MITOXANTRONA KEMEX
MITOXANTHRONE HYDROCHLORIDE
INJECTABLE SOLUTION 2 mg/ml

MADE IN ARGENTINA PRESCRIPTION ONLY

Qualitative and Quantitative Formula:
Each ml of the vial contains:
Mitoxantrone hydrochloride.....2 mg
Sodium Chloride.....9.8 mg
Sodium Acetate 0.005% / Acetic Acid (0.046% w/v) q.s.....pH 3.0 - 4.5
Distilled Water for Injection q.s.....1 ml

PRESENTATIONS
Packages of 10 ml (20 mg) and 12.5 ml (25 mg).

DESCRIPTION
Mitoxantrone (as hydrochloride) is a synthetic anthracenedione antineoplastic agent for intravenous use.

CLINICAL PHARMACOLOGY
Mitoxantrone is an alkylating agent; however, its mechanism of action has not been fully elucidated.
It exhibits an inhibitory effect on cell division in both proliferative and non-proliferative human cells, suggesting a lack of specificity in the cell cycle.
No pharmacokinetic studies were conducted in humans receiving multiple daily doses.
Pharmacokinetic studies in adult patients following single intravenous doses of Mitoxantrone demonstrated multiexponential plasma clearance.
Tissue distribution is rapid.
Drug distribution studies in monkeys indicate slow passage into the brain, spinal cord, eyes, and cerebrospinal fluid. The volume of distribution exceeds 1000 l/m². Drug elimination is slow, with a terminal plasma half-life of 5.8 days (range: 2.3 – 13.0).
In other tissues, the half-life may be longer.
Mitoxantrone binds to plasma proteins by 78% within the observed concentration range of 26 – 456 ng/ml. This binding is independent of concentration and unaffected by phenytoin, methotrexate, prednisone, heparin, or aspirin.
Mitoxantrone is excreted via renal and hepatobiliary systems.
Renal excretion is limited (only 6% - 11% of the dose is recovered in the urine within 5 days after dosing). Of the urine-recovered material, 65% is unchanged drug, and the remaining 35% consists mainly of inactive metabolites and their glucuronic conjugates.
Metabolites are derived from mono- and dicarboxylic acid.
Hepatobiliary elimination seems more significant, accounting for up to 25% of the dose recovered in feces within 5 days of intravenous dosing.
No significant pharmacokinetic differences were observed in Mitoxantrone analysis for 7 patients with moderate hepatic impairment (serum bilirubin levels between 1.3 – 3.4 mg/dl) compared to 16 patients with normal hepatic function.
In the development of two large randomized multicenter research studies, induction therapy for acute non-lymphocytic leukemia (ANLL) was compared using a daily dose of 12 mg/m² of Mitoxantrone over 3 days, administered as a 10-minute intravenous infusion, along with 100 mg/m² of cytarabine over 7 days as a continuous 24-hour infusion and a daily dose of 45 mg/m₂ of daunorubicin over 3 days, given by intravenous infusion, along with the cytarabine dosing schedule used with Mitoxantrone.
Patients with incomplete antileukemic response received a second induction course, during which either Mitoxantrone or daunorubicin was administered over 2 days, while cytarabine was given over 5 days, using the same dosing schedule.

INDICATIONS AND USES
Mitoxantrone, in combination with other authorized drug(s), is indicated for initial therapy of acute non-lymphocytic leukemia (ANLL) in adults. This category includes acute myelogenous, promyelocytic, monocytic, and erythroid leukemias.
In combination with corticosteroids, it is indicated for initial therapy in patients with advanced hormone-refractory prostate cancer.

DOSE AND ADMINISTRATION
Advanced hormone-refractory prostate cancer:
The recommended dose of Mitoxantrone is 12 to 14 mg/m² via intravenous administration every 21 days.

Combination Therapy for ANLL: (In adults)
The recommended initial dose is 12 mg/m² of Mitoxantrone daily for days 1-3, given by intravenous administration, and 100 mg/m² of cytarabine for 7 days, simultaneously administered through a 24-hour infusion for days 1-7.
More complete remissions occur after the initial induction course. If an incomplete antileukemic response occurs, a second induction course may be administered. Mitoxantrone should be given for 2 days, and cytarabine for 5 days, using the same daily dosing level.
In case of severe non-hematological toxicity during the first induction course, the second course should be postponed until toxicity is eliminated.
Consolidation therapy in two important randomized multicenter studies consisted of a daily dose of 12 mg/m² of Mitoxantrone on days 1 and 2, along with 100 mg/m2 of cytarabine for 5 days, given continuously via a 24-hour infusion on days 1-5.
The first course was administered around 6 weeks after the final induction course, while the second course was typically administered 4 weeks after the first course.

