CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-120

FINAL PRINTED LABELING

October 13, 2000

Package Insert

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 cytotoxic chemotherapy agents.

NOVANTRONE should be given slowly into a freely flowing intravenous infusion. It must *never* be given subcutaneously, intramuscularly, or intra-arterially. Severe local tissue damage may occur if there is extravasation during administration. (See **ADVERSE REACTIONS, General,** Cutaneous)

NOT FOR INTRATHECAL USE. Severe injury with permanent sequelae can result from intrathecal administration. (See **WARNINGS, General)**

Except for the treatment of acute nonlymphocytic leukemia, NOVANTRONE therapy generally should not be given to patients with baseline neutrophil counts of less than 1500 cells/mm^3. 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.

Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with NOVANTRONE or months to years after termination of therapy. Use of NOVANTRONE has been associated with cardiotoxicity; this risk increases with cumulative dose. In cancer patients, the risk of symptomatic congestive heart failure (CHF) was estimated to be

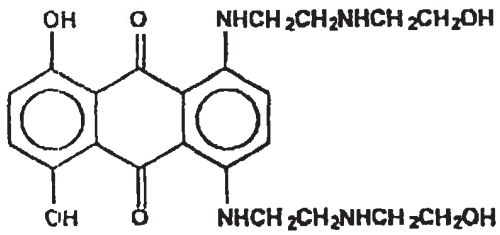
2.6% for patients receiving up to a cumulative dose of 140 mg/m^2. For this reason, patients should be monitored for evidence of cardiac toxicity and questioned about symptoms of heart failure prior to initiation of treatment. Patients with multiple sclerosis who reach a cumulative dose of 100 mg/m^2 should be monitored for evidence of cardiac toxicity prior to each subsequent dose. Ordinarily, patients with multiple sclerosis should not receive a cumulative dose greater than 140 mg/m^2. Active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with NOVANTRONE may occur at lower cumulative doses whether or not cardiac risk factors are present. For additional information, see **WARNINGS, Cardiac Effects**, and **DOSAGE AND ADMINISTRATION.**

Secondary acute myelogenous leukemia (AML) has been reported in cancer patients treated with anthracyclines. NOVANTRONE is an anthracenedione, a related drug. The occurrence of refractory secondary leukemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. Secondary leukemias have been reported in cancer patients treated with NOVANTRONE in combination with other cytotoxic agents; the incidence of these events has not been quantified.

DESCRIPTION

NOVANTRONE (mitoxantrone hydrochloride) is a synthetic antineoplastic anthracenedione for intravenous use. The molecular formula is $C_{22}H_{28}N_4O_6 \cdot 2HCl$ and the molecular weight is 517.41. It is supplied as a concentrate that 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

Mitoxantrone, a DNA-reactive agent that intercalates into deoxyribonucleic acid (DNA) through hydrogen bonding, causes crosslinks and strand breaks. Mitoxantrone also interferes with ribonucleic acid (RNA) and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA. It has a cytocidal effect on both proliferating and nonproliferating cultured human cells, suggesting lack of cell cycle phase specificity.

NOVANTRONE has been shown in vitro to inhibit B cell, T cell, and macrophage proliferation and impair antigen presentation, as well as the secretion of interferon gamma, TNFα, and IL-2.[1-4]

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 1000 L/m^2. Tissue concentrations of mitoxantrone appear to exceed those in the blood during the terminal elimination phase. In the healthy monkey, distribution to brain, spinal cord, eye, and spinal fluid is low.

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

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

Mitoxantrone is excreted in urine and feces as either unchanged drug or as inactive metabolites. In human studies, 11% and 25% of the dose were recovered in urine and feces, respectively, as either parent drug or metabolite during the 5-day period following drug administration. Of the material recovered in urine, 65% was unchanged drug. The remaining 35% was composed of monocarboxylic and dicarboxylic acid derivatives and their glucuronide conjugates. The pathways leading to the metabolism of NOVANTRONE have not been elucidated.

In vitro drug interaction studies have demonstrated that mitoxantrone did not inhibit CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 across a broad concentration range. The results of in vitro induction studies are inconclusive, but suggest that mitoxantrone is a weak inducer of CYP450 2E1 activity.

Special Populations

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

Geriatric: In elderly patients with breast cancer, the systemic mitoxantrone clearance was 21.3 L/hr/m^2, compared with 28.3 L/hr/m^2 and 16.2 L/hr/m^2 for non-elderly patients with nasopharyngeal carcinoma and malignant lymphoma, respectively.

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 > 3.4 mg/dL) have an AUC more than three times greater than that of patients with normal hepatic function receiving the same dose. Patients with multiple sclerosis who have hepatic impairment should ordinarily not be treated with NOVANTRONE. Other patients with hepatic impairment should be treated with caution and dosage adjustment may be required.

Drug Interactions: Pharmacokinetic studies of the interaction of NOVANTRONE with concomitantly administered medications have not been performed. The pathways leading to the metabolism of NOVANTRONE have not been elucidated. To date, post-marketing experience has not revealed any significant drug interactions in patients who have received NOVANTRONE for treatment of cancer. Information on drug interactions in patients with multiple sclerosis is limited.

