PACKAGE LEAFLET

DAUNORUBICINA KEMEX
DAUNORUBICINA 20 mg

Powder, lyophilized, for IV injection

MADE IN ARGENTINA **PRESCRIPTION ONLY MEDICINE**

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Daunorubicin.....21.4 mg daunorubicin hydrochloride (equivalent to 20 mg as base)
Mannitol.....100.0 mg

THERAPEUTIC ACTION
Antineoplastic agent.

CLINICAL PHARMACOLOGY
Mechanism of Action:
Daunorubicin HCL inhibits nucleic acid synthesis, its effect on RNA is particularly rapid and marked. The drug has antibiotic and cytotoxic activity, although its exact mechanism of action is unknown. It also has an immunosuppressive effect. Daunorubicin displays an immunosuppressive action as demonstrated by the inhibition of the production of heterohemagglutinins In vitro, inhibits blast cell transformation of canine lymphocytes at 0.01 mcg/mL.
Daunorubicin has a potent antitumor effect against a wide spectrum of grafted and spontaneous animal tumors.

Pharmacokinetics:
Following intravenous injection of Daunorubicin hydrochloride, plasma levels of daunorubicin decline rapidly, indicating rapid tissue uptake and concentration. Thereafter, plasma levels decline slowly with a half-life of 45 minutes in the initial phase and 18.5 hours in the terminal phase. By 1 hour after drug administration, the predominant plasma species is daunorubicinol, an active metabolite, which disappears with a half-life of 26.7 hours. Further metabolism has been demonstrated by 26.7 hours. Further metabolism via glycosidic bond reduction breakdown, 4-0 demethylation, and sulfate and glucuronide conjugation has been demonstrated. Simple glycosidic cleavage of daunorubicin or daunorubicinol is not a significant metabolic pathway in man. Twenty-five percent of an administered dose of daunorubicin hydrochloride is eliminated in an active form by urinary excretion and an estimated 40% by biliary excretion.
There is no evidence that daunorubicin crosses the blood-brain barrier.

In the treatment of adult acute nonlymphocytic leukemia, daunorubicin hydrochloride, used as a single agent, has produced complete remission rates of 40 to 50%, and in combination with cytarabine, has produced complete remission rates of 53 to 65%.
The addition of daunorubicin HCL to the two-drug induction regimen of vincristine-prednisone in the treatment of childhood acute lymphocytic leukemia does not increase the rate of complete remission.
In children receiving identical CNS prophylaxis and maintenance therapy (without consolidation), there is prolongation of complete remission duration (statistically significant, $p<0.02$) in those children induced with the three drug (daunorubicin-vincristine-prednisone) regimen as compared to two drugs. There is no evidence of any impact of daunorubicin hydrochloride on the duration of complete remission when a consolidation (intensification) phase is employed as part of a total treatment program.
In adult acute lymphocytic leukemia, in contrast to childhood acute lymphocytic leukemia, daunorubicin HCL during induction significantly increases the rate of complete remission, but not remission duration, compared to that obtained with vincristine, prednisone, and L-asparaginase alone. The use of daunorubicin HCL in combination with vincristine, prednisone, and L-asparaginase has produced complete remission rates of 83% in contrast to a 47% remission in patients not receiving daunorubicin hydrochloride.

INDICATIONS AND USAGE
Daunorubicin hydrochloride in combination with other approved anticancer drugs is indicated for remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) of adults and for remission induction in acute lymphocytic leukemia of children and adults.

