

# MATERIAL SAFETY DATA SHEET

## SECTION 1 - CHEMICAL PRODUCT & COMPANY IDENTIFICATION

American Home Products Corporation Wyeth-Ayerst 401 N. Middle Town Road Pearl River, NY 10965 FOR: Immunex Corporation Seattle, WA 98101	Emergency telephone Chemtrec for Chemical Emergencies	(610) 971-5403  (800) 424-9300  1-800-334-6273
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Product name	NOVANTRONE <sup>®</sup> mitoxantrone HCl, 2 mg/mL
Synonyms	Mitoxantrone HCl
Chemical family	Anthraquinone dye ametantrone derivative
Therapeutic use	Antineoplastic agent
Description	Sterile, dark blue aqueous solution; odorless
Chemical name	9,10-Anthracenedione, 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]-, dihydrochloride; 1,4-Dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]anthraquinone dihydrochloride; mitozantrone HCl; CL 232,315; NSC-301379
Product number	00640-03 (20 mg), 00640-05 (25 mg) & 00640-07 (30 mg)
CAS number	Mixture
Trade names	NOVANTRONE <sup>®</sup>

## SECTION 2 - COMPOSITION/INFORMATION ON INGREDIENTS

<u>Ingredient</u>	<u>CAS number</u>	<u>Amount</u>
Mitoxantrone HCl	[70476-82-3]	Proprietary

## SECTION 3 - HAZARDS IDENTIFICATION

Signal word	WARNING!
Statements of hazard	HARMFUL IF INHALED IN HIGH CONCENTRATIONS. CAN BE ABSORBED THROUGH ABRADED (BROKEN) SKIN IN TOXIC AMOUNTS. CAN CAUSE EFFECTS ON THE BONE MARROW, LYMPHOID ORGANS (SPLEEN, THYMUS, LYMPH NODES), GASTROINTESTINAL TRACT, AND KIDNEY (BASED ON ANIMAL DATA). MAY CAUSE EYE IRRITATION.

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**SECTION 3 - HAZARDS IDENTIFICATION...continued**

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<b>Eye effects</b>	May cause eye irritation.
<b>Skin effects</b>	Mitoxantrone hydrochloride can be absorbed through abraded (broken) skin in toxic amounts. Accidental exposure would be expected to cause nausea, vomiting, loose stool, diarrhea, decreased white blood cell count, and increased susceptibility to infection.
<b>Inhalation effects</b>	Inhalation of mists or aerosols would be expected to cause nausea, vomiting, loose stool, diarrhea, decreased white blood cell count, and increased susceptibility to infection.
<b>Ingestion effects</b>	Not an expected route of exposure in the workplace, accidental ingestion will cause similar effect as those discussed, above, under Inhalation.
<b>Known clinical effects</b>	The principal toxic effect noted is a depression of the bone marrow (myelosuppression). This effect is seen clinically as a decrease in white blood cell and platelet counts (leukopenia and thrombocytopenia). Other significant toxicities noted in clinical use include nausea and vomiting, irritation of mucous membranes (mucositis), and hair loss (alopecia).
<b>Other potential health effects</b>	Elevated serum liver enzymes are commonly reported and effects on the heart (congestive heart failure, electrocardiographic abnormalities, decreased left ventricular ejection fraction) have occurred. A blue-green discoloration of the urine (due to compound excretion) is also occasionally reported. Signs and symptoms such as hyperglycemia, edema, anorexia, weight loss, dyspnea, diarrhea, fever in absence of infection, fatigue, bleeding, infection, pain, hematuria, sweats, stomatitis, cardiac dysrhythmia, and central nervous system disorders have also been reported in clinical use.
<b>Route of entry</b>	Inhalation of mists or aerosols; eye or skin contact. Mitoxantrone HCl is poorly absorbed after oral administration. Mitoxantrone HCl may be absorbed through the abraded (broken) skin in toxic amounts.
<b>Additional data</b>	An acute intravenous lethal dose in humans would be expected to be 140 – 180 mg/m <sup>2</sup> (~280-360 mg; ~ 4-5.1 mg/kg).

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**SECTION 4 - FIRST AID MEASURES**

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<b>Eyes</b>	Immediately flush eyes with plenty of cool, low-pressure water for at least 20 minutes. Contact a physician if irritation occurs.
<b>Skin</b>	Promptly wash with soap and cool running water. Remove contaminated clothing and wash before reuse. Destroy contaminated leather items (shoes, belts, etc.). Contact a physician if irritation occurs.
<b>Inhalation</b>	Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Call a physician.
<b>Ingestion</b>	Do not induce vomiting except as directed by medical personnel. Never give anything by mouth to an unconscious person. Never induce vomiting in an unconscious person. Call a physician.

