COMPLETE PRESCRIBING INFORMATION

Pr NOVANTRONE ®

Mitoxantrone for Injection Concentrate USP

INTRAVENOUS INFUSION

ANTINEOPLASTIC AGENT

STERILE

WYETH CANADA
MONTREAL, CANADA

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Intravenous Infusion

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

STERILE

CAUTION

NOVANTRONE IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE "WARNINGS" AND "PRECAUTIONS"). BLOOD COUNTS SHOULD BE TAKEN AT FREQUENT INTERVALS PRIOR, DURING AND POST THERAPY. CARDIAC MONITORING IS ADVISED IN THOSE PATIENTS WHO HAVE RECEIVED PRIOR ANTHRACYCLINES, PRIOR MEDIASTINAL RADIOTHERAPY OR WITH PRE-EXISTING CARDIAC DISEASE.

ACTION AND CLINICAL PHARMACOLOGY

Although its mechanism of action has not been determined, mitoxantrone is a DNA-reactive agent. It induces nuclear aberrations with chromosome scattering in cell cultures (human colon carcinoma line) and is a potent inhibitor of RNA and DNA synthesis. Compared on an equimolar basis, mitoxantrone is seven times more potent than doxorubicin in inhibiting the uptake of ^{3}H-uridine and four times more potent in inhibiting the uptake of ^{3}H-thymidine by mouse lymphoma L5178Y cells *in vitro*.

Mitoxantrone inhibits DNA-topoisomerase II, an essential nuclear enzyme modulating DNA

topology during multiple cellular processes such as DNA replication and chromosome segregation.

INDICATIONS AND CLINICAL USE

NOVANTRONE (mitoxantrone hydrochloride) is indicated for chemotherapy in patients with metastatic carcinoma of the breast. It is also indicated for relapsed adult leukemia, lymphoma patients and patients with hepatoma. NOVANTRONE in combination with other drug(s) is indicated in the initial therapy of acute non-lymphocytic leukemia (ANLL) in adults. The category includes myelogenous, promyelocytic, monocytic and erythroid acute leukemias.

CONTRAINDICATIONS

NOVANTRONE (mitoxantrone hydrochloride) is contraindicated in patients who have hypersensitivity to NOVANTRONE or any of its components, or have demonstrated prior hypersensitivity to anthracyclines.

NOVANTRONE is not indicated for intrathecal injection. There have been reports of neuropathy, including paralysis and bowel and bladder dysfunction following intrathecal injection.

Patients who have received prior substantial anthracycline exposure may not be treated with mitoxantrone if cardiac function is abnormal prior to the initiation of therapy (see WARNINGS

).

Mitoxantrone treatment should not be initiated in patients who have not recovered from severe myelosuppression due to previous treatment with other cytotoxic agents or radiotherapy.

Mitoxantrone should not be used in patients with severe hepatic impairment.

WARNINGS

NOVANTRONE (mitoxantrone hydrochloride) is an active cytotoxic drug which should be used by clinicians familiar with the use of antineoplastic agents, and having the facilities for regular monitoring of clinical, hematological and biochemical parameters during and after treatment.

NOVANTRONE should be given slowly into a freely flowing intravenous infusion. It must never be given subcutaneously, intramuscularly, or intra-arterially. There have been reports of local/regional neuropathy, some irreversible, following intra-arterial injection. **Severe local tissue damage may occur if there is extravasation during administration (See INDICATIONS).**

NOVANTRONE must not be given by intrathecal injection. Severe injury with permanent sequelae can result from intrathecal administration (See CONTRAINDICATIONS).

When NOVANTRONE is used in high doses (>14 mg/m^2 x 3 days), severe myelosuppression will occur. Since NOVANTRONE at any dose can produce myelosuppression [see ADVERSE REACTIONS], it should be used with caution in patients in poor general condition or with pre-existing myelosuppression due to any cause. **Except for the treatment of acute nonlymphocytic leukemia, NOVANTRONE should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm^3.** 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 treatment is used) and patients should be monitored closely during this phase.

There is a high incidence of bone marrow depression, primarily of leukocytes, requiring careful hematological monitoring. Following recommended doses of mitoxantrone, leukopenia is usually transient, reaching its nadir at about 10 days after dosing, with recovery usually occurring by the 21st day. White blood cell counts as low as 1500 mm^3 may be expected following therapy, but white blood cell counts rarely fall below 1000 mm^3 at recommended dosage. **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**. Red blood cells and platelets should be monitored since depression of these elements may also occur. Hematological toxicity may require reduction of dose or suspension or delay of mitoxantrone therapy.

Patients should be advised of the signs and symptoms of myelosuppression.

Topoisomerase II inhibitors, including mitoxantrone, when used concomitantly with other antineoplastic agents and/or radiotherapy, have been associated with the development of Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) (see ADVERSE REACTIONS).

Secondary acute myelogenous leukemia (AML) has been reported in cancer patients treated with anthracyclines. NOVANTRONE is an anthracenedione, a related drug. The occurrence of refactory 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. The cumulative risk of developing treatment-related AML, in 1774 patients with breast cancer who received NOVANTRONE concomitantly with other cytotoxic agents and radiotherapy, was estimated as 1.1% and 1.6% at 5 and 10 years, respectively.

There have been post-marketing reports of acute leukemia, some resulting in death, following mitoxantrone hydrochloride treatment in patients with multiple sclerosis.

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.

Cardiac toxicity with NOVANTRONE may occur at lower cumulative doses whether or not cardiac risk factors are present.

Cases of functional cardiac changes, including congestive heart failure (CHF) and decreases in left ventricular ejection fraction (LVEF) have been reported during and also, for months to years after, mitoxantrone therapy. The risk of cardiotoxicity increases with cumulative doses.

Evaluation of the left-ventricular ejection fraction (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 >100 mg/m^2.

In cancer patients, symptomatic CHF is known to occur in 2.6% of patients receiving up to a cumulative dose of 140 mg/m^2. In comparative oncology trials, the overall cumulative probability rate of moderate or severe decreases in LVEF at this dose was 13%. **These cardiac events may be more common in patients who have had prior treatment with anthracyclines or anthracenediones, concomitant use of other cardiotoxic drugs, prior or concomitant radiotherapy to the mediastinal/pericardial area, or with active or dormant cardiovascular heart disease, indicating a possible increased risk of cardiotoxicity in such patients.**

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.

Acute congestive heart failure may occasionally occur in patients treated with NOVANTRONE for ANLL.