PRECAUTIONS IN PREPARATION AND ADMINISTRATION
MITOXANTRONE CONCENTRATE MUST BE DILUTED BEFORE USE.
Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, if solution and container permit.
Mitoxantrone should be diluted in a minimum of 50 ml of either 0.9% Sodium Chloride Injection or 5% Dextrose Injection.
Mitoxantrone can also be diluted in 5% Dextrose, Water for Injection, Normal Saline Solution, or 5% Dextrose in Normal Saline Solution for immediate use. **DO NOT FREEZE.**
Mitoxantrone should not be mixed in the same infusion with Heparin as it may precipitate.
Due to lack of specific compatibility data, mixing Mitoxantrone in the same infusion with other drugs is not recommended.
The diluted solution should be slowly introduced via a freely flowing intravenous injection of 0.9% Sodium Chloride or a 5% Dextrose injection over at least 3 minutes.
Unused solutions should be promptly discarded. For multiple dose administration, after the vial is penetrated, the remaining undiluted Mitoxantrone concentrate should be stored for no more than 7 days at 15-20º C, or up to 14 days under refrigeration.

DO NOT FREEZE THIS PRODUCT. DOES NOT CONTAIN PRESERVATIVES.

In case of extravasation, restart in another vein. The non-vesicant properties of Mitoxantrone reduce the likelihood of severe local reactions following extravasation.
However, care should be taken to avoid extravasation at the infusion site. Contact of Mitoxantrone with skin, membranes, mucosa, and eyes should be avoided.
If skin contact occurs, rinse with copious warm water. For eye contact, use standard irrigation techniques immediately.
Use gloves, protective eyewear, and appropriate attire when preparing and administering the drug.
Drops spilled on work surfaces can be cleaned with a calcium hypochlorite aqueous solution (mixing 5.5 parts of calcium hypochlorite with 13 parts by weight of water for each part of Mitoxantrone). Absorb the solution with towels and dispose of them in a safe manner.
When working with calcium hypochlorite, use gloves, protective eyewear, and appropriate attire.
Procedures for proper handling and disposal of anticancer drug products should be considered. Various guidelines have been published, but a consensus on whether the recommended procedures are necessary or appropriate has not been reached.

CONTRAINDICATIONS
Mitoxantrone is contraindicated in patients who have demonstrated prior hypersensitivity to this drug.

WARNINGS
WHEN MITOXANTRONE IS USED AT DOSES INDICATED FOR LEUKEMIA TREATMENT, SEVERE MYELOSUPPRESSION WILL OCCUR. THEREFORE, MITOXANTRONA KEMEX SHOULD BE ADMINISTERED BY MEDICAL PROFESSIONALS EXPERIENCED IN CHEMOTHERAPEUTIC TECHNIQUES. SUPPORT SERVICES AND LABORATORY FACILITIES SHOULD BE AVAILABLE TO MONITOR HEMATOLOGICAL AND CHEMICAL PARAMETERS. ADDITIONAL THERAPIES, INCLUDING ANTIBIOTICS, SHOULD BE AVAILABLE. BLOOD BANKS SHOULD BE READILY ACCESSIBLE TO PATIENTS DURING THE EXPECTED PERIOD OF MARROW HYPOPLASIA AND SEVERE MYELOSUPPRESSION.

THE ATTENDING PHYSICIAN SHOULD PAY SPECIAL ATTENTION TO COMPLETE HEMATOLOGICAL RECOVERY BEFORE INITIATING THERAPY.
PATIENTS SHOULD BE MONITORED CONTINUOUSLY DURING THIS PHASE.

Patients with pre-existing myelosuppression from prior drug therapy should not receive Mitoxantrone unless the potential benefit justifies the risk of further marrow suppression.
The safety of Mitoxantrone in patients with hepatic impairment has not been established.
The safety of using this product by routes other than intravenous administration has not been established.

Pregnancy:
Mitoxantrone can cause fetal harm when administered to a pregnant woman.
Adequate and well-controlled studies have not been conducted in pregnant women.
If this drug must be administered during pregnancy or if the patient becomes pregnant while being treated with this product, the patient should be informed about the potential risk this drug poses to the fetus.
Women of childbearing age should avoid becoming pregnant while taking this medication.

Cardiac Effects:
Due to the potential risk of cardiac effects in patients previously treated with doxorubicin, the benefit-risk ratio of Mitoxantrone therapy should be determined before initiating treatment in such patients.

General Considerations:
Functional cardiac changes in left ventricular ejection fraction (LVEF) and irreversible congestive heart failure can occur with Mitoxantrone administration.
Cardiac toxicity may be even more frequent in patients with a history of anthracycline treatment, mediastinal radiotherapy, or preexisting cardiovascular disease.
In this regard, LVEF of these patients should be regularly monitored from the beginning of therapy. During investigational studies carried out with intermittent dosing for various tumor types, patients who received a dose equivalent to a cumulative dose of up to 140 mg/m² had a cumulative probability of 2.6% for clinical congestive heart failure. The overall cumulative probability of moderate or severe decreases in LVEF after this dose was administered was 13% in comparative trials.