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**SECTION 5 - FIRE FIGHTING MEASURES**

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<b>General hazard</b>	Toxic emission may be given off in a fire. See Hazardous combustion products, below.
<b>Fire fighting instructions</b>	Wear NIOH/MSHA approved positive pressure, self contained breathing apparatus and full protective turn out gear. Use caution in approaching fire. Use water to keep fire-exposed containers cool.
<b>Extinguishing media</b>	Water, carbon dioxide, dry chemical, foam.
<b>Hazardous combustion products</b>	Emits toxic fumes of CO, CO <sub>2</sub> and NO <sub>x</sub>
<b>Flash point</b>	Not applicable (N/A)
<b>Autoignition</b>	Not applicable (N/A)
<b>Minimum explosive concentration for dust/vapor</b>	Not applicable (N/A)
<b>Flammability limits</b>	Not applicable (N/A)

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**SECTION 6 - ACCIDENTAL RELEASE MEASURES**

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<b>Occupational spill</b>	Shut off the source of spill or leak. Absorb spills with non-combustible absorbent material and transfer into a labeled container for disposal. Decontaminate spill and spill site as indicated below under <b>DECONTAMINATION PROCEDURES</b> . Clean spill area thoroughly. Prevent entry into drains, sewers, and waterways.
<b>Clean up - large spill</b>	Review Sections 3, 8 and 12 before proceeding with clean up. Contain the source of the spill or leak. Dike or pump spilled material into a labeled recovery or disposal container or absorb with non-combustible material. Decontaminate spill and spill site as indicated below under <b>DECONTAMINATION PROCEDURES</b> . Clean spill area thoroughly. Use appropriate containment to avoid environmental contamination. Prevent runoff from entering drains, sewers, or streams.
<b>DECONTAMINATION PROCEDURES</b>	Decontaminate the spill site by wetting the spill with a mixture of water and household dish detergent, adding bleach until the blue color disappears (slight foaming maybe observed). The amounts of water, detergent, and bleach used to validate this method were arbitrarily set at approximately 25:1:50, but variation on these proportions should still accomplish the decontamination provided the blue color is eliminated. Alternatively, decontaminate with 5.5 parts calcium hypochlorite in 13 parts by weight of water for each 1 part of Mitoxantrone HCl. <b>CAUTION! CHLORINE GAS MAY BE GENERATED DURING EITHER OF THESE DECONTAMINATION PROCEDURES!</b> Once deactivation is completed, the residual material may be flushed to a sanitary sewer with water.

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**SECTION 6 - ACCIDENTAL RELEASE MEASURES**

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**Reporting requirements** The United States Environmental Protection Agency (USEPA) has not established a Reportable Quantity (RQ) for releases of this material. State and Local regulations vary and may impose additional reporting requirements.

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**SECTION 7 - HANDLING AND STORAGE**

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**General handling** Eliminate possible ignition sources (e.g., heat, sparks, flame, impact, friction, and electricity), and follow appropriate grounding and bonding procedures. Use with adequate ventilation. Use appropriate personal protective equipment. Maintain good housekeeping and personal hygiene procedures.

**Storage** Mitoxantrone HCl concentrate for injection should be stored at controlled room temperature. **DO NOT REFRIGERATE OR FREEZE.** NOVANTRONE has a shelf life of 2 years from manufacture.

**Temperature range for storage** 15-25°C (59-77°F)

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

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**Exposure limits**

<u>Ingredient</u>	<u>Issued by</u>	<u>Type</u>	<u>OEL</u>
Mitoxantrone HCl	OSHA	TWA-8 HR	Not established
	ACGIH	TWA-8 HR	Not established
	AHPC	TWA-8 HR	0.2 µg/m <sup>3</sup>

**Measurement method** No data available

**Ventilation** Use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits.

**Eye protection** The use of safety Glasses/Goggles is required.

**Skin protection** Use protective clothing (lab coats, disposable coveralls, etc.) in both production and laboratory areas. Minimize excess handling.

**Hand protection** Two pairs latex exam or rubber gloves should be worn to prevent contact with the skin.

**Respiratory protection** If the applicable AHPC TWA-OEG is exceeded, wear an approved air-purifying respirator with high efficiency cartridges sufficient to reduce exposures to below TWA<sub>g</sub>-OEG.