Dosage and Administration
Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit.
Principles: In order to eradicate the leukemic cells and induce a complete remission, a profound suppression of the bone marrow is usually required. Evaluation of both the peripheral blood and bone marrow is mandatory in the formulation of appropriate treatment plans.
It is recommended that the dosage of daunorubicin hydrochloride be reduced in instances of hepatic or renal impairment. For example, using serum bilirubin and serum creatinine as indicators of liver and kidney function, the following dose modifications are recommended:

Serum Bilirubin	Serum Creatinine	Recommended Dose
1.2 to 3.0 mg %		3/4 normal dose
> 3 mg %	> 3 mg %	1/2 normal dose

Representative Dose Schedules and Combination for the Approved Indication of Remission Induction in Adult Acute Nonlymphocytic Leukemia: 100 mg/m² day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses.
For patients 60 years of age and above, Daunomicin 30 mg/m²/day IV on days 1, 2, and 3 of the first course and on days 1, 2 of subsequent courses AND cytosine arabinoside 100 mg/m²/day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses. This dose-reduction may not be appropriate if optimal supportive care is available. Evaluation of the bone marrow following recovery from the previous course of induction therapy determines whether a further course of induction treatment is required.

Representative Dose Schedule and Combination for the Approved Indication of Remission Induction in Pediatric Acute Lymphocytic Leukemia
In Combination: Daunomicin 25 mg/m² IV on day 1 every week, Vincristine 1.5 mg/m² IV on day 1 every week, Prednisone 40 mg/m² PO daily.
Generally, a complete remission will be obtained within 4 such courses of therapy; however, if after four courses the patient is in partial remission, an additional one or, if necessary, two courses may be given in an effort to obtain a complete remission.
In children less than 2 years of age or below 0.5 m² body surface area, it has been recommended that the Daunomicin dose calculation should be based on weight (1 mg/kg) instead of body surface area.

Representative Dose Schedules and Combination for the Approved Indication of Remission Induction in Adult Acute Lymphocytic Leukemia.
In Combination: Daunomicin 50 mg/m²/day IV on days 1, 2, and 3 AND Vincristine 2 mg IV on days 1, 8, and 15; Prednisone 40 mg/m²/day PO on days 1 through 22, then tapered between days 22 to 29; L-asparaginase 500 IU/kg/day x 10 days IV on days 22 through 32.
The contents of the vial should be reconstituted with 4 ml of sterile water for injection and shaken gently until the material has completely dissolved. The sterile vial contents provide 20 mg of daunomicin, with 5 mg of daunomicin per mL.
The desired dose is withdrawn into a syringe containing 10 mL to 15 mL of 0.9% Sodium Chloride Injection, and then injected into the tubing or sidearm in a rapidly flowing IV infusion of 5% Dextrose Injection, or 0.9% Sodium Chloride Injection. Daunomicin should not be administered mixed with other drugs or heparin.
The reconstituted solution is stable for 24 hours at room temperature and 48 hours in the refrigerator. It should be protected from sun exposure. Procedures for proper drug handling should be considered. Several guides on this topic have been published. There is no general agreement that all the procedures recommended in the guidelines are necessary or appropriate. The diluted solution is stable at room temperature for 24 hours.

Storage and Handling:
Skin reactions associated with daunorubicin have been reported. Care should be taken in handling the powder and preparing the solution. The use of gloves, eye protection, masks and overalls are recommended. If daunorubicin powder or solution comes into contact with the skin or mucosa, immediately wash thoroughly with soap and water.

Guidance for safe preparation and handling:
1. The preparation of antineoplastic solutions must be carried out in a vertical laminar flow hood (Biological safety cabinet - Class II).
2. Personnel preparing daunorubicin solutions must wear PVC gloves, safety goggles and protective overalls. If daunorubicin solutions come into contact with the skin, the area should be washed immediately with soap and water.
3. If an incinerator is not available, the daunorubicin must be detoxified by adding sodium hypochlorite solution to the vial, in sufficient quantity to decolonize the daunorubicin, taking care to vent the vial to avoid the pressure produced by the chlorine that is generated. Discard detoxified vials in the same way.

Needles, syringes, disposable and non-disposable equipment:
Rinse the equipment with an adequate amount of sodium hypochlorite solution. Dispose of solution in sewer with running water and dispose of disposable equipment safely. Carefully wash non-disposable equipment with soap and water.