It is therefore recommended that patients should be monitored for evidence of cardiac toxicity and questioned about symptoms of heart failure prior to initiation of therapy. In addition, it is recommended that regular cardiac monitoring be carried out in patients taking into account the extent to which individual patients have been exposed to these cardiac risk factors. A small proportion of endomyocardial biopsy reports have demonstrated changes consistent with anthracycline toxicity in patients treated with NOVANTRONE, who had not received prior anthracyclines.

Mitoxantrone has not been approved for the treatment of multiple sclerosis. However, patients being treated with NOVANTRONE and who also have multiple sclerosis as a comorbid condition and 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 100 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. Sudden death has been reported in the multiple sclerosis patient population. The causal relationship to NOVANTRONE administration cannot be ruled out.

NOVANTRONE should not ordinarily be administered to multiple sclerosis patients who have received a cumulative lifetime dose of >100 mg/m^2 or those with either LVEF of <50% or a

clinically-significant reduction in LVEF.

Functional cardiac changes may occur in patients with multiple sclerosis treated with NOVANTRONE.

NOVANTRONE may impart a blue-green coloration to the urine for 24 hours after administration, and patients should be advised to expect this during active therapy. A reversible blue coloration in the sclerae has been reported in two cases.

NOVANTRONE is excreted in human milk and significant concentrations (18.0 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.

NOVANTRONE may cause fetal harm when administered to a pregnant woman. In treated rats, at doses of $\geq$0.1 mg/kg (0.05 times the recommended human doses on a mg/m^2 basis) low fetal birth weight and retarded development of the fetal kidney were seen in greater frequency. In treated rabbit, an increased incidence of premature delivery was observed at doses $\geq$0.01 mg/kg (0.01 times the recommended human dose on an mg/m^2 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 child-bearing potential should be

advised to avoid becoming pregnant. Women 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.

The safety of NOVANTRONE in patients with hepatic insufficiency is not established. NOVANTRONE therapy in 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.

NOVANTRONE should not be used in patients with severe hepatic dysfunction (see CONTRAINDICATIONS) and poor performance status. If performance status is favourable, NOVANTRONE in reduced dosage may be used, with careful supervision. Mitoxantrone clearance is reduced by hepatic impairment. Patients with severe 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. Careful supervision is recommended when treating patients with hepatic insufficiency.

Sulfites can cause allergic-type reactions including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma or allergy.

PRECAUTIONS

Full blood counts, including platelets, should be undertaken serially during a course of treatment and in the event that signs and symptoms of infection develop. Dosage adjustments may be

necessary based on these counts (see DOSAGE AND ADMINISTRATION).

Liver function tests should also be performed prior to each course of therapy. NOVANTRONE (mitoxantrone hydrochloride) therapy in 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.

It is recommended that NOVANTRONE not be mixed in the same infusion with other drugs. NOVANTRONE should not be mixed in the same infusion with heparin since a precipitate may form. (See DOSAGE AND ADMINISTRATION).

Immunization may be ineffective when given during NOVANTRONE therapy. Immunization with live virus vaccines are generally not recommended. If patients are treated with immunosuppressive agents and receive a vaccine concomitantly, it has been shown that patients have minimal antibody response after vaccination. Vaccination with live virus may result in severe reactions such as vaccinia gangrenosa, generalized vaccinia, or death.

Hyperuricaemia may occur as a result of rapid lysis of tumour cells by mitoxantrone. Serum uric acid levels should be monitored and hypouricaemic therapy instituted prior to the initiation of antileukemic therapy.

Patients who receive immunosuppressive agents have a reduced immunological response to infection. Systemic infections should be treated concomitantly with or just prior to commencing

therapy with mitoxantrone.

Animal data suggest that if used in combination with other antineoplastic agents, additive myelosuppression may be expected. This has been supported by available clinical data on combination regimens. When used in combination regimens, the initial dose of mitoxantrone should be reduced by 2-4 mg/m^2 below the dose recommended for single agent usage (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Some degree of leukopenia is to be expected following recommended doses of NOVANTRONE (mitoxantrone hydrochloride). With dosing every 21 days, suppression of WBC counts below $1000/mm^3$ is infrequent; leukopenia is usually transient, reaching its nadir at about 10 days after dosing, with recovery usually occurring by the 21st day.

Acute Myeloid Leukemia (AML), acute leukemia and Myelodysplastic Syndrome (MDS): Secondary AML and MDS have been reported following chemotherapy with various DNA topoisomerase II inhibitors, including mitoxantrone. Features of the AML include a latency period of <3 years, short pre-leukemic phase, and non-specific cytogenic alterations including chromosome abnormalities.

Thrombocytopenia can occur, and anaemia occurs less frequently. Myelosuppression may be more severe and prolonged in patients having had extensive prior chemotherapy or radiotherapy

or in debilitated patients.

The most commonly encountered side effects are nausea and vomiting, although in the majority of cases these are mild (WHO Grade 1) and transient. Alopecia may occur, but is most frequently of minimal severity and reversible on cessation of therapy.

Other side effects which have occasionally been reported include allergic reactions anaphylaxis/ anaphylactoid reactions (including shock), abdominal pain, amenorrhoea, anorexia, constipation, diarrhea, dyspnoea, fatigue, weakness, fever, weight changes, edema, gastrointestinal bleeding, stomatitis/mucositis, infection, urinary tract infection, upper respiratory tract infection, pneumonia, marrow hypoplasia, granulocytopenia, neutropenia, hemmorhage/bruise, bleeding, abnormal white blood count, hepatic toxicity, renal toxicity, blue-green discoloration of the urine and non-specific neurological side effects including drowsiness, confusion, headache, anxiety and paresthesia . Tissue necrosis following extravasation has been reported rarely.

Sudden death has been reported in the multiple sclerosis patient population. The causal relationship to NOVANTRONE administration is unknown.

Changes in laboratory test values have been observed infrequently, e.g., increased liver enzyme levels, elevated serum creatinine and blood urea nitrogen levels (with occasional reports of severe impairment of hepatic function in patients with leukemia).

Cardiovascular effects, which have only occasionally been of clinical significance, include

decreased left ventricular ejection fraction (determined by ECHO or MUGA scan), cardiomyopathy, EKG changes and acute arrhythmia. Congestive heart failure has been reported. Such cases generally responded well to treatment with digitalis and/or diuretics. In patients with leukemia there is an increase in the frequency of cardiac events, the direct role of NOVANTRONE in these cases is difficult to assess, since most patients had received prior therapy with anthracyclines and since their course is frequently complicated by anemia, fever, sepsis, and intravenous fluid therapy. Sinus bradycardia, myocardial infarction and hypotension have been occasionally reported.