CLINICAL TRIALS

Multiple Sclerosis

The safety and efficacy of NOVANTRONE in multiple sclerosis were assessed in two randomized, multicenter clinical studies.

One randomized, controlled study (Study 1) was conducted in patients with secondary progressive or progressive relapsing multiple sclerosis. Patients in this study demonstrated significant neurological disability based on the Kurtzke Expanded Disability Status Scale (EDSS). The EDSS is an ordinal scale with 0.5 point increments ranging from 0.0 to 10.0 (increasing score indicates worsening) and based largely on ambulatory impairment in its middle range (EDSS 4.5 to 7.5 points). Patients in this study had experienced a mean deterioration in EDSS of about 1.6 points over the 18 months prior to enrollment.

Patients were randomized to receive placebo, 5 mg/m^2 NOVANTRONE, or 12 mg/m^2 NOVANTRONE administered IV every 3 months for 2 years. High-dose methylprednisolone was administered to treat relapses. The intent-to-treat analysis cohort consisted of 188 patients; 149 completed the 2-year study. Patients were evaluated every 3 months, and clinical outcome was determined after 24 months. In addition, a subset of patients was assessed with magnetic resonance imaging (MRI) at baseline, Month 12, and Month 24. Neurologic assessments and MRI reviews were performed by evaluators blinded to study drug and clinical outcome, although the diagnosis of relapse and the decision to treat relapses with steroids were made by unblinded treating physicians. A multivariate analysis of five clinical variables (EDSS, Ambulation Index [AI], number of relapses requiring treatment with steroids, months to first relapse needing treatment with steroids, and Standard Neurological Status [SNS]) was used to determine primary efficacy. The AI is an ordinal scale ranging from 0 to 9 in one point increments to define progressive ambulatory impairment. The SNS provides an overall measure of neurologic impairment and disability, with scores ranging from 0 (normal neurologic examination) to 99 (worst possible score).

Results of Study 1 are summarized in Table 1.

Table 1
Efficacy Results at Month 24
Study 1

Primary Endpoints	Treatment Groups			p-value
		NOVANTRONE		
	Placebo (N = 64)	5 mg/m² (N = 64)	12 mg/m² (N = 60)	Placebo vs 12 mg/m² NOVANTRONE
Primary efficacy multivariate analysis*	-	-	-	< 0.0001
Primary clinical variables analyzed:				
EDSS change** (mean)	0.23	−0.23	−0.13	0.0194
Ambulation Index change** (mean)	0.77	0.41	0.30	0.0306
Mean number of relapses per patient requiring corticosteroid treatment (adjusted for discontinuation)	1.20	0.73	0.40	0.0002
Months to first relapse requiring corticosteroid treatment (median [1st quartile])	14.2 [6.7]	NR [6.9]	NR [20.4]	0.0004
Standard Neurological Status change** (mean)	0.77	−0.38	−1.07	0.0269
MRI‡				
No. of patients with new Gd-enhancing lesions	5/32 (16%)	4/37 (11%)	0/31	0.022
Change in number of T2-weighted lesions, mean (n)**	1.94 (32)	0.68 (34)	0.29 (28)	0.027

NR = not reached within 24 months; MRI = magnetic resonance imaging.
* Wei-Lachin test.
** Month 24 value minus baseline.
‡ A subset of 110 patients was selected for MRI analysis. MRI results were not available for all patients at all time points.

A second randomized, controlled study (Study 2) evaluated NOVANTRONE in combination with methylprednisolone (MP) and was conducted in patients with secondary progressive or worsening relapsing-remitting multiple sclerosis who had residual neurological deficit between relapses. All patients had experienced at least two relapses with sequelae or neurological deterioration within the previous 12 months. The average deterioration in EDSS was 2.2 points during the previous 12 months. During the screening period, patients were treated with two monthly doses of 1 g of IV MP and underwent monthly MRI scans. Only patients who developed at least one new Gd-enhancing MRI lesion during the 2-month screening period were eligible for randomization. A total of 42 evaluable patients received monthly treatments of 1 g of IV MP alone (n = 21) or ~12 mg/m^2 of IV NOVANTRONE plus 1 g of IV MP (n = 21) (NOV + MP) for 6 months. Patients were evaluated monthly, and study outcome was determined after 6 months. The primary measure of effectiveness in this study was a comparison of the proportion of patients in each treatment group who developed no new Gd-enhancing MRI lesions at 6 months; these MRIs were assessed by a blinded panel.

Additional outcomes were measured, including EDSS and number of relapses, but all clinical measures in this trial were assessed by an unblinded treating physician. Five patients, all in the MP alone arm, failed to complete the study due to lack of efficacy.

The results of this trial are displayed in Table 2.