Spills/ Contamination:
Wear gloves, mask, protective overall. Treat spilled powder or liquid with sodium hypochlorite solution. Carefully absorb the solution with gauze or towels, wash the area with water and absorb with gauze or towels again and place in polyethylene bags, seal, double bag and mark as hazardous waste. Dispose of waste by incineration or other approved methods for hazardous materials. Personnel involved in cleanup should wash with soap and water.

CONTRAINDICATIONS
Daunorubicin hydrochloride is contraindicated in patients who have preexisting heart disease.

WARNINGS
Daunorubicin Hydrochloride Injection must be given into a rapidly flowing intravenous infusion. It must never be given by the intramuscular or subcutaneous route. Severe local tissue necrosis will occur if there is extravasation during administration.
Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The incidence of myocardial toxicity increases after a total cumulative dose exceeding 400 to 550 mg/m² in adults, 300 mg/m² in children more than 2 years of age, or 10 mg/kg in children less than 2 years of age. Severe myelosuppression occurs when used in therapeutic doses; this may lead to infection or hemorrhage.
It is recommended that daunorubicin hydrochloride be administered only by physicians who are experienced in leukemia chemotherapy and in facilities with laboratory and supportive resources adequate to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The physician and institution must be capable of responding rapidly and completely to severe hemorrhagic conditions and/or overwhelming infection.
Dosage should be reduced in patients with impaired hepatic or renal function.

Bone Marrow: Daunorubicin is a potent bone marrow suppressant. Suppression will occur in all patients given a therapeutic dose of this drug. Therapy with daunorubicin should not be started in patients with pre-existing drug-induced bone marrow suppression unless the benefit from such treatment warrants the risk.

Cardiac Effects: Special attention must be given to the potential cardiac toxicity of daunorubicin, particularly in infants and children. Pre-existing heart disease and previous therapy with doxorubicin are co-factors of increased risk of daunorubicin-induced cardiac toxicity and the benefit-to-risk ratio of daunorubicin therapy in such patients should be weighed before starting daunorubicin hydrochloride. In adults, at total cumulative doses less than 550 mg/m², acute congestive heart failure is seldom encountered. However, rare instances of pericarditis-myocarditis, not dose-related, have been reported.
In adults, at cumulative doses exceeding 550 mg/m², there is an increased incidence of drug-induced congestive heart failure. Based on prior clinical experience with doxorubicin, this limit appears lower, namely 400 mg/m², in patients who received radiation therapy that encompassed the heart.
In infants and children, there appears to be a greater susceptibility to anthracycline-induced cardiotoxicity compared to that in adults, which is more clearly dose-related. Anthracycline therapy (including daunorubicin HCl) in pediatric patients has been reported to produce impaired left ventricular systolic performance, reduced contractility, congestive heart failure or death. These conditions may occur months to years following cessation of chemotherapy. This appears to be dose-dependent and aggravated by thoracic irradiation. Consequently, long-term periodic evaluation of cardiac function in such patients should, thus, be performed. In both children and adults, the total dose of daunorubicin HCl administered should also take into account any previous or concomitant therapy with other potentially cardiotoxic agents or related compounds such as doxorubicin.
There is no absolutely reliable method of predicting the patients in whom acute congestive heart failure will develop as a result of the cardiac toxic effect of daunorubicin HCl. However, certain changes in the electrocardiogram and a decrease in the systolic ejection fraction from pre-treatment baseline may help to recognize those patients at greatest risk to develop congestive heart failure. On the basis of the electrocardiogram, a decrease equal to or greater than 30% in limb lead QRS voltage has been associated with a significant risk of drug-induced cardiomyopathy. Therefore, an electrocardiogram and/or determination of systolic ejection fraction should be performed before each course of daunorubicin hydrochloride. In the event that one or the other of these predictive parameters should occur, the benefit of continued therapy must be weighed against the risk of producing cardiac damage.
Early clinical diagnosis of drug-induced congestive heart failure appears to be essential for successful treatment with digitalis, diuretics, sodium restriction, and bed rest.

Evaluation of Hepatic and Renal Function: Significant hepatic or renal impairment can enhance the toxicity of the recommended doses of daunorubicin HCl; therefore, prior to administration, evaluation of hepatic function and renal function using conventional clinical laboratory tests is recommended (see Dosage and Administration section).