In leukemia patients treated with a single course of 12 mg/m^2 IV daily x 5 days, the following drug-related toxicities occurred: moderate or severe jaundice or hepatitis in 8%, moderate nausea or vomiting in 8%, moderate or severe stomatitis/mucositis in 9-29%, diarrhea in 9-13%, and moderate or severe alopecia in 11%.

Dermatologic effects include extravasation at the infusion site, which may result in erythema, swelling, pain, burning, rash, and/or blue discolouration 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 infusion.

Less common reactions include: tumour lysis syndrome (characterized by hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcaemia) which has been observed rarely during single-agent chemotherapy with mitoxantrone, as well as during combination chemotherapy; nail pigmentation and onycholysis; and reversible blue colouration of sclerae has been reported.

CLINICAL RESULTS

Introduction

Clinical trials experience has established the dosage range, efficacy and safety profile of NOVANTRONE (mitoxantrone hydrochloride).

A single dose can be given intermittently every three or four weeks. The recommended initial treatment dose in good risk patients is 14 mg/m^2.

The following efficacy and safety results were generated from analyses of data.

Efficacy:

Breast

Efficacy data are available on 349 patients with locally advanced or metastatic breast carcinoma. Results are dependent on many predisposing factors including prior chemotherapy and/or radiotherapy, the health of the patients, sites of metastases, and dose of the agent employed. In a European multicenter, first-line, single-agent trial using an initial dose of 14 mg/m^2, the overall response rate was 39%, which compared favourably to doxorubicin therapy at a dose of 60 - 75 mg/m^2 when given to patients with similar stage disease. In a study of a direct comparison with doxorubicin, given as second-line therapy to breast cancer patients who failed a standard first-line combination, response rates are 27% for NOVANTRONE and 23% for doxorubicin. The mean duration of response observed after NOVANTRONE was greater than those reported after doxorubicin. Responses have been seen in all major sites of metastases including lymph

nodes, lung, bone, skin and viscera, in patients both with and without prior hormonal therapy. Available data suggest that NOVANTRONE is comparable in efficacy with doxorubicin in the treatment of advanced breast cancer. Myelosuppression with 21-day treatment intervals is comparable with that observed with doxorubicin. Multiple courses of single-agent NOVANTRONE therapy, in some cases for longer than twelve cycles, have been administered with excellent tolerance and a good response. NOVANTRONE showed incomplete cross-resistance with doxorubicin since responses have been observed in patients in whom doxorubicin had failed or who relapsed after response to that drug. A continuing large-scale clinical trials program with combination therapy also demonstrated early positive results for efficacy and safety. In seven studies, over 100 cycles of combination therapy have been given to 77 patients.

Additional Indications

A total of 966 patients have been treated with NOVANTRONE for three other indications of which 259 patients had non-Hodgkin's lymphoma (NHL), 546 had leukemia, and 161 had hepatocellular carcinoma (HCC). The following summarizes the accrual of these 966 patients:

Indication	Lederle-Sponsored Studies (No. Treated)	Independent Studies Reported In the Literature (No. Treated)
NHL	186	73
Leukemia (including pediatric cases)	282	264
HCC	75	86
Totals	543	423

NON-HODGKIN'S LYMPHOMA. Three key studies evaluated single agent NOVANTRONE in 148 patients with relapsed or refractory advanced NHL at a dose of 14 mg/m^2, IV, every 3 weeks. Of 127 patients evaluable for response in two trials, there were 10 complete responses (CR) and 42 partial responses (PR) producing an overall therapeutic response rate of 41%. The median duration of responses in the multicenter study (122 evaluable patients) was 195 days. Many patients' responses lasted in excess of one year. Responses were seen in all histological subtypes of NHL. Response to NOVANTRONE was independent of prior chemotherapy and independent of whether the patient received prior doxorubicin. This demonstrated a lack of complete cross-resistance between NOVANTRONE and other drugs including anthracyclines.

NOVANTRONE was evaluated in combination with other agents for the treatment of NHL. A total of 28 patients were treated with different regimens. A first-line comparative trial of the combination of intermediate dose METHOTREXATE with LEUCOVORIN rescue + bleomycin + doxorubicin + cyclophosphamide + vincristine + dexamethasone (m-BACOD) versus the same combination with 10 mg/m^2 NOVANTRONE replacing doxorubicin (m-BNCOD) has shown activity: 4 PRs in 6 evaluable patients with m-BNCOD and 3 PRs in 6 with m-BACOD. The combination of NOVANTRONE at 10 mg/m^2, daily for 3 days, + vincristine + dexamethasone (NOD) produced 3 PRs in 5 evaluable patients. A first-line comparative trial of the combination of cyclophosphamide + vincristine + prednisone + doxorubicin (CHOP) versus the same combinations with 10 mg/m^2 NOVANTRONE replacing doxorubicin (CNOP) has only recently begun.

NOVANTRONE at 5 mg/m^2, daily for 3 days every 3 weeks produced one CR and 2 PRs in 8

evaluable patients with NHL; ten patients were enrolled. Several other studies reported in the literature and not sponsored by Lederle support the activity of NOVANTRONE in the treatment of NHL.

LEUKEMIA. Four key studies sponsored by Lederle evaluated single agent NOVANTRONE in 181 adult patients with refractory or relapsed acute non-lymphocytic leukemia (ANLL) or chronic myelogenous leukemia in blast crisis (B-CML) at doses ranging from 8 to 12 mg/m^2, IV, daily for 5 days, every 3 weeks. A dose response effect was evident. Optimal activity was seen at a dose of 12 mg/m^2, daily for 5 days. At this dose level, there were 19 CRs in 49 evaluable adult patients with ANLL in relapse producing an overall response rate of 39%. The median duration of complete response in the largest (121 patients) single agent study was 98 days. Several patients had remissions lasting in excess of one year.

There were four studies comprising 63 patients in which NOVANTRONE was evaluated in combination with other agents in the treatment of leukemia. The highest complete remission rate of 49% (11 CRs in 23 evaluable patients with ANLL) was obtained when NOVANTRONE at 10 to 12 mg/m^2, daily for 3 days, was combined with cytosine arabinoside at 100 mg/m^2 daily for 7 days. When NOVANTRONE at 10 mg/m^2, daily for 5 days was combined with the same dose of cytosine arabinoside, it produced 2 CRs in 8 evaluable patients. Treatment of patients with acute lymphoblastic leukemia using 10 mg/m^2 NOVANTRONE, daily for 3 days, + vincristine + prednisone produced 10 responses in 16 evaluable patients, for a response rate of 62.5%.

