MITOMICINA KEMEX
MITOMYCIN 5 & 20 mg
Powder for solution for injection
Administration route: Intravenous

Made in Argentina Under prescription only

Qualitative and quantitative composition
MITOMICINA KEMEX 5 mg
Each vial contains:
Mitomycin.....5.00 mg
Mannitol.....10.00 mg

MITOMICINA KEMEX 20 mg
Each vial contains:
Mitomycin.....20.00 mg
Mannitol.....40.00 mg

THERAPEUTIC ACTION
Antineoplastic agent.
MITOMICINA KEMEX is classified as an antibiotic; however, it is not useful as an antimicrobial due to its toxicity.

THERAPEUTIC INDICATIONS
Accepted
Treatment of carcinomas: adenocarcinoma of the stomach, pancreas, colon or breast, gastrointestinal cancer, some head and neck cancers, advanced biliary carcinomas, lung and cervical squamous cell carcinomas, transitional cell carcinomas of the urinary bladder as well as the local bladder tumour treatment.
Chronic leukemias: Chronic myelocytic leukemia.
The accepted indications for antineoplastic drugs are under constant review. The ongoing studies frequently reveal new indications, dosing schedules, and therapies that often use combination of other approved chemotherapeutic agents that are more useful for treating a tumour than the existing therapy. For specific and current indications, see the literature.

PHARMACOLOGY
Mechanism of action:
Mitomycin is not specific for any phase of the cell cycle, although it is most active in the G and S phases of cell division. After enzymatic activation in tissues, it acts as a bifunctional or trifunctional alkylator. Mitomycin causes DNA crosslinking and, to a lesser extent, also inhibits RNA and protein synthesis.
Distribution: Does not cross the blood-brain barrier.
Metabolism: Clearance is effected primarily by metabolism in the liver, but metabolism occurs in other tissues as well, including kidneys.
Half-life values:
Initial: from 5 to 15 minutes.
Terminal: 50 minutes approximately.
Elimination: Renal 10% unchanged. Small amounts in bile and feces.

PRECAUTIONS
Carcinogenicity/Mutagenicity
In secondary malignancies, delayed effects of many antineoplastics are possible, although it is not clear whether the effect is related to their mutagenic or immunosuppressive action.
The effect of dose and duration of treatment is also unknown, although the risk appears to increase with long-term use. Although the information is scant, the available data seem to indicate that the risk of carcinogenicity is greater with alkylating agents.
Mitomycin has shown to be a potent carcinogen in rats.
Fertility/Pregnancy:
Fertility: In patients undergoing antineoplastic therapy, especially with alkylating agents, gonadal suppression may occur leading to amenorrhea or azoospermia.
In general, these effects appear to be related to dose and duration of therapy and may be irreversible. The prediction of degree of testicular or ovarian dysfunction is complicated by the frequent use of associations of various antineoplastics, which makes it difficult to assess each drug separately.

Pregnancy:
Mitomycin has been reported to be teratogenic in animals.
First quarter: It is generally recommended to avoid, if possible, the use of antineoplastics during the first quarter, especially in combination with other chemotherapy.
Although the information is scant, due to the relatively few examples of administration of antineoplastics during pregnancy, the risk-benefit ratio must be considered due to the mutagenic, teratogenic and carcinogenic potential of these drugs.
Other risks to the fetus include the adverse reactions observed in adults.

Breast-feeding:
Although very little information is available regarding the excretion of antineoplastics in breast milk, lactation is not recommended while Mitomycin is being administered, due to risks to the nursing infant (adverse effects, mutagenicity, carcinogenicity).

Paediatric use:
Although adequate and well-controlled studies have not been performed, response to mitomycin is not expected to be affected in this age group.

Geriatric use:
No information is available.

Odontology:
The bone marrow depressant effects of MITOMICINA KEMEX may result in an increased incidence of microbial infection, delayed healing, and gingival bleeding. Dental work should be terminated, if possible, before starting therapy or postponed until blood counts have returned to normal. Patients should be instructed in correct oral hygiene during treatment, including caution in the use of brushes, floss and dental picks. MITOMICINA KEMEX may also cause stomatitis associated with considerable discomfort.