Use during pregnacy:
Daunorubicin HCl may cause fetal harm when administered to a pregnant woman due to its teratogenic potential. An increased incidence of fetal abnormalities (umbilical hernias, or rachischisis) and abortions was reported in rabbits. Rats showed an increased incidence of esophageal, cardiovascular and urogenital abnormalities as well as rib fusions at doses of 4 mg/kg/day or approximately 1/2 the human dose on a body surface area basis. Decreases in fetal birth weight and post-delivery growth rate were observed in mice. 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 childbearing potential should be advised to avoid becoming pregnant.

Extravasation at Injection Site: Extravasation of daunorubicin hydrochloride at the site of intravenous administration can cause severe local tissue necrosis.

PRECAUTIONS
Therapy with daunorubicin hydrochloride requires close patient observation and frequent complete blood-count determinations. Cardiac, renal, and hepatic function should be evaluated prior to each course of treatment.
Daunorubicin hydrochloride may induce hyperuricemia secondary to rapid lysis of leukemic cells. As a precaution, allopurinol administration is usually begun prior to initiating antileukemic therapy. Blood uric acid levels should be monitored and appropriate therapy initiated in the event that hyperuricemia develops.
Appropriate measures must be taken to control any systemic infection before beginning therapy with daunorubicin.
Daunorubicin hydrochloride may transiently impart a red coloration to the urine after administration, and patients should be advised to expect this.
Carcinogenesis, mutagenesis, impairment of fertility. The product, when administered SC to mice, produces the development of fibrosarcomas at the injection site. When administered orally or intraperitoneally to mice, no carcinogenic effect was observed after 22 months of observation.
In male dogs, at the daily dose of 0.25 mg/kg administered IV, testicular atrophy was observed at autopsy. Histologic examination revealed total aplasia of the spermatocyte series in the seminiferous tubules with complete aspermatogenesis.

ADVERSE REACTIONS
Dose-limiting toxicity includes myelosuppression and cardiotoxicity (see Warning section). Other reactions include:
-Cutaneous: Reversible alopecia occurs in most patients.
-Gastrointestinal: Acute nausea and vomiting occur but are usually mild. Antiemetic therapy may be of some help. Mucositis may occur 3 to 7 days after administration. Diarrhea has occasionally been reported.
-Local: If extravasation occurs during administration, severe local tissue necrosis may occur.
-Acute Reactions: Rarely, anaphylactoid reaction, fever, and chills can occur.

How supplied
Reconstitute 1 vial with 4 ml of water for injection, shaking gently until complete dissolution is obtained in no more than 1 minute. Once reconstituted, it is stable for 24 hours at room temperature and 48 hours in the refrigerator.
Under proper storage conditions the solution should have a translucent red appearance.
Do not use if color change from translucent red to purple blue is observed.

OVERDOSE
Acute overdose increases the toxic effects of mucositis, leukopenia, and thrombocytopenia. Treatment of acute overdose consists of hospitalization of the patient with severe myelosuppression, platelet and granulocyte transfusions, antibiotics, and symptomatic treatment of mucositis. At cumulative doses exceeding 550 mg/m², there is an increased incidence of drug-induced congestive heart failure. Treatment consists of intensive treatment of heart failure with digitalis and diuretics. The use of peripheral vasodilators is also recommended.

INFORMATION FOR THE PATIENT

Read all of this leaflet carefully before you start using this medicine.
-Keep this leaflet as you may need to read it again.
-If you have any further questions, ask your doctor or pharmacist.
-This medicine has been prescribed for you only, and you should not give it to other people even if they have the same symptoms, as it may harm them.
-If you get any side effects that you consider to be serious, or if you notice any side effect not mentioned in this leaflet, tell your doctor or pharmacist.