Activity was also seen in B-CML. Since no standard therapy exists for this disease and bone

marrow is never truly normal in this disorder, both CRs and PRs were considered evidence of efficacy. The optimal dose of NOVANTRONE was 12 mg/m^2, daily for 5 days, producing 6 responses in 17 evaluable patients.

Experience in pediatric leukemia patients is limited. Twenty-four patients were treated with 6 to 8 mg/m^2 NOVANTRONE, daily for 5 days. There were 3 responses in 24 evaluable children.

Fourteen adult leukemia patients received 20 to 37 mg/m^2 NOVANTRONE once every two weeks. No therapeutic responses were observed using this schedule.

Several other studies reported in the literature and not sponsored by Lederle support the activity of NOVANTRONE in the treatment of ANLL and B-CML.

HEPATOCELLULAR CARCINOMA. Three clinical trials sponsored by Lederle have been conducted using NOVANTRONE in the therapy of HCC. NOVANTRONE was administered to 65 patients intravenously at 12 mg/m^2 every 3 weeks in two studies, and in one study with 10 patients at 6 to 10 mg/m^2/day by continuous hepatic artery infusion for three consecutive days, every 3 weeks. Considering the short life span of patients presenting with HCC, a response of stable disease was included along with PRs and CRs in assessing efficacy. In these three studies, the overall therapeutic response rate was 46.7% (11 CRs and PRs + 10 stable disease in 45 evaluable patients). Activity was confirmed in other studies not sponsored by Lederle. Duration of response was variable among these studies and ranged between 3 and 52 weeks.

Safety

Data on the overall safety profile of NOVANTRONE (based on 989 patients) demonstrated advantages of NOVANTRONE compared to the anthracyclines with respect to both the quality of life and the long-term safety of patients. The majority of side effects with NOVANTRONE are mild in nature. Removal of patients from NOVANTRONE treatment for reasons of toxicity has been rare in clinical studies. A number of patients have reported no side effects at all. In addition, the relatively low risk of serious side effects has permitted treatment of patients on an out-patient basis. The most common acute effects were nausea and/or vomiting (only 3.5% severe or very severe with NOVANTRONE, compared to 10 -15% reported with doxorubicin), stomatitis/mucositis (only 0.3% severe or very severe with NOVANTRONE) and alopecia (only 0.9% severe or very severe, and 15% overall with NOVANTRONE compared with 85% severe or very severe and 100% overall reported with doxorubicin). Serious local reactions have been reported rarely following extravasation of NOVANTRONE at the infusion site.

With respect to myelosuppression, initial NOVANTRONE doses of 14 mg/m^2 every three weeks are well-tolerated in good-risk patients. Severe degrees of myelosuppression have been rare. The median white cell nadir in a European second-line study was $2.5x10^3$; in a European first-line study only 4.8% (2/42) of patients experienced a nadir of less than 1,000. The nadir usually occurs around day 10 or 11 and returns to normal baseline value by day 21, in time for the next course of treatment. After multiple courses of NOVANTRONE, white blood cell and platelet nadirs show no further decrease beyond those observed in the first few cycles, indicating no cumulative or permanent effects of NOVANTRONE on marrow reserves.

NOVANTRONE had an exceptional safety profile and was well tolerated by patients treated for NHL, leukemia and hepatoma, as well as for breast cancer. However, due to the pathophysiology of leukemia and the higher doses of NOVANTRONE employed, the safety profile differed from that seen in NHL and in hepatoma (see ADVERSE REACTIONS). The most severe and life-threatening events, i.e. bleeding and infection, are well described morbid complications of acute leukemia. Many of the episodes of hepatic dysfunction were probably related to the increased bilirubin load and increased exposure to hepatitis viruses as a result of the multiple transfusions of blood products necessary in the proper treatment of this disorder.

Cardiotoxicity:

In investigational trials of intermittent single doses, patients who received up to the cumulative dose of 140 mg/m^2 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. In contrast, doxorubicin has been reported to produce chronic cardiomyopathy and irreversible congestive heart failure in up to 11% of patients given nine or more courses of that drug at the usual dose schedule (60 mg/m^2 every three weeks).

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 times greater than that of patients with normal hepatic function receiving the same dose. Patients with hepatic impairment should be treated with caution and dosage adjustment may be required.

Mitoxantrone should not be used in patients with severe hepatic dysfunction (see Contraindications).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no known specific antidote for NOVANTRONE (mitoxantrone hydrochloride). Accidental overdoses have been reported. Some 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 medullary hypoplasia. 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. (See also the sections WARNINGS, PRECAUTIONS and ADVERSE REACTIONS)

DOSAGE AND ADMINISTRATION

Preparation and Administration Precautions

- NOVANTRONE (mitoxantrone hydrochloride) must never be given subcutaneously, intramuscularly, or intra-arterially.

  There have been reports of local/regional neuropathy, some irreversible, following intra-arterial injection. Severe local tissue damage may occur if there is extravasation during administration (See ADVERSE REACTIONS and WARNINGS).

- NOVANTRONE must not be given by intrathecal injection.

  Severe injury with permanent sequelae can result from intrathecal administration. 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 (See WARNINGS).

- Care should be taken during administration to avoid extravasation.

  Care should be taken to avoid extravasation at the infusion site and to avoid contact of NOVANTRONE with the skin, mucous membranes, or eyes. If any signs or symptoms of extravasation have occurred, including burning, pain, pruritus, erythema, swelling, blue discolouration, or ulceration, the injection or infusion should be immediately terminated and restarted in another vein above the previous vein or in the contra lateral arm.

  During intravenous administration of NOVANTRONE, extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If it is known or suspected that subcutaneous extravasation has occurred, it is recommended that intermittent ice packs be placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently

examined and surgery consultation obtained early if there is any sign of a local reaction. The extravasation site should be carefully monitored for signs of necrosis and/or phlebitis that may require further medical attention.

- 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.

Breast Cancer, Lymphoma, Hepatoma

The recommended initial dosage for use of NOVANTRONE as a single agent is 14 mg/m^2 of body surface area, given as a single intravenous dose, which may be repeated at 21-day intervals. A lower initial dose (12 mg/m^2 or less) is recommended in patients with inadequate marrow reserves due to prior therapy or poor general condition.

