

CI 4606-5



# SPECIMEN

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## NOVANTRONE® mitoxantrone for injection concentrate

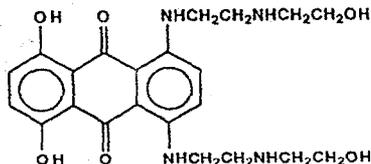
### WARNING

NOVANTRONE® (mitoxantrone for injection concentrate) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Except for the treatment of acute nonlymphocytic leukemia, NOVANTRONE® therapy generally should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm<sup>3</sup>. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving NOVANTRONE®.

### DESCRIPTION

NOVANTRONE® (mitoxantrone hydrochloride) is a synthetic antineoplastic anthracenedione for intravenous use. The molecular formula is C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>6</sub>•2HCl and the molecular weight is 517.41. It is supplied as a concentrate which **MUST BE DILUTED PRIOR TO INJECTION**. The concentrate is a sterile, nonpyrogenic, dark blue aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride (0.80% w/v), sodium acetate (0.005% w/v), and acetic acid (0.046% w/v) as inactive ingredients. The solution has a pH of 3.0 to 4.5 and contains 0.14 mEq of sodium per mL. The product does not contain preservatives. The chemical name is 1,4-dihydroxy-5,8-bis[2-[(2-hydroxyethyl) amino]ethyl]amino]-9,10-anthracenedione dihydrochloride and the structural formula is:



• 2HCl

### CLINICAL PHARMACOLOGY

#### Mechanism of Action

Although its mechanism of action is not fully elucidated, mitoxantrone is a DNA-reactive agent. It has a cytotoxic effect on both proliferating and nonproliferating cultured human cells, suggesting lack of cell cycle phase specificity.

#### Pharmacokinetics

Pharmacokinetics of mitoxantrone in patients following a single intravenous administration of NOVANTRONE can be characterized by a three-compartment model. The mean alpha half-life of mitoxantrone is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours and the mean gamma (terminal or elimination) half-life is 23 to 215 hours (median approximately 75 hours). Pharmacokinetic studies have not been performed in humans receiving multiple daily dosing. Distribution to tissues is extensive: steady-state volume of distribution exceeds 1,000 L/m<sup>2</sup>. Tissue concentrations of mitoxantrone appear to exceed those in the blood during the terminal elimination phase. In the monkey, distribution to brain, spinal cord, eye, and spinal fluid is low.

In patients administered 15-90 mg/m<sup>2</sup> of NOVANTRONE intravenously, there is a linear relationship between dose and the area under the concentration-time curve.

Mitoxantrone is 78% bound to plasma proteins in the observed concentration range of 26-455 ng/mL. This binding is independent of concentration and is not affected by the presence of phenytoin, doxorubicin, methotrexate, prednisone, prednisolone, heparin, or aspirin.

**Metabolism and Elimination:** Metabolism and elimination of mitoxantrone following NOVANTRONE administration are not well characterized. Eleven percent or less of mitoxantrone is recovered in the urine, and 25% or less is recovered in the feces, within five days after drug administration. Of the

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material recovered in the urine, 65% is unchanged drug. The remaining 35% is comprised primarily of a mono- and a dicarboxylic acid derivative and their glucuronide conjugates. These carboxylic acid metabolites are not DNA-reactive/cytocidal, and their route of formation is unknown.

#### **Special Populations:**

**Gender:** The effect of gender on mitoxantrone pharmacokinetics is unknown.

**Geriatric:** Mitoxantrone pharmacokinetics in the elderly are unknown.

**Pediatric:** Mitoxantrone pharmacokinetics in the pediatric population are unknown.

**Race:** The effect of race on mitoxantrone pharmacokinetics is unknown.

**Renal Impairment:** Mitoxantrone pharmacokinetics in patients with renal impairment are unknown.

**Hepatic Impairment:** Mitoxantrone clearance is reduced by hepatic impairment. Patients with severe hepatic dysfunction (bilirubin greater than 3.4 mg/dL) have an AUC more than 3-fold that of patients with normal hepatic function receiving the same dose. For patients with hepatic impairment, there is at present no laboratory measurement that allows for dose adjustment recommendations.

**Drug Interactions:** Pharmacokinetic studies of the interaction of NOVANTRONE with concomitantly administered medications have not been performed. The interaction of mitoxantrone with the human P450 system has not been investigated.

