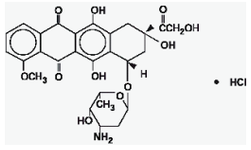
DOXORUBICINA KEMEX
Doxorubicin10 mg and 50 mg
Powder Lyophilizate for Injectable
FOR INTRAVENOUS USE ONLY
Made in Argentina Rx only

Formula
Each glass vial contains:

	DOXORUBICINA KEMEX 10 mg	DOXORUBICINA KEMEX 50 mg
Doxorubicin HCl	10 mg	50 mg
Lactose	50 mg	250 mg

DESCRIPTION
Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of Streptomyces peucetius var. caesius. Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine. Chemically, doxorubicin hydrochloride is (8S,10S) - 10 - [(3 - Amino - 2,3,6 - trideoxy-a-L-lyxo-hexopyranosyl)-oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride. The structural formula is as follows:



THERAPEUTICAL ACTION:
Antineoplastic agent.

INDICATIONS:
Successful results were achieved in tha application of DOXORUBICIN to produce a regression in disseminated neoplastic diseases such as lymphoblastic leukemia, acute myeloblastic leukemia, Tumor Wilms, neuroblastoma, soft tissue sarcoma and osteosarcoma, breast carcinoma, ovarian carcinoma, transitional bladder carcinoma, thyroid glannd carcinoma, gastric carcinoma, "Hodgkin's disease", malignant lymphoma and lung cancer, particularly the small cell variety.

MECHANISM OF ACTION:
Doxorubicin joins nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the double helix DNA. The anthracycline is lipophilic, but the saturated extreme of the ring system contains numeroust hydroxil groups adjacent to the amino sugar. The molecule is amphoteric, and contains acid functions in the ring phenolic groups and a basic function in the amino sugar group. This drug binds to cell membranes and plasma proteins.

DOSAGE AND ADMINISTRATION:
The medium dose is 60 to 75 mg/m2 per cycle of treatment, in a single administration or divided in equal parts in 2 or 3 consecutive days. Each cycle is applied with an interval of 3 to 4 weeks.
The cycles are repeated up to a maximum total dose of 550 mg/m2.
The dosage for children is 1 mg/kg/day in one single dose or 0.8 mg./kg/day for 2 consecutive days or 0.6 mg/kg/day for 3 consecutive days.
The dose is rapidly administered into a tubing of a freely running intravenous infusion of Sodium Chloride Injection or a 5% glucose solution (extravasation must be avoided because this could provoke a local necrosis)

Lyophilized for injection: Reconstitution Directions
It is recommended that Doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein, and the dosage. However, the dose should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.
Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of Doxorubicin. Until specific compatibility data are available, it is not recommended that Doxorubicin be mixed with other drugs.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit

Reconstituted Solution Stability
Vials of Doxorubicin containing 10 mg and 50 should be reconstituted with 5 and 25 ml of sterile sodium chloride 0.9%, to obtain a final concentration of 2 mg / mL of doxorubicin hydrochloride.
After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and under normal room light (100 foot-candles) and 15 days under refrigeration (2° to 8°C). It should be protected from exposure to sunlight. Discard any unused solution. Unused solutions of the multiple dose vial remaining beyond the recommended storage times should be discarded.

CONTRAINDICATIONS:
Doxorubicin should not be administered in pregnant women or during the nursing period.
Doxorubicin therapy should not be applied to patients with a marked myelosuppression induced by previous treatment with other antitumor agents or by radiotherapy. Doxorubicin treatment is contraindicated in patients who have received a previous treatment with cumulative doses of doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenes.

PRECAUTIONS AND ADVERSE REACTIONS:
Limiting toxicities of the doxorubicin therapy are myelosuppression and cardiotoxicity.
Other reactions reported were the following:
Cardiotoxicity: (See WARNINGS).
Cutaneous: in most cases reversible complete alopecia is observed. Hyperpigmentation of the matrix ungis, wrinkles or dermic folds, mainly in children, and onycholysis have been reported in a few cases. with doxorubicin administration there is also an incidence of cutaneous reaction as a result of previous radiotherapy.
Gastrointestinal: Acute nausea and vomiting were frequently observed and can be severe. These desorders can be reduced with antiemetic therapy. Mucositis (stomatitis and esophagitis) can occur 5 to 10 days after starting administration. The effect can be severe, which can lead to ulceration originating severe infections. The dosage regimen consisting of administration of doxorubicin on 3 successive days results in higher incidence and more severe mucositis. (Ulceration and colon necrosis, mainly the cecum, which leads to bleeding or possible fatal infections may occur). This reaction was reported in patients with acute non-lymphocytic leukemia treated with a 3-day doxorubicin intake combined with cytarabine. Some cases of anorexia and diarrhea were also reported.
Vascular: Phlebosclerosis was reported especially when very small veins or the same vein were used for the application of the medicine in repeated ocasions.
Facial redness may occur if the injection is administering too quickly.
Local: if during the medicine administration a doxorubicin extravasation is produced, severe cellulites and vesication will appear. Futhermore, the formation of erythematous stria along the vein next to the place where the injection was given was reported.
Hematological: in a very few patients treated with doxorubicin together with antineoplasic agents that damage DNA, acute myeloid leukemia with or without a preleukemic phase was observed. These cases could have a short latency period (1 to 3 years).
Hypersensitivity reactions: Fever, chills and urticaria were occasionally reported. Anaphylaxis can also occur. A case of an apparent crossing sensitivity to lincomycin was reported.
Other adverse reactions reported: very seldom conjunctivitis and lacrimation.