Dosage modification and timing of subsequent dosing should be determined by clinical judgement depending on the degree and duration of myelosuppression. If 21-day white blood cell and platelet counts have returned to adequate levels, prior doses can usually be repeated. The following Table indicates a guide to dosing based on myelosuppression.

WBC AND PLATELET NADIR	**TIME TO RECOVERY**	**SUBSEQUENT DOSING**
IF WBC NADIR > 1 500 AND PLATELET NADIR > 50 000	RECOVERY≤ 21 DAYS	REPEAT PRIOR DOSE OR INCREASE BY 2 mg/m^2 IF MYELOSUPPRESSION NOT CONSIDERED ADEQUATE
IF WBC NADIR > 1 500 AND PLATELET NADIR > 50 000	RECOVERY > 21 DAYS	WITHHOLD UNTIL RECOVERY THEN REPEAT PRIOR DOSE
IF WBC NADIR < 1 500 OR PLATELET NADIR < 50 000	ANY DURATION	DECREASE BY 2 mg/m^2 FROM PRIOR DOSE AFTER RECOVERY
IF WBC NADIR < 1 000 OR PLATELET NADIR < 25 000	ANY DURATION	DECREASE BY 4 mg/m^2 FROM PRIOR DOSE AFTER RECOVERY

Combination Therapy For Breast Cancer, Lymphoma:

NOVANTRONE has been given in various combination regimens with the following cytotoxic agents for the treatment of breast cancer and lymphomas: cyclophosphamide, fluorouracil, vincristine, vinblastine, bleomycin, METHOTREXATE (standard dose or 200 mg/m^2 with LEUCOVORIN rescue) and glucocorticoids.

As a guide, the initial dose of NOVANTRONE when used with other myelosuppressive agents should be reduced by 2-4 mg/m^2 below the doses recommended for single agent usage; subsequent dosing depends upon the degree and duration of myelosuppression.

Intraperitoneal Administration:

NOVANTRONE has been given by intraperitoneal administration for malignant ascites in advanced breast and gynecologic pelvic cancer.

Dosage for Patients with Acute Leukemia in Relapse:

The recommended dosage for induction is 12 mg/m^2 of body surface area, given as a single intravenous dose daily for five consecutive days (total of 60 mg/m^2).

In clinical studies, with a dosage of 12 mg/m^2 daily for 5 days, patients who achieved a complete remission did so as a result of the first induction course.

Re-induction upon relapse may be attempted with NOVANTRONE and again the recommended dosage is 12 mg/m^2 daily x 5.

Combination Initial Therapy For Acute Non-Lymphocytic Leukemia (ANLL):

NOVANTRONE, together with cytosine arabinoside, has been used successfully for the treatment of both first line and second line patients with acute non-lymphocytic leukemia.

For induction, the recommended dosage is 10-12 mg/m^2 of NOVANTRONE for 3 days (Days 1-3) and 100 mg/m^2 of cytosine arabinoside for 7 days (the latter given as a continuous 24 hour infusion, Days 1-7).

If a second course is indicated, then the second course is recommended with the same combination at the same daily dosage levels but with NOVANTRONE given for only 2 days and cytosine arabinoside for only 5 days.

If severe or life-threatening non-hematological toxicity is observed during the first induction course, the second induction course should be withheld until the toxicity clears (see WARNINGS).

Consolidation therapy, which was used in two large randomized multicenter trials, consists of NOVANTRONE, 12 mg/m^2 given by intravenous infusion daily for 2 days (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 WARNINGS section for information prior to dosing).

Safety and efficacy in pediatric patients have not been established. Experience in pediatric patients is limited; however, complete remissions have been observed with NOVANTRONE as single agent therapy at a dosage of 8 mg/m^2 daily for 5 days.

For patients with hepatic impairment, there are insufficient data that allows for dose adjustment recommendations.

ADMINISTRATION OF SOLUTION

NOVANTRONE (mitoxantrone hydrochloride) solution should be diluted to at least 50 mL with either Sodium Chloride for Injection (U.S.P.) or 5% Dextrose for Injection (U.S.P.). This solution should be introduced slowly into the tubing of a freely-running intravenous infusion of Sodium Chloride for Injection (U.S.P.) or 5% Dextrose for Injection (U.S.P.) administered over not less than three to five minutes intravenously. The tubing should be inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. If extravasation occurs, the administration should be stopped immediately and restarted in another vein. The nonvessicant properties of NOVANTRONE minimize the possibility of severe reactions following extravasation, however, tissue necrosis has been reported rarely.

NOVANTRONE should be administered by individuals experienced in the use of antineoplastic therapy.

A 20 gauge or smaller needle size is recommended as the optimal needle size. Doses should be removed using slightly negative pressure.

Caution in the handling and preparation of NOVANTRONE solutions must be exercised and the use of protective eyeglasses, gloves and other protective clothing is recommended. (See GUIDELINES FOR SAFE USE BY HOSPITAL PERSONNEL section).

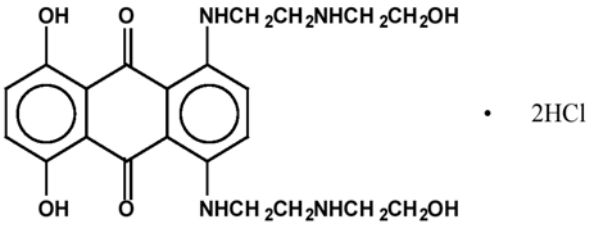
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper name: mitoxantrone hydrochloride

Chemical name: 1,4-Dihydroxy-5,8-bis[[2-[(2-hydroxyethyl) amino]-ethyl]amino]anthraquinone dihydrochloride

Structural formula:



Molecular formula: $C_{22}H_{28}N_4O_6 \bullet 2HCl$

Molecular weight: 517.41

Description: Mitoxantrone hydrochloride, a synthetic anthracenedione is a potent antineoplastic agent. It is a hygroscopic dark blue solid that is moderately soluble in water.

COMPOSITION:

NOVANTRONE is supplied as a sterile, aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride (8 mg/mL), sodium acetate (0.05 mg/mL) and acetic acid (0.46 mg/mL) as inactive ingredients. Sodium

metabisulfite is used during manufacturing to prevent oxidation and may appear in the final product. The product does not contain antibacterial preservatives.