Table 2
Efficacy Results
Study 2

Primary Endpoint	MP alone (N = 21)	NOV + MP (N = 21)	p-value
Patients (%) without new Gd-enhancing lesions on MRIs (primary endpoint)*	5 (31%)	19 (90%)	0.001
Secondary Endpoints			
EDSS change (Month 6 minus baseline)* (mean)	-0.1	-1.1	0.013
Annualized relapse rate (mean per patient)	3.0	0.7	0.003
Patients (%) without relapses	7 (33%)	14 (67%)	0.031

MP = methylprednisolone; N + MP = NOVANTRONE plus methylprednisolone.
* Results at Month 6, not including data for 5 withdrawals in the MP alone group.

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 NPCP (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 led 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^2 by short IV infusion every 3 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 6 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^2 per cycle. The median cumulative NOVANTRONE dose administered was 73 mg/m^2 (range of 12 to 212 mg/m^2).

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 numbers 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 $\geq$ 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 3 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 the basis of progressive symptoms, increases in measurable or osseous disease, or rising PSA levels. NOVANTRONE was administered intravenously at a dose of 14 mg/m^2 every 21 days and hydrocortisone was administered orally at a daily dose of 40 mg. A total of 242 subjects were randomized, 119 to the N + H arm and 123 to the H arm. There were no

differences in survival between the two arms, with a median of 11.1 months in the N + H arm, and 12 months in the H arm (p = 0.3298).

Using NPCP criteria for response, partial responses were achieved in 10 patients (8.4%) randomized to the N + H arm compared with 2 patients (1.6%) randomized to the H arm (p = 0.018). The median time to progression, defined by NPCP criteria, for patients randomized to the N + H arm was 7.3 months compared to 4.1 months for patients randomized to H alone (p = 0.0654).

Approximately 60% of patients on each arm required analgesics at baseline. Analgesic use was measured in this study using a 5-point scale. The best percent change from baseline in mean analgesic use was -17% for 61 patients with available data on the N + H arm, compared with +17% for 61 patients on H alone (p = 0.014). A time trend analysis for analgesic use in individual patients also showed a trend favoring the N + H arm over H alone but was not statistically significant.

Pain intensity was measured using the Symptom Distress Scale (SDS) Pain Item 2 (a 5-point scale). The best percent change from baseline in mean pain intensity was -14% for 37 patients with available data on the N + H arm, compared with +8% for 38 patients on H alone (p = 0.057). A time trend analysis for pain intensity in individual patients showed no difference between treatment arms.

Acute Nonlymphocytic Leukemia

In two large randomized multicenter trials, remission induction therapy for acute nonlymphocytic leukemia (ANLL) with NOVANTRONE 12 mg/m^2 daily for 3 days as a 10-minute intravenous infusion and cytarabine 100 mg/m^2 for 7 days given as a continuous 24-hour infusion was compared with daunorubicin 45 mg/m^2 daily by intravenous infusion for 3 days plus the same dose and schedule of cytarabine used with NOVANTRONE. Patients who had an incomplete antileukemic response received a second induction course in which NOVANTRONE or daunorubicin was administered for 2 days and cytarabine for 5 days using the same daily dosage schedule. Response rates

and median survival information for both the U.S. and international multicenter trials are given in Table 3:

Table 3
Response Rates, Time to Response, and Survival in U.S. and International Trials

Trial	% Complete Response (CR)		Median Time to CR (days)		Survival (days)	
	NOV	DAUN	NOV	DAUN	NOV	DAUN
U.S.	63 (62/98)	53 (54/102)	35	42	312	237
International	50 (56/112)	51 (62/123)	36	42	192	230

NOV = NOVANTRONE® + cytarabine
DAUN = daunorubicin + cytarabine

In these studies, two consolidation courses were administered to complete responders on each arm. Consolidation therapy consisted of the same drug and daily dosage used for remission induction, but only 5 days of cytarabine and 2 days of NOVANTRONE or daunorubicin were given. The first consolidation course was administered 6 weeks after the start of the final induction course if the patient achieved a complete remission. The second consolidation course was generally administered 4 weeks later. Full hematologic recovery was necessary for patients to receive consolidation therapy. For the U.S. trial, median granulocyte nadirs for patients receiving NOVANTRONE + cytarabine for consolidation courses 1 and 2 were 10/mm^3 for both courses, and for those patients receiving daunorubicin + cytarabine nadirs were 170/mm^3 and 260/mm^3, respectively. Median platelet nadirs for patients who received NOVANTRONE + cytarabine for consolidation courses 1 and 2 were 17,000/mm^3 and 14,000/mm^3, respectively, and were 33,000/mm^3 and 22,000/mm^3 in courses 1 and 2 for those patients who received daunorubicin + cytarabine. The benefit of consolidation therapy in ANLL patients who achieve a complete remission remains controversial. However, in the only well-controlled prospective, randomized multicenter trials with NOVANTRONE in ANLL, consolidation therapy was given to all patients who achieved a complete remission. During consolidation in the U.S. study, two myelosuppression-related deaths occurred on the NOVANTRONE arm and one on the daunorubicin arm. However, in the international study there were eight deaths on the NOVANTRONE arm

during consolidation which were related to the myelosuppression and none on the daunorubicin arm where less myelosuppression occurred.