Leukemia:
Acute congestive heart failure can occasionally occur in patients treated with Mitoxantrone for treatment of acute non-lymphocytic leukemia (ANLL). In first-line comparative studies where Mitoxantrone + cytarabine was administered versus daunorubicin + cytarabine in previously untreated adult ANLL patients, congestive heart failure was associated with the therapy in 6.5% of patients in each treatment arm. Establishing a causal relationship between drug therapy and cardiac effects in this context is difficult since myocardial function is often depressed by anemia, fever, infections, and bleeding, which frequently accompany the underlying disease.

Advanced Cancer Patients:
Patients with advanced prostatic cancer refractory to hormonal therapy and treated with Mitoxantrone may develop congestive heart failure.

PRECAUTIONS
General Considerations:
Mitoxantrone therapy should be accompanied by frequent monitoring of laboratory parameters and frequent patient observation.
Hyperuricemia may result from rapid lysis of tumor cells due to Mitoxantrone effect. Serum uric acid levels should be monitored, and hypouricemic therapy should be initiated before starting antileukemic therapy.
Systemic infections should be treated concurrently with or prior to the start of Mitoxantrone therapy.

Patient Information:
Patients should be informed that their urine may turn blue for 24 hours after receiving a dose of Mitoxantrone during therapy. Additionally, bluish discoloration of the sclera may occur. Patients should also be educated about signs and symptoms of myelosuppression.

Laboratory Tests: Both complete blood counts and functional tests are necessary for appropriate dose adjustments. (See DOSAGE AND ADMINISTRATION)

Carcinogenesis. Mutagenesis:
Mitoxantrone can induce chromosomal aberrations in animals and is mutagenic in bacterial systems. It's worth noting that Mitoxantrone caused DNA damage and twin chromatid changes in vitro. Topoisomerase II inhibitors, including Mitoxantrone, in combination with other antineoplastic agents, have been associated with the development of acute leukemia.

Lactating Mothers:
Whether Mitoxantrone is excreted in human milk is unknown. Due to the potential for serious adverse reactions in nursing infants from Mitoxantrone, breastfeeding should be discontinued before starting treatment.

Pediatric Use:
The safety and effectiveness of Mitoxantrone in children have not been established.

ADVERSE REACTIONS
Mitoxantrone has been studied in approximately 600 ANLL patients. In these studies, Mitoxantrone + cytarabine was administered versus daunorubicin + cytarabine. The experience in major international trials was similar. A broader experience in a variety of other tumor types did not reveal additional important reactions other than cardiomyopathy. (See WARNINGS). It should be noted that the adverse reaction categories in this list include certain clinical symptoms that overlap and are linked to the same adverse reaction (e.g., dyspnea, cough, and pneumonia).
Furthermore, adverse reactions listed here may not necessarily be attributed to chemotherapy since it is often impossible to distinguish between the effects of the drug and those of the underlying disease. However, it is clear that the combination of Mitoxantrone + cytarabine was responsible for nausea, vomiting, as well as other reactions such as alopecia, mucositis/stomatitis, and myelosuppression.

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

Skin Reactions:
Phlebitis cases have been reported very rarely at the infusion site. A few cases of tissue necrosis have also been reported after extravasation.

Hematological Reactions:
Mylodepression occurs rapidly at the start of treatment and is consistent with the development of significant marrow hypoplasia to achieve any response. Bleeding and infections were observed during the development of investigations and were consistent with reported normal induction regimens. Topoisomerase II inhibitors, including Mitoxantrone, in combination with other antineoplastic agents, have been associated with the development of acute leukemia.

Gastrointestinal Reactions:
Acute nausea and vomiting were observed in most patients, but generally these adverse reactions were mild to moderate and could be controlled with antiemetics. Mucositis/stomatitis was observed within the first week of therapy.

Cardiovascular Reactions:
Congestive heart failure; tachycardia; changes in ECG results, including arrhythmia, chest pain, and asymptomatic decreases in LVEF.

OVERDOSAGE
No specific antidote for Mitoxantrone is known. Accidental overdoses have been reported. Four patients receiving a single injection dose of 140-180 mg/m2 experienced severe leukopenia accompanied by infection. Hematologic support and antimicrobial therapy may be required during prolonged periods of marrow hypoplasia.
While patients with severe renal dysfunction have not been studied, Mitoxantrone has significant tissue binding. Therefore, peritoneal administration or hemodialysis is unlikely to alleviate therapeutic effects or toxicity.

In case of overdose, seek the nearest hospital or contact poison control centers:
Hospital de Pediatría Ricardo Gutierrez: (011) 4962-6666/2247
Hospital A. Posadas: (011) 4654-6648/658/7777.

STORAGE
Store at controlled temperatures between 15 and 30º C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

Medicinal Specialty Authorized by the Ministry of Health.
Certificate No. 49.903
Manufactured by: LABORATORIO KEMEX S.A.
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kemex laboratorio