#### **Clinical Trials**

##### **Advanced Hormone-Refractory Prostate Cancer**

A multicenter phase 2 trial of NOVANTRONE and low-dose prednisone (N + P) was conducted in 27 symptomatic patients with hormone-refractory prostate cancer. Using NCCP (National Prostate Cancer Project) criteria for disease response, there was one partial responder and 12 patients with stable disease. However, nine patients or 33% achieved a palliative response defined on the basis of reduction in analgesic use or pain intensity.

These findings lead to the initiation of a randomized multicenter trial (CCI-NOV22) comparing the effectiveness of (N + P) to low-dose prednisone alone (P). Eligible patients were required to have metastatic or locally advanced disease that had progressed on standard hormonal therapy, a castrate serum testosterone level, and at least mild pain at study entry. NOVANTRONE was administered at a dose of 12 mg/m<sup>2</sup> by short IV infusion every three weeks. Prednisone was administered orally at a dose of 5 mg twice a day. Patients randomized to the prednisone arm were crossed over to the N + P arm if they progressed or if they were not improved after a minimum of six weeks of therapy with prednisone alone.

A total of 161 patients were randomized, 80 to the N + P arm and 81 to the P arm. The median NOVANTRONE dose administered was 12 mg/m<sup>2</sup> per cycle. The median cumulative NOVANTRONE dose administered was 73 mg/m<sup>2</sup> (range of 12 to 212 mg/m<sup>2</sup>).

A primary palliative response (defined as a 2-point decrease in pain intensity in a 6-point pain scale, associated with stable analgesic use, and lasting a minimum of 6 weeks) was achieved in 29% of patients randomized to N + P compared to 12% of patients randomized to P alone (p = 0.011). Two responders left the study after meeting primary response criterion for two consecutive cycles. For the purposes of this analysis, these two patients were assigned a response duration of zero days. A secondary palliative response was defined as a 50% or greater decrease in analgesic use, associated with stable pain intensity, and lasting a minimum of 6 weeks. An overall palliative response (defined as primary plus secondary responses) was achieved in 38% of patients randomized to N + P compared to 21% of patients randomized to P (p = 0.025).

The median duration of primary palliative response for patients randomized to N + P was 7.6 months compared to 2.1 months for patients randomized to P alone (p = 0.0009). The median duration of overall palliative response for patients randomized to N + P was 5.6 months compared to 1.9 months for patients randomized to P alone (p = 0.0004).

Time to progression was defined as a 1-point increase in pain intensity, or a >25% increase in analgesic use, or evidence of disease progression on radiographic studies, or requirement for radiotherapy. The median time to progression for all patients randomized to N + P was 4.4 months compared to 2.3 months for all patients randomized to P alone (p = 0.0001). Median time to death was 11.3 months for all patients on the N + P arm compared to 10.8 months for all patients on P alone (p = 0.2324).

Forty-eight patients on the P arm crossed over to receive N + P. Of these, thirty patients had progressed on P, while 18 had stable disease on P. The median cycle of crossover was 5 cycles (range of 2 to 16 cycles). Time trends for pain intensity prior to crossover were significantly worse for patients who crossed over than for those who remained on P alone (p = 0.012). Nine patients (19%) demonstrated a palliative response on N + P after crossover. The median time to death for patients who crossed over to N + P was 12.7 months.

The clinical significance of a fall in prostate specific antigen (PSA) concentrations after chemotherapy is unclear. On the CCI-NOV22 trial, a PSA fall of 50% or greater for two consecutive follow-up assessments after baseline was reported in 33% of all patients randomized to the N + P arm and 9% of all patients randomized to the P arm. These findings should be interpreted with caution since PSA responses were not defined prospectively. A number of patients were inevaluable for response, and there was an imbalance between treatment arms in the number of evaluable patients. In addition, PSA reduction did not correlate precisely with palliative response, the primary efficacy endpoint of this study. For example, among the 26 evaluable patients randomized to the N + P arm who had a ≥ 50% reduction in PSA, only 13 had a primary palliative response. Also, among 42 evaluable patients on this arm who did not have this reduction in PSA, 8 nonetheless had a primary palliative response.