INDICATIONS AND USAGE

NOVANTRONE is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses). NOVANTRONE is not indicated in the treatment of patients with primary progressive multiple sclerosis.

The clinical patterns of multiple sclerosis in the studies were characterized as follows: secondary progressive and progressive relapsing disease were characterized by gradual increasing disability with or without superimposed clinical relapses, and worsening relapsing-remitting disease was characterized by clinical relapses resulting in a step-wise worsening of disability.

NOVANTRONE in combination with corticosteroids is indicated as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.

NOVANTRONE in combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults. This category includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias.

CONTRAINDICATIONS

NOVANTRONE is contraindicated in patients who have demonstrated prior hypersensitivity to it.

WARNINGS

WHEN NOVANTRONE IS USED IN HIGH DOSES (> 14 $mg/m^2/d$ x 3 days) SUCH AS INDICATED FOR THE TREATMENT OF LEUKEMIA, SEVERE

MYELOSUPPRESSION WILL OCCUR. THEREFORE, IT IS RECOMMENDED THAT NOVANTRONE BE ADMINISTERED ONLY BY PHYSICIANS EXPERIENCED IN THE CHEMOTHERAPY OF THIS DISEASE. LABORATORY AND SUPPORTIVE SERVICES MUST BE AVAILABLE FOR HEMATOLOGIC AND CHEMISTRY 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. NOVANTRONE ADMINISTERED AT ANY DOSE CAN CAUSE MYELOSUPPRESSION.

General

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 (mitoxantrone for injection concentrate) in patients with hepatic insufficiency is not established (see **CLINICAL PHARMACOLOGY**).

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

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

NOVANTRONE must not be given by intrathecal injection. There have been reports of neuropathy and neurotoxicity, both central and peripheral, following intrathecal

injection. These reports have included seizures leading to coma and severe neurologic sequelae, and paralysis with bowel and bladder dysfunction.

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.

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. Cancer patients who received cumulative doses of 140 mg/m^2 either alone or in combination with other chemotherapeutic agents had a cumulative 2.6% probability of clinical congestive heart failure. In comparative oncology trials, the overall cumulative probability rate of moderate or severe decreases in LVEF at this dose was 13%.

Multiple Sclerosis: Functional cardiac changes may occur in patients with multiple sclerosis treated with NOVANTRONE. In one controlled trial (Study 1, see **CLINICAL TRIALS, Multiple Sclerosis**), two patients (2%) of 127 receiving NOVANTRONE, one receiving a 5 mg/m^2 dose and the other receiving the 12 mg/m^2 dose, had LVEF values that decreased to below 50%. An additional patient receiving 12 mg/m^2, who did not have LVEF measured, had a decrease in another echocardiographic measurement of ventricular function (fractional shortening) that led to discontinuation from the trial (see **ADVERSE REACTIONS, Multiple Sclerosis**). There were no reports of congestive heart failure in either controlled trial.

Evaluation of LVEF (by echocardiogram or MUGA) is recommended prior to administration of the initial dose of NOVANTRONE. Ordinarily, patients with a baseline LVEF of <50% should not be treated with NOVANTRONE. Subsequent LVEF evaluations are recommended if signs or symptoms of congestive heart failure develop, and prior to all doses administered to patients who have received a cumulative dose of ≥ 100 mg/m^2. NOVANTRONE should not ordinarily be administered to multiple sclerosis patients who have received a cumulative lifetime dose of ≥ 140 mg/m^2, or those with either LVEF of < 50% or a clinically significant reduction in LVEF.

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 that 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^2.

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.

Pregnancy

NOVANTRONE may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant. Mitoxantrone is considered a potential human teratogen because of its mechanism of action and the developmental effects demonstrated by related agents. Treatment of pregnant rats during the organogenesis period of gestation was associated with fetal growth retardation at doses $\geq$ 0.1 mg/kg/day (0.01 times the recommended human dose on a mg/m^2 basis). When pregnant rabbits were treated during organogenesis, an increased incidence of premature delivery was observed at doses $\geq$ 0.1 mg/kg/day (0.01 times the recommended human dose on a mg/m^2 basis). No teratogenic effects were observed in these studies, but the maximum doses tested were well below the recommended human dose (0.02 and 0.05 times in rats and rabbits, respectively, on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. Women with multiple sclerosis who are biologically capable of becoming pregnant should have a pregnancy test prior to each dose, and the results should be known prior to administration of the drug. 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 risk to the fetus.

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.

Patients with multiple sclerosis should be provided with the Patient Package Insert at the time that the decision is made to treat with NOVANTRONE and prior to and in close temporal proximity to each treatment. In addition, the physician should discuss the issues addressed in the Patient Package Insert with the patient.

Laboratory Tests

A complete blood count, including platelets, should be obtained prior to each course of NOVANTRONE and in the event that signs and symptoms of infection develop. Liver function tests should also be performed prior to each course of therapy. NOVANTRONE therapy in multiple sclerosis patients with abnormal liver function tests is not recommended because NOVANTRONE clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments.

