

MitOXANTRONE

Injection, USP

Antineoplastic Agent

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Injectable/ 2 mg/mL	For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

INDICATIONS AND CLINICAL USE

Mitoxantrone Injection, USP is indicated for:

- chemotherapy in patients with metastatic carcinoma of the breast;
- relapsed adult leukemia, lymphoma patients, and patients with hepatoma;
- in combination with other drug(s), for the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults. The category includes myelogenous, promyelocytic, monocytic and erythroid acute leukemias.

Pediatrics: Safety and efficacy in pediatric patients have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container, or have demonstrated prior hypersensitivity to anthracyclines. For a complete listing of ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Mitoxantrone Injection, USP 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 AND PRECAUTIONS**).
- 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 AND PRECAUTIONS

Serious Warnings and Precautions

- Mitoxantrone 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 biological parameters during and after treatment.
- Mitoxantrone Injection, USP 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 DOSAGE AND ADMINISTRATION).**
- Mitoxantrone Injection must not be given by intrathecal injection. Severe injury with permanent sequelae can result from intrathecal administration (see **CONTRAINDICATIONS**).
- Secondary acute myelogenous leukemia (see **Hematologic** section below).
- Myocardial toxicity (see **Cardiovascular** section below).

General

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

Cardiovascular

Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with mitoxantrone or months to years after termination of therapy. Use of mitoxantrone has been associated with cardiotoxicity, which increases with cumulative dose.

Cardiac toxicity with mitoxantrone 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 for months to years after, mitoxantrone therapy. The risk of cardiotoxicity increases with cumulative doses.

Evaluation of LVEF (by echocardiogram or MUGA) is recommended prior to administration of the initial dose of mitoxantrone. 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/m².

In cancer patients, symptomatic CHF is known to occur in 2.6% of patients receiving up to a cumulative dose of 140 mg/m². 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 cardio-toxic 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 mitoxantrone therapy in such patients should be determined before starting therapy.

Acute congestive heart failure may occasionally occur in patients treated with mitoxantrone 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 mitoxantrone, who had not received prior anthracyclines.

Mitoxantrone has not been approved for the treatment of multiple sclerosis. However, patients being treated with mitoxantrone and who also have multiple sclerosis as a comorbid condition and who reach a cumulative dose of 100 mg/m² 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/m². 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 mitoxantrone administration cannot be ruled out.

Mitoxantrone should not ordinarily be administered to multiple sclerosis patients who have received a cumulative lifetime dose of >100 mg/m² 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 mitoxantrone.

Hematologic

When mitoxantrone is used in high doses (>14 mg/m² x 3 days), severe myelosuppression will occur. Since mitoxantrone 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, mitoxantrone should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm³.** 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 1,500/mm³ may be expected following therapy, but white blood cell counts rarely fall below 1,000/mm³ 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 mitoxantrone.** 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 AML has been reported in cancer patients treated with anthracyclines. Mitoxantrone 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. The cumulative risk of developing treatment-related AML, in 1,774 patients with breast cancer who received mitoxantrone concomitantly with other cytotoxic agents and radiotherapy, was estimated as 1.1% and 1.6% at 5 and 10 years, respectively.

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

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/m² below the dose recommended for single-agent use (see **DOSAGE AND ADMINISTRATION**).

Hepatic/Biliary/Pancreatic

The safety of mitoxantrone in patients with hepatic insufficiency is not established. Mitoxantrone therapy in patients with abnormal liver function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments.

Mitoxantrone should not be used in patients with severe hepatic dysfunction (see **CONTRAINDICATIONS**) and poor performance status. If performance status is favourable, mitoxantrone 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.

Immune

Immunization may be ineffective when given during mitoxantrone 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.

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.

Renal

Mitoxantrone may impart a blue-green colouration to the urine for 24 hours after administration, and patients should be advised to expect this during active therapy.

A reversible blue colouration in the sclerae has been reported in two cases.

