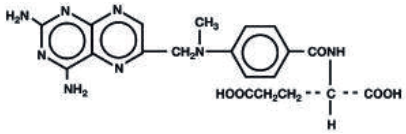
PACLITAXEL KEMEX
PACLITAXEL 30, 100 and 300 mg
Powder for Solution for Injection 6 mg/ml
CAUTION: MUST BE DILUTED PRIOR TO IV INFUSION
RX only

Formula:
Each vial of Paclitaxel Kemex 30 mg contains:
Paclitaxel.....30.0 mg
Polyethoxylated castor oil.....2.635 g
Absolute ethanol.....5.0 ml
Each vial of Paclitaxel Kemex 100 mg contains:
Paclitaxel.....100.0 mg
Polyethoxylated castor oil.....8.783 g
Absolute ethanol.....16.7 ml
Each vial of Paclitaxel Kemex 300 mg contains:
Paclitaxel.....300.0 mg
Polyethoxylated castor oil.....26.35 g
Absolute ethanol.....50.0 ml

WARNING
Paclitaxel Kemex should only be administered under the supervision of a qualified oncologist specialized in the administration of cytotoxic agents.. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2%–4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients must have been premedicated with corticosteriods, diphenhydramine, and H2 antagonists before receiving Paclitaxel. (See DOSAGE AND ADMINISTRATION.) Patients who experience severe hypersensitivity reactions to paclitaxel should be discontinued. Paclitaxel Kemex therapy should not be given to patients with solid tumors who have baseline neutrophil counts less than 1.500 cells/mm³ and should not be given to patients with AIDS-associated Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm³. 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 Paclitaxel Kemex.

DESCRIPTION
Paclitaxel Kemex is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Paclitaxel Kemex is available in 30 mg (5 mL), 100 mg (16.7 mL) and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purifed Cremophor® EL1 (polyoxyethylated castor oil) and 1 ml of absolute alcohol.
Paclitaxel is a natural product with antitumor activity. Paclitaxel is obtained via a semi-synthetic process from Taxus baccata. The chemical name for paclitaxel is 5b,20-Epoxy-1,2a,4,7b,10-b,13ahexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine.
Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216–217°C.

THERAPEUTIC ACTION
Paclitaxel is a new antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability inhibits the normal dynamic reorganization of the microtubule network, which is essential for vital interphase and mitotic cellular functions.
Paclitaxel pharmacokinetics was evaluated on a wide range of doses above 300 mg/m², and 3 to 24 hour extended infusion programs. After intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentration. The rapid initial decline relates to the distribution in the peripheral compartment and to disposal; the following phase is partly due to the relatively slow flow of paclitaxel from the peripheral compartment.
The pharmacokinetics of paclitaxel were determined following 3- and 24-hour infusions at doses of 135 and 175 mg/m². The mean half-life was between 3.0 and 52.7 hours.. The mean steady-state volume of distribution was between 198 and 688 l/m², indicating extensive extravascular distribution and/or tissue binding.
There is no evidence of paclitaxel accumulation during multiple treatments. On average, 89% of this drug is bound to plasma proteins. Cimetidine, ranitidine, dexamethasone or diphenhydramine were not found to affect the protein binding of paclitaxel.
The cumulative excretion of unchanged paclitaxel in the urine has been between 1.3% and 12.6% of the dose on average, which is an indication of extensive non-renal clearance.
The main metabolites are the hydroxylated ones which have isolated themselves in the bile. Hepatic metabolism and biliary clearance are possibly the principal mechanisms for elimination of paclitaxel; this has not been investigated.
The paclitaxel clearance has not been affected by previous treatment with cimetidine.