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.

Women with multiple sclerosis who are biologically capable of becoming pregnant, even if they are using birth control, should have a pregnancy test, and the results should be known, before receiving each dose of NOVANTRONE (see **WARNINGS, Pregnancy**).

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 at a dose of 0.03 mg/g (0.02 fold the recommended human dose, on a mg/m^2 basis), and hepatocellular adenoma in male mice at a dose of 0.1 mg/kg (0.03 fold the recommended human dose, on a mg/m^2 basis). Intravenous treatment of rats, once every 21 days for 12 months with NOVANTRONE resulted in an increased incidence of external auditory canal tumors in rats at a dose of 0.3 mg/kg (0.15 fold the recommended human dose, on a mg/m^2 basis).

Mutagenesis: NOVANTRONE was clastogenic in the in vivo rat bone marrow assay. NOVANTRONE was also clastogenic in two in vitro assays; it induced DNA damage in primary rat hepatocytes and sister chromatid exchanges in Chinese hamster ovary cells. NOVANTRONE was mutagenic in bacterial and mammalian test systems (Ames/Salmonella and E. coli and L5178Y TK+/-mouse lymphoma).

Drug Interactions

Mitoxantrone and its metabolites are excreted in bile and urine, but it is not known whether the metabolic or excretory pathways are saturable, may be inhibited or induced, or if mitoxantrone and its metabolites undergo enterohepatic circulation. To date, post-marketing experience has not revealed any significant drug interactions in patients who have received NOVANTRONE for treatment of cancer. Information on drug interactions in patients with multiple sclerosis is limited.

Following concurrent administration of NOVANTRONE with corticosteroids, no evidence of drug interactions has been observed.

Special Population

Hepatic Impairment: Patients with multiple sclerosis who have hepatic impairment should ordinarily not be treated with NOVANTRONE. NOVANTRONE

should be administered with caution to other patients with hepatic impairment. In patients with severe hepatic impairment, the AUC is more than three times greater than the value observed in patients with normal hepatic function.

Pregnancy

Pregnancy Category D (see **WARNINGS**).

Nursing Mothers

NOVANTRONE is excreted in human milk and significant concentrations (18 ng/mL) have been reported for 28 days after the last administration. Because of the potential for serious adverse reactions in infants from NOVANTRONE, breast feeding should be discontinued before starting treatment.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Multiple Sclerosis

NOVANTRONE has been administered to 149 patients with multiple sclerosis in two randomized clinical trials, including 21 patients who received NOVANTRONE in combination with corticosteroids.

In Study 1, the proportion of patients who discontinued treatment due to an adverse event was 9.7% (n = 6) in the 12 mg/m^2 NOVANTRONE arm (leukopenia, depression, decreased LV function, bone pain and emesis, renal failure, and one discontinuation to prevent future complications from repeated urinary tract infections) compared to 3.1% (n = 2) in the placebo arm (hepatitis and myocardial infarction). The following clinical adverse experiences were significantly more frequent in the

Table 4a summarizes clinical adverse events of all intensities occurring in ≥ 5% of patients in either dose group of NOVANTRONE and that were numerically greater on drug than on placebo in Study 1. The majority of these events were of mild to moderate intensity, and nausea was the only adverse event that occurred with severe intensity in more than one patient (three patients [5%] in the 12 mg/m^2 group). Of note, alopecia consisted of mild hair thinning.

Two of the 127 patients treated with NOVANTRONE in Study 1 had decreased LVEF to below 50% at some point during the 2 years of treatment. An additional patient receiving 12 mg/m^2 did not have LVEF measured, but had another echocardiographic measure of ventricular function (fractional shortening) that led to discontinuation from the study.

Table 4a
Adverse Events of Any Intensity Occurring in ≥ 5% of Patients on Any Dose of NOVANTRONE and That Were Numerically Greater Than in the Placebo Group
Study 1

	Percent of Patients		
Preferred Term	Placebo (N = 64)	5 mg/m^2 NOVANTRONE (N = 65)	12 mg/m^2 NOVANTRONE (N = 62)
Nausea	20	55	76
Alopecia	31	38	61
Menstrual disorder *	26	51	61
Amenorrhea *	3	28	43
Upper respiratory tract infection	52	51	53
Urinary tract infection	13	29	32
Stomatitis	8	15	19
Arrhythmia	8	6	18
Diarrhea	11	25	16
Urine abnormal	6	5	11
ECG abnormal	3	5	11
Constipation	6	14	10
Back pain	5	6	8
Sinusitis	2	3	6
Headache	5	6	6

* Percentage of female patients.

The proportion of patients experiencing any infection during Study 1 was 67% for the placebo group, 85% for the 5 mg/m^2 group, and 81% for the 12 mg/m^2 group.

However, few of these infections ~~required~~ resulted in hospitalization: one placebo patient (tonsillitis), three 5 mg/m^2 patients (enteritis, urinary tract infection, viral infection), and four 12 mg/m^2 patients (tonsillitis, urinary tract infection [two], endometritis).