1. What Daunorubicina Kemex is and what it is used for
Daunorubicina Kemex contains the active substance Daunorubicin Hydrochloride. It is a cancer drug.
Daunorubicin Kemex is used for inducing remissions of acute lymphocytic leukemia (myelogenous, monocytic, erythroid) in adults, and for inducing remissions of acute lymphocytic leukemia in children and adults. May be used in combination with other anticancer drugs.

2. Before you use Daunorubicina Kemex
Do not use Daunorubicina Kemex, if:
- You are allergic (hypersensitive) to Daunorubicin or any of the other ingredients of this medicine.
Warnings and precautions:
- The drug must be given into a rapidly flowing intravenous infusion. It must never be given by the intramuscular or subcutaneous route. Severe local tissue necrosis will occur if there is extravasation during administration.
- Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy..
- Administered at therapeutic doses, the product produces severe myelosuppression.
- Daunorubicin is a potent drug and should be used only by professionals experienced in the use of chemotherapy for leukemia and with access to adequate laboratory and maintenance supplies to control tolerance to the drug and to protect and maintain a patient compromised by the toxicity of the drug.
- The dose should be reduced in patients with impaired liver or kidney function.
- Daunorubicin therapy should not be started in patients with preexisting drug-induced bone marrow suppression unless the benefit of treatment justifies the risk.
- Special attention should be paid to the potential cardiac toxicity of the product, particularly in infants and children.
- In adults, at cumulative doses above 550 mg/m, there is an increased incidence of drug-induced congestive heart failure. Based on previous clinical experience with doxorubicin, this limit appears lower, i.e., 400 mg/m, in patients receiving radiation therapy involving the heart.
- In infants and children, there appears to be an increased susceptibility to anthracycline (including daunorubicin HCl)-induced cardiotoxicity in pediatric patients, resulting in impaired left ventricular systolic function, reduced contractility, congestive heart failure, or death. These conditions can occur months to years after chemotherapy ends.
- This appears to be dose related and is aggravated by thoracic irradiation.
- In both children and adults, the total dose of daunorubicin HCL administered must take into account any previous or concomitant therapy with other potentially cardiotoxic agents or related compounds such as doxorubicin.
- Perform an electrocardiogram and/or determination of the systolic ejection fraction before each course of daunorubicin. In the event that one or the other of these predictive parameters could occur, the benefit of therapy must be weighed against the risk of cardiac damage.
- Significant hepatic or renal insufficiency may increase the toxicity of recommended doses of daunorubicin HCL; therefore, prior to administration, evaluation of liver function and renal function using conventional clinical laboratory tests is recommended.
- Can cause severe localized tissue necrosis.
Before each course of treatment, cardiac, renal and hepatic function should be evaluated.
- Daunorubicin can induce hyperuricemia secondary to rapid lysis of leukemic cells.
- As a precaution, the administration of allopurinol is usually started before starting antileukemic therapy. Blood uric acid levels should be monitored, and appropriate therapy initiated if hyperuricemia develops.
- Adequate measures should be taken to control any systemic infection before starting daunorubicin therapy.
- The product can transiently impart a reddish color to the urine after administration, patients should be warned of this consequence.

Pregnancy and Breastfeeding
Daunorubicin 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 is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be advised of the potential risk to the fetus. Women of childbearing potential should be advised to avoid it.
Since it is unknown whether daunorubicin passes into breast milk, breast-feeding should be discontinued if the mother is receiving treatment with daunorubicin. If you are a man, you should avoid fathering a child during treatment and for 6 months after stopping daunorubicin treatment.
Daunorubicin treatment can cause irreversible sterility and it is recommended that you receive advice on the possibility of saving your sperm before starting treatment.
Consult your doctor or pharmacist before taking any medicine.

Effects on ability to drive and use machines
Take special care when driving or using machines if you experience side effects such as dizziness or blurred vision. It is not known if Daunorubicina Kemex can affect your ability to drive or use machines.