Special Populations

Pregnant Women: Mitoxantrone may cause fetal harm when administered to a pregnant woman. In treated rats, at doses of ≥ 0.1 mg/kg (0.05 times the recommended human dose on a mg/m² basis), low fetal birth weight and retarded development of the fetal kidney were seen in greater frequency. In treated rabbits, an increased incidence of premature delivery was observed at doses ≥ 0.01 mg/kg (0.01 times the recommended human dose on a mg/m² basis). Mitoxantrone 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.

Nursing Women: Mitoxantrone 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 mitoxantrone, breast-feeding should be discontinued before starting treatment.

Monitoring and Laboratory Tests

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 **DOSE AND ADMINISTRATION**).

Liver function tests should also be performed prior to each course of therapy.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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.

Some degree of leukopenia is to be expected following recommended doses of mitoxantrone. With dosing every 21 days, suppression of WBC counts below 1,000/mm³ is infrequent, leukopenia is usually transient, reaching its nadir at about 10 days after dosing, with recovery usually occurring by the 21st day.

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 nonspecific cytogenetic alterations including chromosome abnormalities.

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

Clinical Trial Adverse Drug Reactions

Thrombocytopenia can occur, and anemia occurs less frequently. Myelosuppression may be more severe and prolonged in patients having had extensive prior chemotherapy or radiotherapy or in debilitated patients. In leukemia patients treated with a single course of 12 mg/m² i.v. 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%.

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

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 mitoxantrone hydrochloride 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.

Dermatologic effects include extravasation at the infusion site, which may result in erythema, swelling, pain, burning, rash, and/or blue discoloration of the skin. Extravasation can result in tissue necrosis with resultant need for débridement and skin grafting. Phlebitis has also been reported at the site of infusion.

Less Common Clinical Trial Adverse Drug Reactions

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

Abnormal Hematologic and Clinical Chemistry Findings

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).

DRUG INTERACTIONS

Drug-Drug Interactions

Congestive heart failure (CHF) 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 (see **WARNINGS AND PRECAUTIONS**).

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

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**.)

DOSE AND ADMINISTRATION

CAUTION

Mitoxantrone Injection, USP 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.

General Considerations

Preparation and Administration Precautions

• Mitoxantrone Injection 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 AND PRECAUTIONS**).

• Mitoxantrone Injection 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 AND PRECAUTIONS**).

• 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 mitoxantrone with the skin, mucous membranes, or eyes. If any signs or symptoms of extravasation have occurred, including burning, pain, pruritus, erythema, swelling, blue discoloration, or ulceration, the injection or infusion should be immediately terminated and restarted in another vein above the previous vein or in the contralateral arm.

During intravenous administration of Mitoxantrone Injection, 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.

• Mitoxantrone Injection 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 Mitoxantrone Injection not be mixed in the same infusion with other drugs.

Recommended Dose and Dosage Adjustment

Breast Cancer, Lymphoma, Hepatoma: The recommended initial dosage for use of Mitoxantrone Injection as a single agent is 14 mg/m² of body surface area, given as a single intravenous dose, which may be repeated at 21-day intervals. A lower initial dose (12 mg/m² 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 judgment 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 \leq 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:

Mitoxantrone 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/m² with leucovorin rescue) and glucocorticoids.

As a guide, the initial dose of mitoxantrone when used with other myelosuppressive agents should be reduced by 2 - 4 mg/m² below the doses recommended for single-agent usage; subsequent dosing depends upon the degree and duration of myelosuppression.

Dosage for Patients with Acute Leukemia in Relapse:

The recommended dosage for induction is 12 mg/m² of body surface area, given as a single intravenous dose daily for five consecutive days (total of 60 mg/m²). In clinical studies, with a dosage of 12 mg/m² 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 mitoxantrone and again the recommended dosage is 12 mg/m² daily x 5.

Combination Initial Therapy for Acute Nonlymphocytic Leukemia (ANLL): Mitoxantrone, 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/m² of mitoxantrone for 3 days (Days 1 - 3) and 100 mg/m² 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 mitoxantrone given for only 2 days and cytosine arabinoside for only 5 days.