Table 4b summarizes laboratory abnormalities that occurred in ≥ 5% of patients in either NOVANTRONE dose group, and that were numerically more frequent than in the placebo group.

Table 4b
Laboratory Abnormalities Occurring in ≥ 5% of Patients* on Either Dose of NOVANTRONE and That Were More Frequent Than in the Placebo Group
Study 1

	Percent of Patients		
Event	Placebo (N = 64)	5 mg/m^2 NOVANTRONE (N = 65)	12 mg/m^2 NOVANTRONE (N = 62)
Leukopenia [a]	0	9	19
Gamma-GT increased	3	3	15
SGOT increased	8	9	8
Granulocytopenia [b]	2	6	6
Anemia	2	9	6
SGPT increased	3	6	5

* Assessed using World Heath Organization (WHO) toxicity criteria.
a. < 4000 cells/mm^3
b. < 2000 cells/mm^3

There was no difference among treatment groups in the incidence or severity of hemorrhagic events.

In Study 2, NOVANTRONE was administered once a month. Clinical adverse events most frequently reported in the NOVANTRONE group included amenorrhea (53% of female patients), alopecia (33% of patients), nausea (29% of patients), and asthenia (24% of patients). Tables 5a and 5b respectively summarize adverse events and laboratory abnormalities occurring in > 5% of patients in the NOVANTRONE group and numerically more frequent than in the control group.

Table 5a
Adverse Events of Any Intensity Occurring in > 5% of Patients* in the NOVANTRONE Group and Numerically More Frequent Than in the Control Group
Study 2

	Percent of Patients	
Event	MP (n = 21)	N + MP (n = 21)
Amenorrhea [a]	0	53
Alopecia	0	33
Nausea	0	29
Asthenia	0	24
Pharyngitis/throat infection	5	19
Gastralgia/stomach burn/epigastric pain	5	14
Aphthosis	0	10
Cutaneous mycosis	0	10
Rhinitis	0	10
Menorrhagia [a]	0	7

N = NOVANTRONE, MP = methylprednisolone
* Assessed using National Cancer Institute (NCI) common toxicity criteria.
a. Percentage of female patients.

Table 5b
Laboratory Abnormalities Occurring in > 5% of Patients* in the NOVANTRONE Group and Numerically More Frequent Than in the Control Group
Study 2

	Percent of Patients	
Event	MP (n = 21)	N + MP (n = 21)
WBC low [a]	14	100
ANC low [b]	10	100
Lymphocytes low	43	95
Hemoglobin low	48	43
Platelets low [c]	0	33
SGOT high	5	15
SGPT high	10	15
Glucose high	5	10
Potassium low	0	10

N = NOVANTRONE, MP = methylprednisolone.
* Assessed using National Cancer Institute (NCI) common toxicity criteria.
a. < 4000 cells/mm^3
b. < 1500 cells/mm^3
c. < 100,000 cells/mm^3

Leukopenia and neutropenia were reported in the N +MP group (see Table 5b). Neutropenia occurred within 3 weeks after NOVANTRONE administration and was always reversible. Only mild to moderate intensity infections were reported in 9 of 21 patients in the N +MP group and in 3 of 21 patients in the MP group; none of these

required hospitalization. There was no difference among treatment groups in the incidence or severity of hemorrhagic events. There were no withdrawals from Study 2 for safety reasons.

Leukemia

NOVANTRONE has been studied in approximately 600 patients with ANLL. Table 6 represents the adverse reaction experience in the large U.S. comparative study of mitoxantrone + cytarabine vs daunorubicin + cytarabine. Experience in the large international study was similar. A much wider experience in a variety of other tumor types revealed no additional important reactions other than cardiomyopathy (see **WARNINGS**). It should be appreciated that the listed adverse reaction categories include overlapping clinical symptoms related to the same condition, e.g., dyspnea, cough and pneumonia. In addition, the listed adverse reactions cannot all necessarily be attributed to chemotherapy as it is often impossible to distinguish effects of the drug and effects of the underlying disease. It is clear, however, that the combination of NOVANTRONE + cytarabine was responsible for nausea and vomiting, alopecia, mucositis/stomatitis, and myelosuppression.

Table 6 summarizes adverse reactions occurring in patients treated with NOVANTRONE + cytarabine in comparison with those who received daunorubicin + cytarabine for therapy of ANLL in a large multicenter randomized prospective U.S. trial.

Adverse reactions are presented as major categories and selected examples of clinically significant subcategories.