3. How to use Daunorubicina Kemex
Representative dose and combination schedule for the approved indication of remission induction in pediatric acute lymphocytic leukemia.
In combination: Daunorubicin 25 mg/m IV on day 1 every week, Vincristine 1.5 mg/m IV on day 1 every week, prednisone 40 mg/m PO daily.
Generally, a complete remission will be achieved within 4 series of therapy, however if after four series the patient is in partial remission, an additional series or if necessary two more series may be given in an effort to obtain a complete remission.
In children less than 2 years of age or below 0.5 m body surface area, it has been recommended that daunorubicin dose calculation should be based on weight (1 mg/kg) rather than body surface area.
Representative dose and combination schedule for the approved indication of remission induction in adult acute lymphocytic leukemia.
In combination: Daunorubicin 50 mg/m per day IV on days 1, 2 and 3 and Vincristine 2 mg/m IV on days 1, 8 and 15; prednisone 40 mg/m per day PO on days 1 through 22, then taper on days 22 through 29; L-asparaginase 500 IU/kg/per day x 10 days IV on days 22 to 32.
The contents of the bottle should be reconstituted with 4 ml of sterile water for injection and shaken gently until the material has completely dissolved. The content of the bottle provides an activity of 20 mg of Daunorubicin, with 5 mg of Daunorubicin per ml.
The dose is taken into a syringe containing 10 ml to 15 ml of normal saline and then injected into the tube in an IV infusion of 5% dextrose or 0.9% sodium hydrochloride injection.
Daunorubicin should not be administered with other drugs or heparin.
The reconstituted solution is stable for 24 hours at room temperature and 48 hours in the refrigerator.
It should be protected from sun exposure. Procedures for proper drug handling should be considered. Several guides on this topic have been published. There is no general agreement that all the procedures recommended in the guidelines are necessary or appropriate.

If you take more Daunorubicina Kemex than you should
Contact your doctor immediately.
You may have an increase in side effects and your doctor may need to stop your treatment.

If you forget to take Daunorubicina Kemex
If you forget to take one or more doses of Daunorubicina Kemex, contact your doctor as soon as possible.
Do not take a double dose to make up for a dose you forgot to take.
If you stop taking Daunorubicina Kemex
It is important to take Daunorubicina Kemex every day and for as long as your doctor prescribes it.
If you have any further questions on the use of this medicine, ask your doctor.

4. Possible adverse effects
Dose-limiting toxicity includes myelosuppression and cardiotoxicity (see Warnings). Other reactions include:
-Cutaneous: Alopecia is observed in most patients.
-Gastrointestinal: Acute nausea and vomiting are recorded but are usually mild. Antiemetic therapy may be of some help. Mucositis can be observed as early as 7 days after administration. Diarrhea has occasionally been observed.
-Local: If extravasation occurs during administration, necrosis may be observed at the injection site.
-Acute reactions: Rarely, anaphylactoid reactions, fever, chills and skin rash may occur.

In the event of an overdose, go to the nearest hospital or contact the poison centers:
Hospital de Niños Dr. Ricardo Gutiérrez: Phone #.: (011) 4962-9247/9248/9212
Hospital Pedro de Elizalde: Phone #.: (011) 4363-2100/2200
Hospital Dr. Juan A. Fernández: Phone #: (011) 4808-2600/2650
Hospital Dr. A. Posadas Phone #: (011) 4469-9200/9300

Any questions **CONSULT YOUR DOCTOR.**

PHARMACEUTICAL FORM
Package containing 1 vial.

ROOM TEMPERATURE (< 30ºC)
PROTECTED FROM LIGHT IN ITS ORIGINAL PACKAGING

KEEP OUT OF THE REACH OF CHILDREN.
DO NOT USE AFTER THE EXPIRATION DATE.

"This medicine must be used exclusively under prescription and cannot be repeated without a new prescription."

Medicinal specialty authorized by the Ministry of Health (ANMAT). Certificate No. 58,995
Technical Director: Natalia Alonso – Pharmacist.
Laboratory Kemex S.A. – Nazarre 3446/54 - (C1417DXH) –City of Buenos Aires. Argentina.
Phone number: 011-4138-1000
www.kemexlab.com
farmacovigilancia@kemexlab.com

05105.00

kemex laboratorio