WARNINGS
Special attention must be paid to the cardiotoxicity induced by doxorubicin. An irreversible myocardic toxicity, manifested in its most severe form due to different risky and potentially fatal congestive heart failures may occur, either during therapy or several months after therapy has concluded. The possibility of developing myocardic function disorder, based on the existence of a combined number of signs, symptoms and a declination of the left ventricle ejection fraction (LVEF) is estimated in 1 to 2% corresponding to a total cumulative doxorubicin dose of 300 mg/m^2 , 3 to 5% when a 400 mg/m^2 dose is administered, 5 to 8% when a 450 mg/m^2 dose is administered and 8 to 20% when a 500 mg/m^2 dose is administered, through the injection of a bolus every 3 weeks. The possibilities of developing congestive heart failure were reported to be 5 over 188 patients (i.e 3%) when a cumulative 430 mg/m^2 doxorubicin dose is administered, 8/110 patients (7%) with a 575 mg/m^2 dose and 3/14 (21%) with a 728 mg/m^2. The CHF (congestive heart failure) cumulative incidence was 2.2%. A doxorubicin prospective study showed that the cumulative incidence of congestive heart failure was 5 to 6% when the drug is administered combined with cyclophosphamide, fluorouracil and/or vincristine to patients suffering from breast cancer or small cell lung cancer. The probability of CHF once several cumulative doxorubicin doses were administered was: 1.5% with 300 mg/m^2 dose, 4.9% with 400 mg/m^2 dose, 7.7% with 450 mg/m^2 dose and 20.5% with a 500 mg/m^2 dose. Cardiotoxicity may be observed when low doses are administered to patients with a previous mediastinal irradiation, a therapy concurrent with cyclofosfamide or who are elderly. According to other data, a preexisting heart disease has been noticed to be a co-factor in the increase of doxorubicin-caused cardiotoxicity risk. In these cases, heart toxicity may be produced when the administered doses are lower than the recommended cumulative doxorubicin doses. Some research has suggested that concomitant administration of doxorubicin and calcium channel blocking drugs may also increase the risk of cardiotoxicity caused by doxorubicin. Moreover, the total doxorubicin dose administered to each patient in particular should be considered, as well as the course with other related compounds such as daunorubicin, idarubicin and mitoxantrone.
Several months or even years after the doxorubicin therapy has been discontinued, there may be cases of cardiomyopathy and/or congestive heart failure. The risk of suffering from congestive heart failure and other acute manifestations caused by doxorubicin cardiotoxicity may be higher or lower in children than in adults.
Children seem to pose a particular risk regarding the development of a delayed heart toxicity, since doxorubicin induced cardiomyopathy hinders myocardial growth and the child´s maturing. This probably causes a congestive heart failure during the first years of adulthood, as many as 40% of children may have subclinical heart disroder and 5 to 10% of children may develop a congestive heart failure over a long term follow-up period. This late heart toxicity may be related to the doxorubicin dose. The longer the follow-up period, the greater the frequency by which disorders are detected. Treatment of doxorubicin-induced congestive heart failure includes the use of digitals, diuretics, after the administration of blood presure reducers such as angiotensin I converting enzyme (ACE) inhibitors, as well as a low salt diet, and complete rest. The kind of treatment may relieve symptoms and improve the functional status condition.
Heart Function Monitoring: In adult patients, severe heart toxicity may occur with no history of ECG changes. Anthracyclines-induced cardiomyopathy is usually associated to very typical histopathologic changes in an endomyocardic biopsy (EM biopsy), and to a decrease in the left ventricle ejection fraction (LVEF), according to the results obtained from an angiography and echocardiogram, based on the values of the baseline recorded prior to the adopted treatment. However, it was not shown whether the ejection fraction monitoring is useful to predict the moment in which a particular patient is near the maximum tolerated cumulative doxorubicin dose. The heart function should be carefully monitored during treatment to minimize the risk of heart toxicity. An assesment of the line recorded with an ECG, LVEF, and/or an echocardiogram (ECHO) are recommended especially for those patients with increased heart toxicity risk factors (which involves history of heart disease, mediastinal irradiation, or a therapy concurrent with cyclophosphamide). In a cumulative doxorubicin dose of, at least, 400 mg/m^2, subsequent assesments should be periodically be made during the course of therapy. Children are an increased risk condition regarding the possibility of developing cardiotoxicity after doxorubicin administration and thus, periodic heart follow-up assesments to monitor this delayed cardiotoxicity are recommended. In adults, a 10% decreases in LVEF under the lower limit of a normal or an absolute value LVEF , at any level, indicates an impairment of the heart function. In children, heart function impairment during or after the doxorubicin therapy shows a fall recorded in the fractional shortening (FS) by an absolute value of 10 percentile units or under 29%, and a LVEF decrease under 55%. In general, if test results shows a doxorubicin-associated heart function impairment, a continued therapy bebefits should be thoroughly considered against the risk of producing irreversible heart damage. Acute arrhythmias cases , with risk to the patient´s life, have been reported. These disorders occur during doxorubicin administration or within the subsequent two hours period. There is a high incidence of bone marrow depression, mainly of leukocytes, which demands a careful hematological monitoring. Following the recommended dose schedule, leukopenia is usually transitory, reaching its nadir 10 to 14 days after treatment and usually recovering around day 21. in general, during the treatment with the usual doxorubicin dose, a leukocite counts as low as 1000/mm3 is expected. Futhermore, erythrocyte and platelet counts should be monitored since they may also present reduced values. To this effect, hematological toxicity may demand a dose reduction or interruptio or a delay in the development of doxorubicin therapy. Persisting severe myelosuppression may result in a superinfection or hemorrhage.
Doxorubicin may increase the toxicity of other anticancer therapies. In this sense, an exacerbation of cyclophosphamide induced hemorrhagic cystitis and the 6-mercaptopurine hepatotoxicity increase were reported. Also, an increased radiation induced toxicity affecting the myocardium, mucosa, skin or liver were reported, as an effect of doxorubicin administration. Since doxorubicin metabolism and excretion are produced mainly through the hepatobiliary route, the doxorubicin dose may be increased by the existence of hepatic disorders. Thus, before applying a specific dose, the hepatic function should be evaluated through conventional laboratory tests such as SGOT, SGPT, alkaline phosphatase and. Cases of colitis manifested by typhlitis (cecal inflammation), bloody fecal matter and severe and even fatal infections have been associated with a combination of doxorubicin daily administered intravenously during 3 days and cytarabine administered through a daily continuous infusion during 7 or more days. Being doxorubicin administered intravenously, extravasation may occur with or without the pain caused by a subcutaneous injection or burning sensation, even when blood returns during the infusion needle aspiration. If any signs or symptoms of extravasation have observed, the injection or infusion must be immediately concluded and restarted in another vein.