Table 6
Adverse Events Occurring in ANLL Patients Receiving NOVANTRONE or Daunorubicin

	Induction [% pts entering induction]		Consolidation [% pts entering induction]	
Event	NOV N = 102	DAUN N = 102	NOV N = 55	DAUN N = 49
Cardiovascular	26	28	11	24
CHF	5	6	0	0
Arrhythmias	3	3	4	4
Bleeding	37	41	20	6
GI	16	12	2	2
Petechiae/ecchymoses	7	9	11	2
Gastrointestinal	88	85	58	51
Nausea/vomiting	72	67	31	31
Diarrhea	47	47	18	8
Abdominal pain	15	9	9	4
Mucositis/stomatitis	29	33	18	8
Hepatic	10	11	14	2
Jaundice	3	8	7	0
Infections	66	73	60	43
UTI	7	2	7	2
Pneumonia	9	7	9	0
Sepsis	34	36	31	18
Fungal infections	15	13	9	6
Renal failure	8	6	0	2
Fever	78	71	24	18
Alopecia	37	40	22	16
Pulmonary	43	43	24	14
Cough	13	9	9	2
Dyspnea	18	20	6	0
CNS	30	30	34	35
Seizures	4	4	2	8
Headache	10	9	13	8
Eye	57	6	2	4
Conjunctivitis	5	1	0	0

NOV = NOVANTRONE, DAUN = daunorubicin.

Hormone-Refractory Prostate Cancer

Detailed safety information is available for a total of 353 patients with hormone-refractory prostate cancer treated with NOVANTRONE, including 274 patients who received NOVANTRONE in combination with corticosteroids.

Table 7 summarizes adverse reactions of all grades occurring in ≥ 5% of patients in Trial CCI-NOV22.

Table 7
Adverse Events of Any Intensity Occurring in ≥ 5% of Patients
Trial CCI-NOV22

Event	N + P (n = 80) %	P (n = 81) %
Nausea	61	35
Fatigue	39	14
Alopecia	29	0
Anorexia	25	6
Constipation	16	14
Dyspnea	11	5
Nail bed changes	11	0
Edema	10	4
Systemic infection	10	7
Mucositis	10	0
UTI	9	4
Emesis	9	5
Pain	8	9
Fever	6	3
Hemorrhage/bruise	6	1
Anemia	5	3
Cough	5	0
Decreased LVEF	5	0
Anxiety/depression	5	3
Dyspepsia	5	6
Skin infection	5	3
Blurred vision	3	5

N = NOVANTRONE, P = prednisone.

No nonhematologic adverse events of Grade 3/4 were seen in > 5% of patients.

Table 8 summarizes adverse events of all grades occurring in ≥ 5% of patients in Trial CALGB 9182.

Table 8
Adverse Events of Any Intensity Occurring in ≥ 5 % of Patients
Trial CALGB 9182

	N + H (n = 112)		H (n = 113)	
Event	n	%	n	%
Decreased WBC	96	87	4	4
Granulocytes/bands	88	79	3	3
Decreased hemoglobin	83	75	42	39
Lymphocytes	78	72	27	25
Pain	45	41	44	39
Platelets	43	39	8	7
Alkaline Phosphatase	41	37	42	38
Malaise/fatigue	37	34	16	14
Hyperglycemia	33	31	32	30
Edema	31	30	15	14
Nausea	28	26	9	8
Anorexia	24	22	16	14
BUN	24	22	22	20
Transaminase	22	20	16	14
Alopecia	20	20	1	1
Cardiac function	19	18	0	0
Infection	18	17	4	4
Weight loss	18	17	13	12
Dyspnea	16	15	9	8
Diarrhea	16	14	4	4
Fever in absence of infection	15	14	7	6
Weight gain	15	14	16	15
Creatinine	14	13	11	10
Other gastrointestinal	13	14	11	11
Vomiting	12	11	6	5
Other neurologic	11	11	5	5
Hypocalcemia	10	10	5	5
Hematuria	9	11	5	6
Hyponatremia	9	9	3	3
Sweats	9	9	2	2
Other liver	8	8	8	8
Stomatitis	8	8	1	1
Cardiac dysrhythmia	7	7	3	3
Hypokalemia	7	7	4	4
Neuro/constipation	7	7	2	2
Neuro/motor	7	7	3	3
Neuro/mood	6	6	2	2
Skin	6	6	4	4
Cardiac ischemia	5	5	1	1
Chills	5	5	0	0
Hemorrhage	5	5	3	3
Myalgias/arthralgias	5	5	3	3
Other kidney/bladder	5	5	3	3
Other endocrine	5	6	3	4
Other pulmonary	5	5	3	3
Hypertension	4	4	5	5
Impotence/libido	4	7	2	3
Proteinuria	4	6	2	3
Sterility	3	5	2	3

N= NOVANTRONE, H= hydrocortisone

General

Allergic Reaction: Hypotension, urticaria, dyspnea, and rashes have been reported occasionally.

Cutaneous: Extravasation at the infusion site has been reported, which may result in erythema, swelling, pain, burning, and/or blue discoloration of the skin. Extravasation can result in tissue necrosis with resultant need for debridement and skin grafting. Phlebitis has also been reported at the site of the infusion.

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

Leukemia: Myelosuppression is rapid in onset and is consistent with the requirement to produce significant marrow hypoplasia in order to achieve a response in acute leukemia. The incidences of infection and bleeding seen in the U.S. trial are consistent with those reported for other standard induction regimens.