DRUG INTERACTIONS AND/OR MEDICAL PROBLEMS:
The following drug interactions and/or associated medical problems have been selected based on their potential clinical significance. The possible mechanisms in the cases are indicated in parentheses.
Note: Associations containing any of the following drugs, depending on the quantity present, may interact with this medication.
Medications that cause blood dyscrasia.
-Bone marrow depressants, others.
-Radiotherapy.
(Simultaneous use may increase the bone marrow depressant effects of these drugs and radiation therapy, the dosage may need to be decreased).
Doxorubicin
(Use may lead to increased cardiotoxicity, it is recommended that the total dose of doxorubicin not exceed 450 mg/m² body surface area).
Vaccines with live viruses:
(Since the normal defense mechanisms are suppressed, simultaneous use with live virus vaccines can enhance the replication of the vaccine virus, decrease the patient's humoral response to the vaccine. The immunization of these patients should only be approached with great care after a careful review of the patient's haematological status and only with the knowledge and consent of the supervising physician giving treatment with Mitomycin.
The time interval during the discontinuation of drugs that produce immunosuppression and the recovery of the ability to response to the vaccine depends on the intensity and type of immunosuppressive medication used, the underlying disease and other factors; estimations range from 3 months to 1 year.
Patients with leukemia in remission should not receive live virus vaccines until at least 3 months after receiving the last chemotherapy. In addition, immunization with oral poliovirus vaccines should be postponed in persons in close contact with the patient, especially family members.)

INTERFERENCE WITH THE DIAGNOSIS
With physiological values
Blood urea nitrogen (BUN) concentrations and serum creatinine concentrations (may be increased, indicating renal toxicity).
Medical problems
This medication should not be used when the following medical problems exist (reasons are given where appropriate):
- Existing or recent chickenpox (including patient exposure).
- Herpes zoster (risk of severe generalized disease).
The risk/benefit ratio should be assessed in the following clinical situations (reasons are given where appropriate):
- Depression of the bone marrow.
- Coagulation disorders.
- Infection.
- Kidney dysfunction.
-Caution should also be exercised in patients who have undergone prior treatment with cytotoxic drugs or radiotherapy.
Patient monitoring
The patient's monitoring is especially important (other tests may be carried out in some patients, depending on their condition):
- Uremia.
- Hematocrit.
- Platelet count.
- Serum alanine aminotransferase (ALAT [GPT]).
- Serum aspartate aminotransferase (ASAT [GOT]).
- Serum bilirubin.
- Serum creatinine.
- Serum lactate dehydrogenase (LDH).
- Serum uric acid.
- Total and differential leukocyte count.
(Determinations are recommended prior to therapy initiation and at periodic intervals during therapy; frequency varies depending on clinical condition, drug, dose, and other drugs used concurrently).
Note: It is recommended that renal and haematological function be followed for several months after treatment with mitomycin to detect possible haemolytic-uremic syndrome.

SIDE EFFECTS/ADVERSE EFFECTS:
Note: Many side effects are unavoidable and represent the pharmacological action of the medication. Some of them (e.g., leukopenia and thrombocytopenia) are used as indicators of medication efficacy and facilitate individual dosage adjustment.
The following side/adverse effects have been selected based on their possible clinical significance (possible causes are specified in parentheses, where appropriate).

Requires medical attention:
-Very common incidence:
Fever, chills, or sore throat (leukopenia; infection).
Unusual bleeding or bruising (thrombocytopenia).
Note: Leukopenia and thrombocytopenia appear within 3 to 8 weeks of starting treatment, and leukocyte counts return to normal within 10 weeks of discontinuing treatment, although in about 25% of the events counts are not retrieved. The duration of myelosuppression appears to be inversely related to baseline counts. The severity of bone marrow depression is variable and determines subsequent mitomycin dosing.
-Very common incidence:
Loss of appetite, nausea or vomiting.
Note: nausea and vomiting usually appear within 1 to 2 hours; vomiting usually stops in 3 to 4 hours, while nausea may persist for 2 to 3 days.
-Less common incidence:
Haematuria.
Decreased urination.
Dyspnoea.
Note: Haemolytic uraemic syndrome (HUS) (consisting of microangiopathic haemolytic anaemia, renal failure, thrombocytopenia, and pulmonary hypertension) has usually developed several months after treatment and is commonly fatal. Renal failure without haemolysis has also been described.
Cough. (Lung disease: usually occurs after multiple doses.)
Lesions in the mouth and lips (stomatitis).
- *Less common incidence:* Numbness or tingling in the fingers and toes.
Purple bands on the nails; with repeated doses, skin rash, tiredness, or weakness: may last from several days to 3 weeks.
-Rare incidence:
Haematemesis. Redness or pain at the injection site (thrombus ebitis; cellulitis; extravasation).
Note: Delayed erythema and ulceration, at or away from the injection site, has occurred weeks to months after mitomycin administration.
They require medical attention only if they persist or are bothersome:

Do not require medical attention:
- *Less common incidence:* Alopecia.
Require medical attention if they occur after the discontinuation of the medication:
Hematuria.
Decreased urination.
Dyspnoea.
Edema in the feet or legs (possible haemolytic-uremic syndrome).
Fever, chills, or sore throat.
Unusual bleeding or bruising (bone marrow suppression).
Note: With repeated dosing, cumulative myelosuppression may occur.

PROPER USE OF MEDICATION
Precaution steps should be taken with combination chemotherapy: administer each drug at the right time.
Nausea and vomiting are common; it is important to continue with the medication despite gastric discomfort.

PRECAUTIONS DURING THE USE OF THE MEDICATION
- Close monitoring of the patient by the doctor is important.
- Avoid immunizations unless the doctor approves them.
- Avoid contact with people with bacterial or viral infections, especially during periods when blood counts are low.
- There is the possibility of local injury that leaves scar tissue if infiltration of the intravenous solution occurs. Immediately inform the doctor or nurse in case redness, pain, or swelling appears at the injection site.

GENERAL INFORMATION ON DOSAGE
Patients undergoing treatment with MITOMICINA KEMEX should be under the supervision of a physician experienced in anticancer chemotherapy.
Various regimens and dosing regimens of MITOMICINA KEMEX are used in association with other antitumor drugs. The physician can consult the medical literature and that of the manufacturer to choose the specific dosage.
The use of MITOMICINA KEMEX is not recommended in patients with coagulation disorders, thrombocytopenia, or serum creatinine greater than 1.7 mg per 100 mL.
MITOMICINA KEMEX is usually administered intravenously via intravenous catheter.
Care must be taken to avoid extravasation during intravenous administration, due to the risk of severe ulceration and necrosis.
If extravasation occurs during intravenous administration manifested by stinging or local itching the injection should be discontinued immediately, and the dose completed in another vein.
Surgical excision of the affected area may be necessary.
MITOMICINA KEMEX should not be administered intramuscularly or subcutaneously as it will cause local tissue necrosis.
MITOMICINA KEMEX should not be administered intra-arterially (e.g., into the haepatic artery) to treat some tumours.
Dosage of MITOMICINA KEMEX after the initial course should be adjusted to meet the individual requirements of each patient, based on the patient's haematological response to the previous dose. An additional cycle of MITOMICINA KEMEX should only be administered after circulating blood elements have returned to acceptable levels (white blood cells above 3,000 per cubic millimeter and platelets above 75,000 per cubic millimeter).
cubic millimeter).
Patients who do not respond after 2 cycles of MITOMICINA KEMEX are unlikely to respond.
Due to delayed suppression and bone marrow accumulation caused by mitomycin, the drug should not be administered more than every 6 weeks.
If leukocyte (particularly granulocyte) or platelet counts drop sharply, or if there is a progressive decline in either, it is recommended to temporarily discontinue MITOMICINA KEMEX therapy until levels return to normal.
Special precautions are recommended in patients who develop thrombocytopenia as a result of administration of MITOMICINA KEMEX. These may include: extreme care in performing invasive tests; regular inspection of intravenous puncture sites, skin (including perirectal area), and mucous membrane surfaces for signs of bleeding or bruising; limit the frequency of venipuncture or intramuscular injections: tests of urine, vomit, feces and secretions to detect hidden blood; safety razor blades and nail clippers; avoid constipation and lastly be careful to avoid falls and other injuries. Such patients should avoid excessive alcohol intake and intake of any formula containing acetylsalicylic acid, due to the risk of gastrointestinal bleeding.
Platelet transfusions may be necessary.
Patients presenting with leukopenia should be carefully monitored for signs of infection. Antibiotics may be necessary to administer to these patients. Neutropenic patients who develop fever should be initiated empirically with broad-spectrum antibiotic coverage, pending the results of bacterial cultures and appropriate diagnostic tests.
In the treatment of small urinary bladder papilloma, topical instillations in the bladder with 20 to 40 mg of mitomycin at a concentration of 1 mg per ml of distilled water, which is retained as long as possible (usually 2 to 3 hours).
Usual Adult Dose:
Intravenous, 10 to 20 mg/m² body surface area as a single dose, repeated every six to eight weeks, or 2 mg/m² body surface area per day for five days, with two drug-free days off, then 2 mg/m² body surface area per day for a further five days (total 20 mg/m² body surface area for twelve days) repeated every six to eight weeks.
A suggestion for adjusting the dosing schedule for subsequent doses is the following:

