.4 mg/l, EC50: 113 mg/l, EC100: > 100 mg/l (Species: daphnia magna (water flea), Exp. time: 48 h)
Method: OECD 202 * 1984 acute toxicity.

Algae toxicity:

IC0: 11 mg/l, IC50: > 100 mg/l (Species: Scenedesmus subspicatus 86.81 sag. green algae, Exp time: 72 h)
Method: OECD 201 * 1984. Growth inhibition

Bacteria toxicity (respiration inhibition):
IC50: > 100 mg/l, IC20: > 100 mg/l (Species: activated sludge, Exp. time: 3 h) Method: OECD 209 * 1984 activated sludge. 'Respiration inhibition'.

## SECTION 13. DISPOSAL CONSIDERATIONS

**Waste Disposal Method:** All wastes must be disposed of in accordance with local, state and federal laws and regulations. (Contact local or state environmental agency for specific rules).

**EPA Hazardous Waste Number:** None

## SECTION 14. TRANSPORTATION INFORMATION

Ground Regulations:

**Proper Shipping Description:** Drugs, N.O.I., NMFC Item 60000
**DOT Proper Shipping Name:** Not Applicable
**DOT Hazard Class:** Not Applicable
**DOT Identification Number:** Not Applicable
**Packing Group:** Not Applicable
**Hazard Label:** Not Applicable
**Package Weight Limits:** Not Applicable
**Special Requirements:** Not Applicable
**Exceptions:** Not Applicable
**Non-Bulk Requirements:** Not Applicable
**Bulk Requirements:** Not Applicable
**Reportable Quantity (lbs.):** Not Applicable
**Stowage:** Not Applicable
**Other Requirements:** Not Applicable

Air Regulations:

**Proper Shipping Description:**
**IATA Proper Shipping Name:**
**IATA Hazard Class:**
**IATA Identification Number:**
**Packing Group:**
**Hazard Label:**
**Special Requirements:**
**Max. wgt/pkg - Passgr. Aircraft:**
**Max. wgt/pkg - Cargo Only Air:**

## SECTION 15. REGULATORY INFORMATION

**OSHA (Occupational Safety & Health Administration):** This Material Safety Data Sheet contains the information required by the Federal OSHA Hazard Communication Standard (29 CFR 1910.1200).

**OSHA PSM (Process Safety Management):** Not listed (29 CFR 1910.119, Appendix A)

**NJ TCPA (Toxic Catastrophe Prevention Act):** This product contains NONE of the substances subject to the reporting requirements of Section N.J.A.C. 7:31 of this act.

**TSCA (Toxic Substance Control Act):** Not applicable

**CERCLA (Comprehensive Response Compensation & Liability Act):** Not listed

**SARA Title III (Superfund Amendments & Reauthorization Act):**

Section 302 Extremely Hazardous Substances: Not listed
Section 311/312 Hazard Categories: Acute health effects, chronic health effects
Section 313 Reportable Ingredients: None

**RCRA (Resource Conservation & Recovery Act):** Not listed

**Other State Regulatory Information:**

New Jersey: NJ RTK Threshold Planning Quantity = 10,000 lbs.

**Other USA Regulations:** None

**California Proposition 65:** The following statement is made in order to comply with the California Safe Drinking Water and Toxic Enforcement Act of 1986. *This product contains* Dihydroergotamine mesylate *an ingredient known to the State of California to cause reproductive (developmental) toxicity.*

**Canada:** WHMIS Ingredient Disclosure List
Not listed

**EEC Classification (European Economic Community):**
Warning Symbol:
Xn - Harmful
Risk Phrases:
R20/22 Harmful by inhalation and if swallowed.
Safety Phrases:
S22 Do not breathe dust

## SECTION 16. OTHER INFORMATION

**Reason for Issue:** New

| | | | |
|---|---|---|---|
| **Written By:** | N. Roden | **Date:** | 16 Jun 99 |
| **Approved By:** | J. Affuso | **Date:** | 2 Jul 99 |

**To the best of our knowledge, the information contained herein is accurate. However, Novartis Pharmaceuticals Corporation does not assume any liability whatsoever for the accuracy or completeness of the information contained**