Hormone-Refractory Prostate Cancer: In a randomized study where dose escalation was required for neutrophil counts greater than $1000/mm^3$, Grade 4 neutropenia (ANC < $500/mm^3$) was observed in 54% of patients treated with NOVANTRONE + low-dose prednisone. In a separate randomized trial where patients were treated with 14 mg/m^2, Grade 4 neutropenia in 23% of patients treated with NOVANTRONE + hydrocortisone was observed. Neutropenic fever/infection occurred in 11% and 10% of patients receiving NOVANTRONE + corticosteroids, respectively, on the two trials. Platelets < $50,000/mm^3$ were noted in 4% and 3% of patients receiving NOVANTRONE + corticosteroids on these trials, and there was one patient death on NOVANTRONE + hydrocortisone due to intracranial hemorrhage after a fall.

Gastrointestinal: Nausea and vomiting occurred acutely in most patients and may have contributed to reports of dehydration, but were generally mild to moderate and

could be controlled through the use of antiemetics. Stomatitis/mucositis occurred within 1 week of therapy.

Cardiovascular: Congestive heart failure, tachycardia, EKG changes including arrhythmias, chest pain, and asymptomatic decreases in left ventricular ejection fraction have occurred. (See WARNINGS)

Pulmonary: Interstitial pneumonitis has been reported in cancer patients receiving combination chemotherapy that included NOVANTRONE.

OVERDOSAGE

There is no known specific antidote for NOVANTRONE. Accidental overdoses have been reported. Four patients receiving 140-180 mg/m^2 as a single bolus injection died as a result of severe leukopenia with infection. Hematologic support and antimicrobial therapy may be required during prolonged periods of severe myelosuppression.

Although patients with severe renal failure have not been studied, NOVANTRONE is extensively tissue bound and it is unlikely that the therapeutic effect or toxicity would be mitigated by peritoneal or hemodialysis.

DOSAGE AND ADMINISTRATION (See also WARNINGS)

Multiple Sclerosis

The recommended dosage of NOVANTRONE is 12 mg/m^2 given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months.

Evaluation of LVEF (by echocardiogram or MUGA) is recommended prior to administration of the initial dose of NOVANTRONE. Subsequent LVEF evaluations are recommended if signs or symptoms of congestive heart failure develop, and prior to all doses administered to patients who have received a cumulative dose of $\geq$ 100 mg/m^2. NOVANTRONE should not ordinarily be administered to multiple sclerosis patients who

have received a cumulative lifetime dose of $\geq$ 140 mg/m^2, or those with either LVEF of < 50% or a clinically-significant reduction in LVEF.

Complete blood counts, including platelets, should be monitored prior to each course of NOVANTRONE and in the event that signs or symptoms of infection develop. NOVANTRONE generally should not be administered to multiple sclerosis patients with neutrophil counts less than 1500 cells/mm^3. Liver function tests should also be monitored prior to each course. NOVANTRONE therapy in multiple sclerosis patients with abnormal liver function tests is not recommended because NOVANTRONE clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments.

Women with multiple sclerosis who are biologically capable of becoming pregnant, even if they are taking birth control, should have a pregnancy test, and the results should be known, before receiving each dose of NOVANTRONE (see **WARNINGS, Pregnancy**).

Hormone-Refractory Prostate Cancer

Based on data from two Phase 3 comparative trials of NOVANTRONE plus corticosteroids versus corticosteroids alone, the recommended dosage of NOVANTRONE is 12 to 14 mg/m^2 given as a short intravenous infusion every 21 days.

Combination Initial Therapy for ANLL in Adults

For induction, the recommended dosage is 12 mg/m^2 of NOVANTRONE daily on Days 1-3 given as an intravenous infusion, and 100 mg/m^2 of cytarabine for 7 days given as a continuous 24-hour infusion on Days 1-7.

Most complete remissions will occur following the initial course of induction therapy. In the event of an incomplete antileukemic response, a second induction course may be given. NOVANTRONE should be given for 2 days and cytarabine for 5 days using the same daily dosage levels.

If severe or life-threatening nonhematologic toxicity is observed during the first induction course, the second induction course should be withheld until toxicity resolves.

Consolidation therapy which was used in two large randomized multicenter trials consisted of NOVANTRONE, 12 mg/m^2 given by intravenous infusion daily on Days 1 and 2 and cytarabine, 100 mg/m^2 for 5 days given as a continuous 24-hour infusion on Days 1-5. The first course was given approximately 6 weeks after the final induction course, the second was generally administered 4 weeks after the first. Severe myelosuppression occurred. (See **CLINICAL PHARMACOLOGY**)

Hepatic Impairment

For patients with hepatic impairment, there is at present no laboratory measurement that allows for dose adjustment recommendations. (See **CLINICAL PHARMACOLOGY, Special Populations,** Hepatic Impairment)

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 extravasation site should be carefully monitored for signs of necrosis and/or phlebitis that may require further medical attention. Care should be taken to avoid extravasation at the infusion site and to avoid contact of NOVANTRONE with the skin, mucous membranes or eyes. NOVANTRONE SHOULD NOT BE ADMINISTERED SUBCUTANEOUSLY.

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.[5-11] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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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.

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IMMUNEX®

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