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**SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES**

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<b>Physical form</b>	Sterile, non-pyrogenic aqueous solution
<b>Color</b>	Dark blue
<b>Odor</b>	Odorless
<b>Taste</b>	Not applicable
<b>Molecular weight</b>	Mixture
<b>Molecular formula</b>	Mixture
<b>pH</b>	3.0 – 4.5 (0.05% aqueous solution)
<b>Boiling point</b>	No data available
<b>Melting point</b>	250°C
<b>Vapor pressure</b>	Not applicable
<b>Relative vapor density</b>	Not applicable
<b>Water solubility</b>	Mitoxantrone HCl is soluble to ~ 12% in water
<b>Solvent solubility</b>	Mitoxantrone HCl is slightly soluble in methanol, practically insoluble in acetonitrile, chloroform, and acetone

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**SECTION 10 - STABILITY AND REACTIVITY**

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<b>Reactivity</b>	Stable
<b>Conditions to avoid</b>	No data available
<b>Incompatibilities</b>	Oxidizing agents (hypochlorite or permanganate)
<b>Hazardous decomposition products</b>	Emits toxic fumes of CO, CO <sub>2</sub> and NO <sub>x</sub> . Bulk Mitoxantrone HCl will decompose exothermically at 250°C.
<b>Hazardous polymerization</b>	Will not occur.

**DUST HAZARD INFORMATION:**

**Explosibility classification – A/B Test** Not applicable (N/A)

**Minimum ignition energy (MIE)** Not applicable (N/A)

**Minimum ignition temperature (MIT)** Not applicable (N/A)

**Hazard dust class (St value)** Not applicable (N/A)

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**SECTION 11 - TOXICOLOGY INFORMATION**

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**Acute toxicity**

<u>Compound</u>	<u>Type</u>	<u>Route</u>	<u>Species</u>	<u>Dosage</u>
Mitoxantrone HCl	LD50	Oral	Rat	682-720 mg/kg
Mitoxantrone HCl	LD50	Intravenous	Rat	4.8-7.1 mg/kg
Mitoxantrone HCl	LD50	Intravenous	Mice	9.7-12.2 mg/kg
Mitoxantrone HCl	LDLo	Dermal	Rat (abraded Skin)	500 mg/kg
Mitoxantrone HCl	LDLo	Dermal	Rabbit (abraded skin)	125 mg/kg

**Skin**

Mitoxantrone HCl is absorbed through the skin, producing mortality at dose levels of 125 mg/kg or 500 mg/kg when applied to abraded rabbit and rat skin, respectively. Mitoxantrone HCl did not cause dermal sensitization in guinea pigs (maximization test) nor was it a skin irritant in rabbits.

**Eye**

Administered as a neat material, Mitoxantrone HCl produced significant ocular irritation, causing swelling, discharge, reddening of the conjunctiva, and damage to the cornea and iris. The damage initially observed progressed in severity over time. Washing of the eye immediately after exposure prevented much of the damage from occurring. Ocular administration of a preparation of Mitoxantrone HCl at 2 mg/ml in buffer caused only mild reddening of the conjunctiva.

**Inhalation**

No data available

**Ingestion**

Acute oral LD50s are listed, above in the table. Acute toxicity was characterized by generalized debilitation of the animals, with loose stools or diarrhea being a prominent observation. The primary target organs for toxicity were bone marrow and kidney.

**Mutagenicity**

As would be expected with most anti-cancer drugs, mitoxantrone HCl was positive in the Ames test, producing point mutations in bacteria, and the mouse lymphoma assay. It induced unscheduled DNA synthesis in primary rat hepatocyte cultures and induced sister chromatid exchanges in Chinese hamster ovary cells *in vitro*. Mitoxantrone showed no mutagenic effect *in vivo* in a dominant lethal test (male rats; 0.5-2 mg/kg/day IP for 5 days). In an *in vivo* cytogenecity assay in which rats were administered 0.3 mg/kg mitoxantrone IV once or in 2 doses 21 days apart, chromosomal aberrations were seen on day 1 after dosing, but no residual effect was evident after 21 days.

Although the mechanism of action of mitoxantrone HCl is not fully understood, its toxic effects can be directly related to its therapeutic activity. It is believed that mitoxantrone HCl acts as a cytotoxic (cell-killing) agent by inhibiting nucleic acid (RNA and DNA) synthesis, resulting in the death of cells that are dividing and growing (proliferating) as well as those that are in resting (non-proliferative) stages.