INDICATIONS
Paclitaxel Kemex is indicated as first-line and subsequent therapy for the treatment of advanced ovarian carcinoma.
As first-line therapy, a combination therapy of paclitaxel and cisplatin is recommended. Paclitaxel is indicated for the adjuvant treatment of node-positive breast cancer administered in combination with doxorubicin. In the clinical trial, there was an overall favorable effect on disease-free and overall survival in the total population of patients with receptor-positive and receptor-negative tumors, but the bene t has been specifically demonstrated by available data (median follow-up 30 months) only in the patients with estrogen and progesterone receptor-negative tumors. Paclitaxel is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. In combination with cisplatin, paclitaxel is indicated for the treatment of non-small cell lung cancer for potentially curative surgery and/or radiation therapy. Paclitaxel is indicated as second-line treatment of AIDS-related Kaposi's sarcoma.

CONTRAINDICATIONS
Paclitaxel is contraindicated in patients with a history of severe hypersensitivity to the drug or to other compounds which include cremophor EL in their formula (polyoxyethylated castor oil). It is also contraindicated in patients with neutropenia (less than 1500 cell/mm³). The risk-benefit should be considered when administering paclitaxel in cases of:
-Cardiac function impairment, including: angina, anomalies in cardiac conduction, myocardial infarction
-Varicella or recent exposure to such disease.
-Herpes Zoster
-Infection
-Precaution must be taken in the case of patients who have undergone therapies with cytotoxic drugs, including radiotherapy.

WARNING
Paclitaxel must be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Adequate management of complications is possible onlywhenthere is an adequate diagnosis and treatment.
Paclitaxel must be administered diluted in intravenous infusion. Patients must be pretreated with corticosteroids (such as dexamethasone), antihistamines (diphenhidramine) and H2 antagonists (cimetidine or ranitidine), prior to drug administration.
Severe hypersensitivity reactions characterized by dyspnea, hypotension, rubor, chest pain and tachycardia occur in about 2% of patients. These reactions are probably histamine-mediated.
In the case of severe hypersensitivity, paclitaxel infusion should be discontinued immediately and patients should not be challenged with paclitaxel.
Minor hypersensitivity reactions such as rubor, rash, etc., do not require discontinuation of the therapy.
Suppression of the bone marrow function is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted during treatment with paclitaxel.
Patients should not be retreated until the neutrophil count is below 1500 cell/m³.
In case of severe neutropenia (less than 1500 cell/m³) during treatment, a 20% reduction in dose is recommended for subsequent cycles in the paclitaxel therapy.
Cases of severe abnormalities in cardiac conduction have been very rarely reported. In this case, the patients should be subjected to the appropriate therapy and to continuous electrocardiographic monitoring during subsequent administration of paclitaxel.

PREGNANCY AND NURSING MOTHERS
Paclitaxel may cause fetal harm when administered to pregnant women. The drug has shown to be both embryotoxic and fetotoxic in rabbits and has been shown to reduce fertility in rats. No studies have been performed in pregnant women.
If paclitaxel is used during pregnancy or if the patient becomes pregnant during treatment, the patient must be informed of the potential risks.
Women in fertile age must be informed of the potential risks so as to avoid pregnancy during therapy with paclitaxel.
It is not known whether paclitaxel is excreted in human milk. Since many drugs are excreted in human milk and considering the potential adverse reactions in infants fed with breast milk, breast feeding should be discontinued for the duration of therapy with paclitaxel.

PRECAUTIONS
Cardiovascular system: hypotension and bradycardia have been observed during paclitaxel administration, but generally these events do not require treatment. The vital signs should be frequently monitored, especially during the first hours of infusion. A continuous cardiacmonitoring is not necessary, except in patients with severe cardiac conduction abnormalities.
Nervous system: even if peripheral neuropathy frequently occurs, the development of a servere symptomatology is rare. In these cases, the dose should be reduced by 20% in subsequent treatments.
Liver: There is no evidence that paclitaxel toxicity increases in patients with moderate liver dysfunction, but there is no available data on subjects with previous severe cholestasis.
Since the liver plays a major role in paclitaxel metabolism, precaution must be taken when paclitaxel is administered to patients with severe hepatic harm.