STABILITY AND STORAGE RECOMMENDATIONS:

NOVANTRONE should be stored at 15-25°C.

Following preparation of the infusion, the diluted solution should be stored at room temperature and used within 24 hours. Any original solution which remains in the vial should be discarded. NOTE: LIKE THE ORIGINAL SOLUTIONS, THE DILUTIONS SHOULD ALSO NOT BE FROZEN.

GUIDELINES FOR SAFE USE BY HOSPITAL PERSONNEL

Individuals who have contact with anti-cancer drugs or work in areas where these drugs are used may be exposed to these agents in air or through direct contact with contaminated objects. Potential health effects may be reduced by adherence to institutional procedures, published guidelines and local regulations for preparation, administration, transportation and disposal of hazardous drugs. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

<u>Handling:</u>

1. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

2. Personnel preparing NOVANTRONE solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks.

3. Personnel regularly involved in the preparation and handling of antineoplastics should have bi-annual blood examinations.

Disposal:

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.

2. All needles, syringes, vials, ampoules and other materials which have come in contact with NOVANTRONE should be segregated in plastic bags, sealed and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.

3. If incineration is not available, mitoxantrone hydrochloride may be detoxified by adding 5.5 parts by weight of calcium hypochlorite to each 1 part by weight of mitoxantrone hydrochloride in 13 parts by weight of water. The calcium hypochlorite should be added GRADUALLY and the procedure carried out with adequate ventilation since chlorine gas is liberated.

Vials:

Prepare an adequate quantity of calcium hypochlorite solution (eg: Add 43.5 g calcium hypochlorite to 100 mL of water*). Withdraw any NOVANTRONE remaining in the vial with the aid of a hypodermic syringe. Add to the prepared calcium hypochlorite solution slowly, preferably in chemical fume hood or biological safety cabinet - Class II. Add an appropriate quantity of the calcium hypochlorite solution to the vial to detoxify any remaining drug.

* Appropriate safety equipment such as goggles and gloves should be worn while working with calcium hypochlorite solution since it is corrosive.

Withdraw the solution and discard in the sewer system with running water. Dispose of the detoxified vials in a safe manner.

Needles, syringes, disposable and non-disposable equipment:

Rinse equipment with an appropriate quantity of calcium hypochlorite solution (43.5 g per 100 mL of water*). Discard the solution in the sewer system with running water and discard disposable equipment in a safe manner. Thoroughly wash non-disposable equipment in soap and water.

* Appropriate safety equipment such as goggles and gloves should be worn while working with calcium hypochlorite solution since it is corrosive.

Spillage/Contamination:

Wear gloves, mask, protective clothing. Place spilled material in an appropriate container (i.e. cardboard for broken glass) and then in a polyethylene bag; absorb remains with gauze pads or towels; wash area with water and absorb with gauze or towels again and place in bag; seal, double bag and mark as a hazardous waste. Dispose of waste by incineration or by other methods approved for hazardous materials. Personnel involved in cleanup should wash with soap and water.

AVAILABILITY OF DOSAGE FORMS

NOVANTRONE (mitoxantrone hydrochloride) for intravenous injection is supplied as a sterile aqueous solution at a concentration equivalent to 2 mg mitoxantrone free base per mL, and is available in the following vial sizes:

10mL/vial (20mg)

12.5mL/vial (25mg)

Identification:

Glass vials containing 10 and 12.5mL of a clear, dark blue solution.

PHARMACOLOGY

Synopsis

Mitoxantrone, a synthetic anthracenedione, is a potent antineoplastic agent. It has a cytocidal effect on both proliferating and non-proliferating cultured human cells. It is four to seven times more potent than doxorubicin in inhibiting nucleic acid synthesis. In experimental tumour systems in mice, the therapeutic index of mitoxantrone is eight to fifteen times that of doxorubicin.

Antitumour Activity

Mitoxantrone increases life span and numbers of long-term survivors among mice with leukemias P388 and L1210 leukemias or with B16 melanoma and colon carcinoma 26 solid neoplasms. It is active by the intraperitoneal, subcutaneous, and intravenous routes in mice, but oral activity has not been demonstrated. In conventional mouse test systems, mitoxantrone shows improved antineoplastic activity over that of doxorubicin, cyclophosphamide, 5-fluorouracil, methotrexate, cytosine arabinoside, and vincristine against intraperitoneally implanted tumours; data are presented in the table below.

Mitoxantrone Activity Compared with Other Antineoplastic Agents

	Increase in Life Span (%)[a] in Mice With:			
Drug	**P388 leukemia**	**L1210 leukemia**	**B16 melanoma**	**Colon 26 carcinoma**
Mitoxantrone	>200	>226	>300	>224
Doxorubicin	159	>118	>224	>155
Cyclophosphamide	112	89	98	77
5-Fluorouracil	117	100	73	136
Methotrexate	149	96	< 25	< 25
Cytosine arabinoside	≥ 90	85	--	--
Vincristine	132	65	91	27

[a] Percent increase in life span over untreated controls on day 30.

Similar results have been reported by other investigators in comparative studies with antitumour antibiotics in mice with P388 or L1210 leukemias, or B16 melanoma implanted intraperitoneally, or with subcutaneously implanted Lewis Lung carcinoma; data are presented in the following table.

Mitoxantrone Activity Compared with Antitumour Antibiotics[a]

Drug	P388	L1210	B16	Lewis Lung
Mitoxantrone	4+*	3+	4+	1+
Doxorubicin	3+	1+	4+	1+
Daunomycin	3+	3+	1+	--
Aclarubicin	2+	1+	--	--
Mitomycin C	4+	1+	2+	--
Bleomycin	--	--	--	--
Neocarzinostatin	2+	2+	1+	--
Chromomycin A_3	3+	1+	–	--

[a] Modified from Fujimoto and Ogawa 1982

* criteria is equivalent to "curable" rating.

The therapeutic index of mitoxantrone was shown to be eight to fifteen times greater than that of doxorubicin against intraperitoneally implanted leukemias.

Increasing amounts of mitoxantrone produce a progressive reduction in mouse bone marrow cellularity. A cytocidal effect in both actively proliferating and non-proliferating human cell cultures has been shown . These results indicate that mitoxantrone is not cell cycle phase-specific.

PHARMACOKINETICS

Synopsis

Mitoxantrone demonstrates rapid plasma clearance, a long elimination half-life, and extensive tissue distribution in both animals and humans. It is excreted primarily in the bile. There is little

uptake by the brain, spinal cord and cerebrospinal fluid, indicating that mitoxantrone does not cross the blood-brain barrier to any appreciable extent.