Minimum after dose (cells/mm³)		**Dose Percentage prior to administration**
Leukocytes	Platelets	
≥ 4000	≥ 100000	100
3000-3900	75000-99999	100
2000-2900	25000-74999	70
< 2000	< 25000	50

Usual Prescription Limit for Adults:
Doses greater than 20 mg/m² body surface appear to be no more common than lower doses and increase the risk of toxicity.
Usual pediatric doses:
See Usual Adult Dose.

PACKAGING AND STORAGE
Store at room temperature below 30°C.
Reconstituted solution: In a refrigerator for 14 days and at room temperature for 7 days.
Preparation of the pharmaceutical form:
MITOMICINA KEMEX for Injection is reconstituted for intravenous use by adding 10 mL (5 mg vial) or 40 mL (20 mg vial) of sterile water for injections to the vial and shaking to dissolve; allow to stand at room temperature if necessary until dissolution occurs; a blue-gray solution will be obtained.
Reconstituted solutions may be further diluted with 5% Glucose Injection, 0.98% Sodium Chloride Injection for administration by intravenous infusion.

STABILITY
MITOMICINA KEMEX reconstituted solutions are stable for 14 days refrigerated, or 7 days at room temperature when protected from light. when they are diluted. The diluted solutions, which are subsequently diluted for administration by intravenous infusion, are stable for 3 hours in 5% glucose injection, 24 hours in sodium chloride injection in the refrigerator.

HANDLING AND DISPOSAL
As with all cytotoxic preparations, precautions must be taken for their safe preparation, handling and disposal.
1- Only trained personnel should handle the drug. This operation should exclude pregnant women.
2- The handling must be carried out in a specially designated area. The work area should be covered with absorbent paper, laminated on disposable plastic.
3- Appropriate protective clothing must be worn, that is: PVC gloves, safety glasses, tunics and disposable masks. In case of contact with the eyes or mucous membranes, wash with copious amounts of water or saline solution.
4- Use syringes and equipment with LUER LOCK adjustment.
5- All unused material, needles, syringes, vials and other items that have been in contact with cytotoxic drugs must be separated, placed in double-walled polyethylene bags, sealed and incinerated at 1000ºC or at a higher temperature.
Waste should receive a similar treatment.

PRESENTATION
Packages containing 1 vial.

OVERDOSE
Toxicological Reference Center - Poison Center: Specialized care for children:
Dial (01) if you live in the interior of the country (01) 962-2247/6666.
Ricardo Gutierrez Children's Hospital. Sanchez de Bustamante 1399 Federal Capital.
Specialized care for adults: Dial (01) if you live in the interior of the country (01) 801-5555.
Fernandez Hospital. Cervino 3356 Federal Capital.

KEEP THIS MEDICINE AWAY FROM THE CHILDREN'S REACH
IF YOU HAVE ANY QUESTIONS, CONTACT YOUR DOCTOR

MEDICINAL SPECIALTY AUTHORIZED BY THE MINISTRY OF HEALTH
CERTIFICATE No. 48,535

Manufactured by: LABORATORIO KEMEX S.A.
Nazarre 3446/54 - (C1417DXH) - City of Buenos Aires - Argentina.
Technical Direction: Natalia C. Alonso, Pharmacist.
www.kemexlab.com
farmacovigilancia@kemexlab.com

05150.00

kemex laboratorio