DRUGS INTERACTIONS
In the Phase 1 studies using increasing doses of paclitaxel (110-200 mg/m²) and cisplatin (50 or 75 mg/m²) administered as a sequential infusion, myelosuppresion was more intensive when paclitaxel was administered after cisplatin than when the opposite was done.
The pharmacokinetic studies of these patients showed a decrease of about 33% in the clearance when paclitaxel was administered after cisplati. According to in vitro data, paclitaxel metabolism might be inhibited in patients treated with ketaconazol. Therefore, precautions should be taken when administering paclitaxel to patients who are concomitantly receiving ketaconazole.
The combination of paclitaxel with the drugs listed below may cause bone marrow suppression depending on the dose: aldesleukin, altretamine, antoferecine B, antithyroid agents, azathoprine, busulfan, chlorambucil, chloramphenicol, chromic phosphate, clozapine, colchicine, cyclophosphamide, dacarbazine, dactinomycin, didanocine, ephornitina, floxuridine, flucytosine, gancyclovir, iradubicine, gamma and alpha interferon, carboplatinium, cisplatinium, citarabina, doxorubicin, etoposide, mercaptopurine, methotrexate, mitoxantrone, vinblastine, vincristine, azidothymidine, floxuridine, hydroxyurea, ifosfamide, lomustine, mitomycin, pentostatin. The combination of paclitaxel and the drugs below can cause blood dyscrasia, usually in a minority of patients, and not dose related: aminopyrine, inhibitors of the angiotensin-convertase enzyme, anticonvulsants, tricyclic antidepressants, oral antidiabetic agents, non-steroid antiinflamatories, carbamazepine, chloramphenicol, cozapine, dapsone, divalproex, foscarnet, levamisole, penicillamine, phenothiazine, primaquine, primidone, procainamide, propafenone, rifampicin e, sulfonamides, tioxantenos, trimetropine, valproic acid. Killed virus vaccine: Since normal defense mechanisms may be suppressed as a result of paclitaxel therapy, the patient's immune response may be lowered.
The interval between the discontinuity of the drug causing immunosuppression and the patient's ability to respond to the vaccine depends on the type of immunosuppression caused by the drug used. The estimated time is between 3 months and 1 year.
Live virus vaccine: Since normal defense mechanisms may be suppressed as a result of paclitaxel therapy, the patient's immune response to the vaccine may be lowered and adverse and side effects of the vaccine virus may increase. The patient's immunization must be performed with extreme precaution and after a careful study of the hematologic state, and it must be monitored by a specialist.
The interval between the discontinuation of the drug causing immunosuppression and the patient's capacity to respond to the vaccine depends on the type and intensity of immunosuppression caused by the drug used. The estimated time is between 3 months and 1 year.
Immunization with oral polyvirus vaccine must be postponed in people who are in close contact with the patients undergoing paclitaxel therapy, especially the family members.

MONITORING OF PATIENTS
It will be especially important to closely monitor the following:
- Hematocrit and Hemoglobin
- Leukocytes count
- Platelets count
- Vital signs

CARCINOGENESIS, MUTAGENESIS AND FERTILITY
The carcinogenic potential of paclitaxel has not been studied.
Paclitaxel has shown to be mutagenic both in vitro and in vivo mammalian test systems.
A decrease in fertility and in the number of live fetus implantations has been observed in rats

receiving the drug.
Paclitaxel has proven to be embryotoxic and fetotoxic in rabbits treated during organogenesis.

ADVERSE REACTIONS
The following table is based on the experience of 812 patients with breast and ovarian carcinomas treated with clinical assays of paclitaxel at a dose of 135 - 300 mg/m² per cycle and with 3 to 24 hour administration cycle. The table also includes data for a subset of 181 patients treated with the recommended dose of 175 mg/m² administered intravenously over 3 hours.
No effects clearly influenced by age have been observed:

	Percentage of patients	
	Total (n=812)	At the recommended dose (n=181
Hematology		
-Neutropenia		
(less than 2000 cell/mm3)	90	87
(less than 500 cell/mm3)	52	27
-Leukopenia		
(less than 4000 cell/mm3)	90	86
(less than 1000 cell/mm3)	17	4
-Thrombocytopenia		
(less than 10000 cell/mm3)	20	6
(less than 5000 cell/mm3)	7	1
-Anemia (less than 11g/dl)	78	62
(less than 8g/dl)	16	6
-Infections	30	18
-Bleeding	14	9
-Required red blood cells	25	13
-Required platelets	2	0
Peripheral neuropathies		
-Some symptom	60	64
-Severe symptoms	3	4
Cardiovascular		
-Bradycardia (first 3 hours)	3	3
-Hypotension (first 3 hours)	12	11
-Severe Events	1	2
Abnormalities in EKG		
-All the patients	23	13
-Normal EKG at the beginning	14	8
Hypersensitivity reactions		
All	41	40
Severe	2	1
Myalgia/Arthralgia		
-Some symptom	60	54
-Severe symptoms	8	12
Gastrointestinal		
-Nausea and vomits	52	44
-Diarrhea	38	25
-Mucositis	31	20
Alopecia	87	93
Hepatic (patients with normal base line)		
-Elevated bilirubin	7	4
-Elevated alkaline phosphatase	22	18
-Elevated ALC (SGOT)	19	18
Reaction on the site of injection	13	4

Unless the opposite has been observed, the following is based on the experience of 181 patients who received the recommended dose of paclitaxel, administered in the indicated time (175 mg/m² in a 3-hour infusion).
All patients were pretreated to minimize hypersensitivity reactions.
Myelosuppression and peripheral neuropathy were the main adverse reactions associated with the paclitaxel dose.
Comparing the 24-hour infusion program, neutropenia was less usual when paclitaxel was administered as a 3-hour infusion. Neutropenia was rapidly reversible and it did not worsen with accumulated exposure. The frequency of neurologic symptoms increased with the repetition of applications.
Hematologic: a severe neutropenia (less than 500 cell/mm³) is shown in 27% of patients.
Neutropenia was not more severe or frequent in patients who had previously received radiotherapy. Likewise, neutropenia does not appear to be affected by the duration of treatment or by the quantity of exposures.
Infection was reported in 18% of patients and in 5% of treatment cycles, there being no fatal cases. (In the total experience with 812 patients, 5 septic episodes associated with severe neutropenia which could be attributed to paclitaxel had a fatal end).
There were hemorrhagic episodes in 9% of patients, which did not require transfusion of platelets. Anemia occurred in 62% of patients and it was severe in 6% of them.
Hypersensitivity: even with pretreatment, there were severe hypersensitivity reactions in 1% of patients with the recommended dose and the program indicated for paclitaxel. These reactions are generally observed in the early cycles of treatment and within the first hour of infusion.
The most frequent manifestations were dyspnea, rubor, pain chest and tachycardia. The paclitaxel dose or time schedule has no effect on the frequency of hypersensitivity reactions, in a 21% of cases associated with them. Most were minor reactions such as rubor, rash and hypotension.
Cardiovascular: during infusion hypotension and bradycardia was observed in 24% and 4% of patients respectively. They did not appear simultaneously in the same cycle and no treatment was required.
Severe cases of cardiovascular disorders included hypertension, venous thrombosis and tachycardia; discontinuation of treatment was not required in any of the patients. The 8% of patients with normal EKG at the beginning of the study had normal EKGs during treatment. In most cases there was not a clear relation with paclitaxel and were of little significance.
Neurology: peripheral neuropathy is dose related in 60% of the asymptomatic patients who experienced symptoms during treatment. In 4% of patients symptoms were severe when receiving the recommended doses.
Neurological symptoms may appear following the first cycle and the frequency of symptoms may increase with the increase in exposures to paclitaxel.
Sensorial symptoms improved or resolved several months after paclitaxel discontinuation.
Pre-existent neuropathies resulting from previous treatments are not a contraindication for the treatment with paclitaxel.
Other rare cases of reported neurological disturbances include grand mal crisis and encephalopathies.
Hepatic: as to patients with normal hepatic functions, 4% of them showed an increase in bilirubin, 18% showed an increase in alkaline phosphatase and 18% showed an increase in SGOT.
Arthralgia and myalgia: they occurred in 54% of cases. Symptoms were generally transitory, appearing 2 to 3 days after paclitaxel administration and they disappeared in few days.
Reactions on the site of injection: after intravenous administration of paclitaxel, phlebitis may appear. Extravasation may lead to edema, pain, erythema. The extravasation may occasionally cause cellulitis. It can also cause skin decoloration.
A specific treatment for the extravasation reactions is unknown to date.
Others: alopecia has been observed in almost all patients.
Moderate and transitory changes in skin and nails have been observed.
Gastrointestinal effects such as nausea, vomits, diarrhea and mucositis have been observed in 44%, 25% and 20% of patients receiving the recommended doses, respectively. These manifestations were generally moderate.