Plasma and Whole Body Elimination

In rats, dogs, and monkeys given intravenous doses of 0.25 to 0.75, 0.37, and 1.0 mg/kg ^{14}C-mitoxantrone respectively, radioactivity concentrations disappear rapidly from both plasma and whole blood during the first 2 hours after dosing; thereafter, concentrations decreased slowly. In all three species, mitoxantrone is concentrated in red cells during early sampling times. Prolonged, though low (<5 ng/mL), plasma levels were seen in dogs and monkeys through at least 58 and 35 days, respectively.

Total radioactivity has linear, sex-independent, and dose-independent characteristics. Pharmacokinetic parameters of mitoxantrone, studied most extensively in the rat, reveal an elimination half-life of 12 days, a final volume of distribution of 392 L/kg, and clearance values for total plasma, renal, and non-renal compartments of 15.8, 1.7, and 14.1 mL/min/kg, respectively.

In rats, dogs, and monkeys, 10 days after a single IV dose of ^{14}C-mitoxantrone, 65 to 85% of the administered radioactivity is accounted for in the excreta; 80 to 90% of the recovered radioactivity being excreted in the feces and 10 to 20% excreted in the urine. While excretion is prolonged, only slightly detectable amounts are still being excreted daily 2 to 4 months after dosing.

Bile is the major excretory route in rats; within 6 hours of dosing, 22% of the radioactivity was excreted in the bile of bile-cannulated rats given 0.5 mg/kg radiolabelled mitoxantrone intravenously. Little radioactivity was found in the bile of the rats given radiolabelled mitoxantrone orally, confirming the poor absorption of the drug.

Tissue Distribution and Metabolism:

Mitoxantrone is rapidly and extensively distributed into the organs of rats, dogs, and monkeys; distribution is independent of dose. One or two days after dosing, radioactivity was highest in bile, gallbladder (except rats), liver, spleen, and kidney. In all three species, tissue concentrations are greater than respective plasma levels; radioactivity levels decrease with time. Little or no radioactivity is detected in brain, spinal cord, and cerebrospinal fluid indicating poor penetration of mitoxantrone through the blood-brain barrier. Amounts found in testes are also relatively low.

In pregnant rats, fetal uptake is negligible and amniotic fluid contains no appreciable amount of drug; these findings along with results showing appreciable uptake of radioactivity by the placenta indicate that the placenta is an effective barrier.

In all pharmacokinetic studies, the evidence suggests that rats, dogs, and monkeys are similar to humans relative to absorption, elimination, and tissue distribution. In clinical trials, studies in patients following IV administration of 12 mg/m^2 (0.35 mg/kg)[a] ^{14}C-mitoxantrone also demonstrate a rapid plasma clearance, a long elimination half-life and persistent tissue

concentrations. Published clinical results also indicate that mitoxantrone is taken up rapidly by tissue and released slowly.

Studies to determine the extent of metabolism and identity of metabolites of mitoxantrone are ongoing.

[a] A conversion factor of 34 based on a 50 kg person, 5 feet tall, with a surface area of 1.45 m^2 was used (Documenta Geigy Scientific Tables, 6th edition, Konrad Diem editor, Geigy Pharmaceuticals, Ardsley, N.Y., U.S.A. 1962).

TOXICOLOGY

Synopsis:

Mitoxantrone has an exceptionally favourable toxicity profile relative to other antineoplastic agents, including doxorubicin. Most importantly, the chronic toxicity of mitoxantrone does not include the dose-limiting progressive cardiomyopathy that is characteristic of chronic IV administration of anthracyclines in animals and humans. Moreover, compared to other antineoplastic agents, the severity of gastrointestinal effects of mitoxantrone is less, atrophy of hair follicles is not produced, and no irritation occurs when accidentally extravasated. Mitoxantrone is also not teratogenic in rats or rabbits, a finding which is probably attributable to an effective placental barrier in these species. The reversibility of clastogenic effects of mitoxantrone in rats given tolerated doses every 3 weeks and the absence of a dominant lethal effect may suggest that with clinical use dosing, there may be little mutagenic risk to humans receiving mitoxantrone.

In rats, dogs, and monkeys, mitoxantrone produces myelosuppression typical of other antineoplastic agents. Since myelosuppression is the sole dose-limiting effect of mitoxantrone, the degree of leukopenia is indicative of the maximum tolerated dose (MTD) in both animals and humans. In all three animal species, doses above the single or multiple MTD produce life-threatening myelosuppression. For this reason, the degree of leukopenia should be carefully monitored in the clinical use of mitoxantrone.

Single Dose (Acute) Toxicity Studies:

The acute lethality of mitoxantrone following single intravenous doses in mice and rats is shown below.

Acute Lethality in Mice and Rats Given Mitoxantrone IV

Species	**Sex**	**LD_{10} (mg/kg)**	**LD_{50} (mg/kg)**
Mouse	M	7.8	11.3
	F	7.1	9.7
Rat	M	3.5	4.8
	F	3.6	5.2

Similar LD_{50}'s were determined for mice and rats dosed intraperitoneally. Signs of toxicity for mice and rats via IV or IP routes included salivation, paleness, rough fur, decreased body weight gain and weight loss, abdominal distension, diarrhea, epistaxis, chromodacryorrhea, swelling of the nasal region, lacrimation, and hematuria.

In dogs and monkeys, the lethal single IV dose of mitoxantrone was 0.5 mg/kg for dogs and ≥1 mg/kg for monkeys. In contrast, the single lethal IV dose of doxorubicin has been reported to be 2.5 mg/kg for dogs and 4.2 mg/kg for monkeys. For mitoxantrone, signs of acute toxicity are related primarily to effects on the gastrointestinal tract and include emesis and diarrhea (dogs) and decreased food consumption and body weight (both species). Erythropenia and leukopenia are accompanied by bone marrow hypocellularity and lymphocytic depletion of lymphoid organs.

Multiple Dose Studies:

Multiple dose IV studies in rats, dogs, and monkeys were designed to investigate the chronic toxicity of mitoxantrone with careful attention being paid to the presence or absence of cardiomyopathy characteristic of anthracyclines. Repeated administration of doxorubicin in animals or man is associated with progressive cardiomyopathy leading to congestive heart failure.