Drug interactions:
Allopurinol colchicine or probenecid: Doxorubicin may increase the blood level of uric acid, because of this it is needed to adjust the dose of these drugs in patients receiving this medication.
Medicament producer of blood discracia, bone marrow depressor or radiation: Doxorubicin use together with this therapies may increase the bone marrow depressor effect.
Cyclophosphamide, dactinomicine or mitomicine: the concomitant use with Doxorubicin may increase the cardiotoxicity. It is recommended that the total dose does not exceed 400 mg/m.
Hepatotoxic medication: the use together with Doxorubicin may increase the incidence of the adverse effects.
Store at room temperature (15 – 30 ºC). Once the solution was prepared, it must be stored in refrigerator and used within 24 hours.

OVERDOSE:
Overdose with doxorubicin increases the toxic effect of mucositis, leukopenia and thrombocytopenia. Treatment for severe overdose consists of treatment of the severely myelosuppressed patient´s hospitalization, antimicrobials treatment, platelet transfusions and symptomatic treatment of mucositis.
Use of hemopoietic growth factor can be also considered. The cumulative dose of doxorubicin increases the risk of cardiomyopathy and cardiac congestive problems (See WARNINGS). Treatment consists of vigorous handling of cardiac congestive disorders with digitalic and diuretics compound remedies and back load reducers such as ACE inhibitors.
In the event of an overdose attend the nearest hospital or contact the Center for Toxicology.

HOW SUPPLIED:
Doxorubicina Kemex lyophilized for injection is available in vials of 10 mg and 50 mg with 1 and 5 vials , and for hospital usage containing 50 and 100 vials.

STORAGE:
Store the vial between 15 °C and 30 °C.
After adding the diluent, the vial should be shaken to ensure thorough dissolution of the contents.
The reconstituted solution remains stable at room temperature for 7 days under normal lighting conditions.
When refrigerated (at a temperature between 2 °C and 8 °C), this solution will remain stable for 15 days.
Direct exposure to sunlight should be avoided.
Any unused contents of single-dose vials containing 10 mg and 50 mg should be discarded entirely.
Once the storage period has expired, any unused medication up to that date should be completely discarded.

"This medicine must be used exclusively under medical supervision and can not be repeated without any new medical prescription".

KEEP OUT OF REACH OF CHILDREN
MEDICAMENT AUTHORIZED BY THE MINISTRY OF HEALTH
CERTIFICATE No. 47,527

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