OVERDOSAGE
No antidote is known for paclitaxel overdosage. The primary complication of overdosage are bone marrow suppression, peripheral neuropathy and mucositis.
In the event of overdosage, go to the nearest hospital or contact the Toxicologycal Centers:
-Hospital de Pediatría Dr. Ricardo Gutiérrez: (011) 4962-6666/2247
-Hospital Dr. A. Posadas: (011) 4654-6648/4658-7777

DOSAGE AND ADMINISTRATION
All patients must be pretreated to avoid severe hypersensitivity reactions.
Such pretreatment may consist in dexametasone 20 mg per day, administered orally 6 and 12 hours before paclitaxel. diphenhidramine (or equivalent) 50 mg IV 30 to 60 minutes before paclitaxel; and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 min. prior to paclitaxel administration.
The recommended dose of paclitaxel is 175 mg/m², administered as a 3-hour intravenous infusion every 3 weeks.
Paclitaxel must not be administered before the neutrophil count reaches at least 1500 cell/mm³ and that of platelets 100000 cell/mm³. The patients who experienced severe neutropenia or peripheral neuropathy must receive the dose reduced by 20% in the following cycles.

PRECAUTIONS FOR PREPARATION
As it is a cytotoxic drug, it must be handled with extreme care. Rubber gloves should be used. If the solution touches the skin, this must be immediately washed with water and soap. If it contacts the mucosa, this must be washed with abundant water.
The contact of the concentrated not diluted solution with PVC (polyvinyl chloride) equipment used to prepare the solution must be avoided.
With the aim of minimizing the patient's exposure to the plasticizer DEHP (di-(2-ethylhexilphthalato)) which can come out of the PVC infusion bag, the dilute solution must be stored in glass or polyethylene bottles and it must be administered through a polyethylene guide.
Paclitaxel must be administered with a filter in the line no larger than 0.22 microns.
PREPARATION OF THE INTRAVENOUS ADMINISTRATION
The paclitaxel solution must be diluted before administration. It must be diluted in sodium chloride 0.9%, dextrose 5%, a mixture of both or dextrose 5% in Ringer's solution, to obtain a final concentration of 0.3 to 1.2 mg/ml.
Products must be inspected for particulate matter and discoloration prior to administration.
After preparation the solution may show turbidity caused by the preparation solvent.

STABILITY
Unopened vials of Paclitaxel Kemex (paclitaxel) Injection are stable until the date indicated on the package when stored between 2°–8° C , in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components in the Paclitaxel Kemex vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.

HOW SUPPLIED
30 mg/5 mL: packaged in a carton containing 1 and 5 vials, for hospital usage containing 50 vials.
100 mg/16.7 mL: packaged in a carton containing 1 and 5 vials, for hospital usage containing 50 vials.
300 mg/50 mL: packaged in a carton containing 1 and 5 vials, for hospital usage containing 50 vials.

STORAGE
Store the vials in their original cartons between 2º - 8°C. Protect from light.

"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
Medicinal Specialty authorized by the Health Ministry.
CERTIFICATE Nº 50,237

Laboratorio Kemex S.A. – Nazarre 3446/54 – Capital Federal (C1417DXH)
Technical Director: Dr. Natalia Alonso – Pharmacist
Made in Argentina

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