In rats, both daily and intermittent (once every 3 weeks) multiple dose studies were conducted. In the daily study, rats were given doses ranging from 0.003 to 0.3 mg/kg once daily for 1 month. In the intermittent study, rats were given doses of 0.03, 0.3, 0.6, and 0.9 mg/kg IV once every 3 weeks for 18 dosing cycles. In both studies, sublethal and lethal doses of mitoxantrone did not produce progressive anthracycline-like cardiomyopathy. Subchronic and chronic toxicity was limited to effects on the kidneys and the hematopoietic system, effects similar to those reported for doxorubicin in rats. Ongoing studies in rats to investigate carcinogenicity of

mitoxantrone have also revealed no evidence of progressive anthracycline-like cardiomyopathy after 21 dosing cycles (once/3 weeks) at IV doses of 0.01, 0.03, and 0.10 mg/kg.

In dog and monkey studies, doxorubicin was studied simultaneously as a model for anthracycline-induced cardiomyopathy. Mitoxantrone was given intravenously to dogs and monkeys once every 3 weeks at dose levels of 0.125 and 0.25 mg/kg: doxorubicin was administered at a single dose level of 1.64 mg/kg similarly. Doses selected for these studies approximated one-half the single lethal IV dose of each compound in dogs and monkeys. From range-finding studies, these doses were also those which would produce degrees of leukopenia generally tolerated without producing life-threatening myelosuppression in either species and were therefore considered to be maximum tolerated doses (MTD's) in dogs and monkeys.

The results of these dog and monkey multiple dose studies revealed that mitoxantrone produced a generally comparable (at the low dose) or greater (at the high dose) degree of leukopenia than doxorubicin. Therefore, mitoxantrone was evaluated for chronic toxicity under conditions more severe than doxorubicin. Only doxorubicin displayed treatment-limiting toxicity, i.e., progressive cardiomyopathy in both dogs and monkeys necessitating sacrifice of animals before the intended completion of the studies. Mitoxantrone animals received 10 (dog) or 12 (monkey) dosing cycles while doxorubicin animals received 8-9 (dog) or 9-10 (monkey) dosing cycles.

Findings relative to effects on the heart of dogs and monkeys receiving mitoxantrone IV were not representative of anthracycline toxicity. Neither irreversible cellular damage nor functional signs of cardiotoxicity were seen in dogs or monkeys receiving mitoxantrone. In contrast, dogs

given doxorubicin showed evidence of progressive cardiomyopathy following the fourth dose. The myocyte changes progressed in severity with time and cumulative dose to irreversible cardiomyopathy characteristic of anthracyclines. Clinical signs of congestive heart failure in doxorubicin-treated dogs were also evident. In monkeys given doxorubicin, similar irreversible cardiac changes and clinical signs of cardiotoxicity, the latter characterized by progressive decreases in mean blood pressure and ECG changes, were also detected. Therefore, these chronic studies in dogs and monkeys clearly show that, in spite of myelosuppression which was at least as great with mitoxantrone as with doxorubicin, chronic progressive cardiomyopathy was not present for mitoxantrone. However, typical anthracycline-induced cardiomyopathy was present for doxorubicin.

Additional studies in dogs and rabbits have been sponsored by the National Cancer Institute. From these studies, descriptions of acute toxic response to mitoxantrone include effects on the heart. Because doses in these particular studies were lethal doses in which death resulted from renal, hepatic, and hematopoietic immune failure, the cardiac effects (thrombosis, myocarditis, necrosis and fibrosis) were secondary to generalized organ toxicity involving the kidney, liver, and bone marrow. The cardiac effects from these studies are neither predictive nor typical of progressive anthracycline-like cardiomyopathy.

Mutagenicity and Cytogenetic Studies:

In microbial mutagenicity tests, mitoxantrone causes frame-shift mutations. In primary rat hepatocyte cultures assayed for unscheduled DNA synthesis (DNA repair), mitoxantrone causes DNA damage. Mitoxantrone does not cause a dominant lethal effect in rats. The spectrum of

genetic activity seen with mitoxantrone is similar to other antineoplastic drugs and is consistent with its activity as a DNA-reactive agent.

When an in vivo cytogenetic study was conducted using intraperitoneal doses of 0.5 to 2.0 mg/kg once daily for 5 consecutive days, mitoxantrone caused chromosomal aberrations. However, when the study was repeated using a dosing regimen that more closely resembled a clinically used regime (single 0.3 mg/kg intravenous doses at 21-day intervals), chromosomal damage, noted one day after the first dose, did not accumulate or persist. The incidence of chromosome damage, 21 days after one or two doses, resembled that noted in controls. Thus, at a dose approximating clinical use levels, the clastogenic effect is reversible.

Reproductive Toxicology and Teratology:

In these studies at the highest tolerated daily doses allowing evaluation of reproduction and teratology, mitoxantrone had no effect on reproductive performance, fertility, or gestation in rats. Slight dose-related decreases in epididymal weights were noted in the F_0 generation. However, F_1 and F_2 generations were not affected by dosing of the F_0 generation.

Mitoxantrone, given IV to pregnant rats and rabbits, was not teratogenic in either species. Decreased fetal body weight in high-dose rats was attributed to maternal toxicity although an increased incidence of premature delivery was noted in rabbits. In contrast, doxorubicin is known to be embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits.

Rationale for Expression of Mitoxantrone Doses in mg/kg:

Throughout our studies with mitoxantrone, doses have been expressed on a body weight basis rather than on a body surface area basis. Although clinical oncologists generally use body surface area as the basis for determining doses in man, the use of body weight in comparing doses between animals and man is considered more appropriate in the case of mitoxantrone and doxorubicin.

Based on the use of body surface area, an apparently wide discrepancy between MTD's in animals and man exists for both compounds. For example, when body surface area is used to compare doses for mitoxantrone in dogs, monkeys, and man, the MTD's are 5, 3, and 12-14 mg/m^2, respectively; for doxorubicin, the values for dogs, monkeys, and man are 34, 19.7, and 65 mg/m^2, respectively. However, on a body weight basis, the MTD's for dogs, monkeys, and man for mitoxantrone are 0.25, 0.25, and 0.35 - 0.41 mg/kg, respectively; likewise, the MTD's for doxorubicin are respectively 1.6, 1.6, and 1.9 mg/kg. Essentially no difference exists between animals and man relative to the MTD's when doses are expressed on a mg/kg basis. Therefore, the use of body weight is a more direct and accurate way to compare mitoxantrone doses between animals and humans.

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