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

Consolidation therapy, which was used in two large randomized multicentre trials, consists of mitoxantrone, 12 mg/m² given by intravenous infusion daily for 2 days (Days 1 and 2), and cytarabine, 100 mg/m² 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 AND PRECAUTIONS** 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 mitoxantrone as single-agent therapy at a dosage of 8 mg/m² daily for 5 days.

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

Administration

Mitoxantrone Injection solution should be diluted to at least 50 mL with either Sodium Chloride for Injection, USP or 5% Dextrose for Injection, USP. This solution should be introduced slowly into the tubing of a freely-running intravenous infusion of Sodium Chloride for Injection, USP or 5% Dextrose for Injection, USP 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 nonvesicant properties of Mitoxantrone Injection minimize the possibility of severe reactions following extravasation; however, tissue necrosis has been reported rarely.

Mitoxantrone Injection 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 Mitoxantrone Injection solutions must be exercised and the use of protective eyeglasses, gloves, and other protective clothing is recommended (see **SPECIAL HANDLING INSTRUCTIONS**).

As with all parenteral products, intravenous admixtures should be inspected for clarity of solutions, particulate matter, precipitate, discoloration, and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

Intraperitoneal Administration: Mitoxantrone has been given by intraperitoneal administration for malignant ascites in advanced breast and gynecologic pelvic cancer.

OVERDOSAGE

There is no known specific antidote for mitoxantrone. Accidental overdoses have been reported. Some patients receiving 140 - 180 mg/m² 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, mitoxantrone is extensively tissue bound and it is unlikely that the therapeutic effect or toxicity would be mitigated by peritoneal or hemodialysis (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS** sections).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 ³H-uridine and four times more potent in inhibiting the uptake of ³H-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.

Pharmacodynamics

Mitoxantrone increases life span and numbers of long-term survivors among mice with leukemia P388 and L1210 leukemias or with B16 melanoma and colon 26 carcinoma solid neoplasms. It is active by the intraperitoneal, subcutaneous, and intravenous routes in mice, but oral activity has not been demonstrated.

Pharmacokinetics

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.

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 i.v. administration of 12 mg/m² (0.35 mg/kg) of ¹⁴C-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.

Mitoxantrone is rapidly and extensively distributed into the organs of rats, dogs, and monkeys; distribution is independent of dose.

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

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 i.v. dose of ¹⁴C-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.

Special Populations and Conditions

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**).

STORAGE AND STABILITY

Mitoxantrone Injection, USP should be stored between 15 and 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.**

SPECIAL HANDLING INSTRUCTIONS

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.

Handling:

1. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).
2. Personnel preparing mitoxantrone 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 mitoxantrone should be segregated in plastic bags, sealed and marked as hazardous waste. Incinerate at 1,000°C or higher. Sealed containers may explode if a tight seal exists.
3. If incineration is not available, mitoxantrone may be detoxified by adding 5.5 parts by weight of calcium hypochlorite to each 1 part of 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 (e.g., add 43.5 g calcium hypochlorite to 100 mL of water*). Withdraw any Mitoxantrone Injection remaining in the vial with the aid of a hypodermic syringe. Add to the prepared calcium hypochlorite solution slowly, preferably in a 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.

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 nondisposable 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 nondisposable equipment in soap and water.

Spillage/Contamination:

Wear gloves, mask, and 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 clean-up should wash with soap and water.

DOSE FORMS, COMPOSITION AND PACKAGING

Composition

Mitoxantrone Injection, USP 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. The product does not contain antibacterial preservatives. Single-use vials. Discard unused portion. Vial stoppers do not contain natural rubber latex.

Availability of Dosage Forms

Mitoxantrone Injection, USP 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:

C132010 10 mL single-use vials containing 20 mg mitoxantrone free base/10 mL solution (2 mg/mL) packaged individually.

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

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