Investigators at Cancer and Leukemia Group B (CALGB) conducted a phase III comparative trial of NOVANTRONE plus hydrocortisone (N + H) versus hydrocortisone alone (H) in patients with hormone-refractory prostate cancer (CALGB 9182). Eligible patients were required to have metastatic disease that had progressed despite at least one hormonal therapy. Progression at study entry was defined on



### NOVANTRONE (mitoxantrone for injection concentrate)

ISTRY MONITORING AND ADJUNCTIVE THERAPIES, INCLUDING ANTIBIOTICS. BLOOD AND BLOOD PRODUCTS MUST BE AVAILABLE TO SUPPORT PATIENTS DURING THE EXPECTED PERIOD OF MEDULLARY HYPOPLASIA AND SEVERE MYELOSUPPRESSION. PARTICULAR CARE SHOULD BE GIVEN TO ASSURING FULL HEMATOLOGIC RECOVERY BEFORE UNDERTAKING CONSOLIDATION THERAPY (IF THIS TREATMENT IS USED) AND PATIENTS SHOULD BE MONITORED CLOSELY DURING THIS PHASE.

Patients with preexisting myelosuppression as the result of prior drug therapy should not receive NOVANTRONE unless it is felt that the possible benefit from such treatment warrants the risk of further medullary suppression.

The safety of NOVANTRONE in patients with hepatic insufficiency is not established. (See **CLINICAL PHARMACOLOGY** section.)

Safety for use by routes other than intravenous administration has not been established.

NOVANTRONE is not indicated for intra-arterial injection. There have been reports of local/regional neuropathy, some irreversible, following intra-arterial injection.

NOVANTRONE should not be given by intrathecal injection. There have been reports of neuropathy including paralysis and bowel and bladder dysfunction following intrathecal injection.

**Pregnancy** - NOVANTRONE may cause fetal harm when administered to a pregnant woman. In treated rats, at doses of  $\geq 0.1$  mg/kg (0.05 fold the recommended human dose on a mg/m<sup>2</sup> basis) low fetal birth weight and retarded development of the fetal kidney were seen in greater frequency. In treated rabbits, an increased incidence of premature delivery was observed at doses  $\geq 0.01$  mg/kg (0.01 fold the recommended human dose on a mg/m<sup>2</sup> basis). NOVANTRONE was not teratogenic in rabbits. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Topoisomerase II inhibitors, including NOVANTRONE, in combination with other antineoplastic agents, have been associated with the development of acute leukemia.

#### Cardiac Effects

Because of the possible danger of cardiac effects in patients previously treated with daunorubicin or doxorubicin, the benefit-to-risk ratio of NOVANTRONE therapy in such patients should be determined before starting therapy.

**General** - Functional cardiac changes including decreases in left ventricular ejection fraction (LVEF) and irreversible congestive heart failure can occur with NOVANTRONE. Cardiac toxicity may be more common in patients with prior treatment with anthracyclines, prior mediastinal radiotherapy, or with preexisting cardiovascular disease. Such patients should have regular cardiac monitoring of LVEF from the initiation of therapy. In investigational trials of intermittent single doses in other tumor types, patients who received up to the cumulative dose of 140 mg/m<sup>2</sup> had a cumulative 2.6% probability of clinical congestive heart failure. The overall cumulative probability rate of moderate or serious decreases in LVEF at this dose was 13% in comparative trials.

**Leukemia** - Acute congestive heart failure may occasionally occur in patients treated with NOVANTRONE for ANLL. In first-line comparative trials of NOVANTRONE + cytarabine vs daunorubicin + cytarabine in adult patients with previously untreated ANLL, therapy was associated with congestive heart failure in 6.5% of patients on each arm. A causal relationship between drug therapy and cardiac effects is difficult to establish in this setting since myocardial function is frequently depressed by the anemia, fever and infection, and hemorrhage which often accompany the underlying disease.

**Hormone-Refractory Prostate Cancer** - Functional cardiac changes such as decreases in LVEF and congestive heart failure may occur in patients with hormone-refractory prostate cancer treated with NOVANTRONE. In a randomized comparative trial of NOVANTRONE plus low-dose prednisone vs low-dose prednisone, 7 of 128 patients (5.5%) treated with NOVANTRONE had a cardiac event defined as any decrease in LVEF below the normal range, congestive heart failure (n = 3), or myocardial ischemia. Two patients had a prior history of cardiac disease. The total NOVANTRONE dose administered to patients with cardiac effects ranged from >48 to 212 mg/m<sup>2</sup>.