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**SECTION 11 - TOXICOLOGY INFORMATION...continued**

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**Subchronic effects**

Subchronic toxicity of mitoxantrone has been investigated in rats, rabbits, dogs, and monkeys. Target organs affected in these studies included the bone marrow, lymphoid organs (spleen, thymus, lymph nodes), gastrointestinal tract, and kidney. Decreases in circulating red and white blood cells were also seen. In rats, daily intravenous (IV) doses of mitoxantrone at 0.003 to 0.3 mg/kg/day for 30 days caused death to all animals receiving 0.3 mg/kg and 0.003 mg/kg was established as a non-effect level. Signs of toxicity seen at the mid-doses were primarily related to bone marrow suppression. In rabbits, IV doses of mitoxantrone at 0.125 or 0.25 mg/kg once a week for 15 weeks developed renal changes. At the high-dose, the renal effects were accompanied by the presence of cardiac changes. Dogs administered daily IV doses of mitoxantrone at 0.05 – 0.2 mg/kg/day for 14 days displayed bone marrow suppression, lymphoid depletion, and visceral congestion. The maximum tolerated dose in this study was 0.05 mg/kg. In monkeys, daily administration of mitoxantrone at 2.4 mg/kg/day for 5 days was lethal, but animals given up to 1.2 mg/kg/day survived through day 6 post-treatment.

**Chronic toxicity**

In a 12 months intravenous toxicity study, rats were given mitoxantrone once every 21 days for the length of the study, 0.03 mg/kg was the maximum tolerated dose. Kidney toxicity was the primary effect, but effects were also seen in lymphoid tissue and bone marrow. Dogs given IV doses once every 21 days for 10 dosing cycles tolerated 0.25 mg/kg of mitoxantrone. Signs of toxicity included erythropenia, leukopenia, excessive salivation, emesis, soft feces/diarrhea, testicular atrophy, lymphoid depletion, and dilation of the sarcoplasmic reticulum. Monkeys tolerated IV doses of 0.125 or 0.25 mg/kg given once every 21 days for 12 dosing cycles. Signs of toxicity seen at 0.25 mg/kg included erythropenia, leukopenia, lymphoid depletion, and myocytic changes; progressive cardiomyopathy was not seen.

**Chronic effects/  
carcinogenicity**

Mitoxantrone was not carcinogenic when administered once every 21 days for 2 years at doses ranging from 0.01 to 0.4 mg/kg in mice or from 0.01 to 0.1 mg/kg in rats.

**OSHA carcinogen**

Not listed

**Carcinogen status**

Formulation is not listed in (NTP), (IARC), or (OSHA).

**NTP carcinogen**

Not listed

**IARC carcinogen**

Not listed

**Reproductive effects**

No effects on reproduction or fertility were produced in rats given daily IV doses of mitoxantrone at 0.03 mg/kg/day prior to mating and continuing through mating, pregnancy, and lactation. No effects were seen on the F<sub>1</sub> or F<sub>2</sub> generations. There was no evidence of testicular changes related to mitoxantrone treatment in rats or monkeys during repeated-dose studies. The only evidence of such an effect was observed in dogs, the species most sensitive to mitoxantrone's effects.

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**SECTION 11 - TOXICOLOGY INFORMATION...continued**

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<b>Teratogenicity</b>	Mitoxantrone was not teratogenic in pregnant rats or rabbits given maternally toxic IV doses of 0.20 or 0.05 mg/kg/day, respectively, through the period of organogenesis.
<b>Target organs</b>	Bone marrow, lymphoid organs (spleen, thymus, lymph nodes), gastrointestinal tract, and kidney
<b>At increased risk from exposure</b>	Mitoxantrone HCl is contraindicated in patients who have demonstrated prior hypersensitivity to it.

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**SECTION 12 - ECOLOGICAL INFORMATION**

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**Environmental overview** No environmental effects data are available

**Aquatic toxicity** No data available

<u>Compound</u>	<u>Type</u>	<u>Species</u>	<u>Dosage</u>
Mitoxantrone HCl	N/A	N/A	N/A

**Degradability** No data available

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**SECTION 13 - DISPOSAL INFORMATION**

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**Disposal procedure** Dispose of in accordance with all Federal, State, and Local regulations. Incineration is recommended at a permitted facility. This is not a RCRA regulated hazardous waste.

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**SECTION 14 - TRANSPORTATION INFORMATION**

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**Proper shipping name** NOVANTRONE<sup>®</sup> mitoxantrone HCl, 2 mg/mL

**Identification number** Not applicable (N/A)

**General shipping instructions** Not regulated

**Hazard class** Not applicable (N/A)

**Packing group** Not applicable (N/A)

**IMDG class** Not applicable (N/A)

**IATA class** Not applicable (N/A)

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**SECTION 15 - REGULATORY INFORMATION**

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**TSCA status** Not listed

**SARA section 302** Not reportable

**SARA section 313** Mitoxantrone HCl is not reportable under Section 313 and contains no constituents, which are reportable under this section.

**RCRA number** None

**California proposition 65** listed

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**SECTION 16 - OTHER**

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**Sources of data**

The data contained in this MSDS may have been gathered from confidential internal sources, mitoxantrone OEG and clinical investigator brochure, raw material suppliers, or from the published literature.

**Preparation and Revision information****Prepared by**  
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