Among 112 patients evaluable for safety on the NOVANTRONE + hydrocortisone arm of the CALGB trial, 18 patients (19%) had a reduction in cardiac function, 5 patients (5%) had cardiac ischemia, and 2 patients (2%) experienced pulmonary edema. The range of total NOVANTRONE doses administered to these patients is not available.

#### PRECAUTIONS

**General:** Therapy with NOVANTRONE should be accompanied by close and frequent monitoring of hematologic and chemical laboratory parameters, as well as frequent patient observation.

Systemic infections should be treated concomitantly with or just prior to commencing therapy with NOVANTRONE.

**Information for Patients:** NOVANTRONE may impart a blue-green color to the urine for 24 hours after administration, and patients should be advised to expect this during therapy. Bluish discoloration of the sclera may also occur. Patients should be advised of the signs and symptoms of myelosuppression.

**Laboratory Tests:** Serial complete blood counts and liver function tests are necessary for appropriate dose adjustments. (See **DOSAGE AND ADMINISTRATION** section.)

In leukemia treatment, hyperuricemia may occur as a result of rapid lysis of tumor cells by NOVANTRONE. Serum uric acid levels should be monitored and hypouricemic therapy instituted prior to the initiation of antileukemic therapy.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis:** Intravenous treatment of rats and mice, once every 21 days for 24 months, with NOVANTRONE resulted in an increased incidence of fibroma and external auditory canal tumors in rats

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**Preparation and Administration Precautions: NOVANTRONE CONCENTRATE MUST BE DILUTED PRIOR TO USE.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The dose of NOVANTRONE should be diluted to at least 50 mL with either 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP). NOVANTRONE may be further diluted into Dextrose 5% in Water, Normal Saline or Dextrose 5% with Normal Saline and used immediately. DO NOT FREEZE.

NOVANTRONE should not be mixed in the same infusion as heparin since a precipitate may form. Because specific compatibility data are not available, it is recommended that NOVANTRONE not be mixed in the same infusion with other drugs. The diluted solution should be introduced slowly into the tubing as a freely running intravenous infusion of 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP) over a period of not less than 3 minutes. Unused infusion solutions should be discarded immediately in an appropriate fashion. In the case of multidose use, after penetration of the stopper, the remaining portion of the undiluted NOVANTRONE concentrate should be stored not longer than 7 days between 15°-25° C (59°-77° F) or 14 days under refrigeration. DO NOT FREEZE. CONTAINS NO PRESERVATIVE.

If extravasation occurs, the administration should be stopped immediately and restarted in another vein. The nonvesicant properties of NOVANTRONE minimize the possibility of severe local reactions following extravasation. However, care should be taken to avoid extravasation at the infusion site and to avoid contact of NOVANTRONE with the skin, mucous membranes or eyes.

Skin accidentally exposed to NOVANTRONE should be rinsed copiously with warm water and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.<sup>1-7</sup> There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

**REFERENCES**

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985; 253 (11):1590-1592.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc D, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia*. 1983; 1:426-428.
5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. *Ca - A Cancer Journal for Clinicians*. Sept/Oct 1983; 258-263.
6. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990; 47:1033-1049.
7. OSHA Work-Practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. *Am J Hosp Pharm*. 1986; 43:1193-1204.

**HOW SUPPLIED**

NOVANTRONE® (mitoxantrone for injection concentrate) is a sterile aqueous solution containing mitoxantrone hydrochloride at a concentration equivalent to 2 mg mitoxantrone free base per mL supplied in vials for multidose use as follows:

- |                  |                                  |
|------------------|----------------------------------|
| NDC 58406-640-03 | - 10 mL/multidose vial (20 mg)   |
| NDC 58406-640-05 | - 12.5 mL/multidose vial (25 mg) |
| NDC 58406-640-07 | - 15 mL/multidose vial (30 mg)   |

NOVANTRONE® (mitoxantrone for injection concentrate) should be stored between 15°-25°C (59°-77°F). DO NOT FREEZE.

**IMMUNEX®**

Manufactured for IMMUNEX CORPORATION, Seattle, WA 98101  
by LEDERLE PARENTERALS, INC., Carolina, Puerto Rico 00987

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