1. NAME OF DRUG

CICLOFOSFAMIDA KEMEX
CICLOPHOSFAMIDE 200 and 1000 mg, Lyophilized powder for injection
Administration Route: IV

Argentine Industry
Under prescription only

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CICLOFOSFAMIDA KEMEX 200 mg
Each vial contains:
Cyclophosphamide 200 mg
Mannitol 150 mg

CICLOFOSFAMIDA KEMEX 1000 mg
Each vial contains:
Cyclophosphamide 1000 mg
Mannitol 750 mg

3. DOSAGE FORM
Lyophilized powder for injection

4. CLINICAL DATA
4.1. Indications and usage
Cyclophosphamide Kemex is used alone or in combination with other chemotherapy drugs, depending on the indications, to treat:
- Chronic lymphocytic leukemia (CLL)
- Acute lymphocytic leukemia (ALL)
- In preparation for bone marrow transplantation, in the treatment of acute lymphoblastic leukemia, chronic myeloid leukemia and acute myeloid leukemia, in combination with whole body irradiation or busulfan.
- Hodgkin's lymphoma, non-Hodgkin's lymphoma and multiple myeloma.
- Metastatic breast and ovarian carcinoma. - Adjuvant treatment of breast carcinoma.
- Ewing's sarcoma.
- Small cell carcinoma of the lung.
- Advanced or metastatic neuroblastoma.
- Life-threatening autoimmune diseases such as severe progressive forms of lupus nephritis and Wegener's granulomatosis.

4.2. Dosage and administration
Cyclophosphamide should only be used by physicians experienced in the use of cancer chemotherapy. Cyclophosphamide should only be administered there are facilities for regular monitoring of clinical, biochemical and hematological parameters before, during, and after administration and under the direction of a specialist oncology service.

Posology
Dosage must be individualized. Doses and duration of treatment and/or treatment intervals depend on the therapeutic indication, the scheme of a combination therapy, the patient's general state of health and organ function, and the results of laboratory monitoring (in particular, blood cell monitoring).
In combination with other cytostatic of similar toxicity, a dose reduction or extension of the therapy-free intervals may be necessary.
Use of hematopoiesis stimulating agents (colony-stimulating factors and erythropoiesis stimulating agents) may be considered to reduce the risk of myelosuppressive complications and/or help facilitate the delivery of the intended dosing.
Prior, during and immediately after the administration, adequate amounts of fluid should be ingested or infused to force diuresis to reduce the risk of urinary tract toxicity. Therefore, Cyclophosphamide should be administered in the morning. See Section 4.4.
It is within the responsibility of the physician to decide on the use of Cyclophosphamide according to the operative treatment guidelines.

The doses below can be regarded as general guidelines:
Hematologic and solid tumor
a) For daily treatment: 3-6 mg/kg body weight (= 120-240 mg/m² body surface area), injected intravenously.
b) For intermittent treatment: 15 mg/kg body weight (= 400 – 600 mg/m² body surface area), injected intravenously, with therapy-free intervals of 2 to 5 days.
c) For high-dose- intermittent treatment: 20 – 40 mg/kg body weight (= 800 – 1600 mg/m² body surface area), injected intravenously, with therapy-free intervals of 21 to 28 days.

As preparation for a bone marrow transplantation
2 days 60 mg/kg or 4 days 50 mg/kg body weight injected intravenously.
If a busulfan-cyclophosphamide (Bu/Cy) regimen is applied, the first dose of cyclophosphamide must be administered at least 24 hours after the last dose of busulfan (see section 4.4 and 4.5).

Autoimmune diseases
Per month 500 – 1000 mg/m² body surface area.

Patients with Hepatic Impairment
Severe hepatic impairment may be associated with a decreased activation of cyclophosphamide. This may alter the effectiveness of the cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected. (See section 4.4).
The dose must be reduced in patients with severe hepatic impairment. A dose reduction of 25 % is recommended in patients with serum bilirubin concentrations of 3.1 – 5 mg/100 ml (= 0.053 – 0.086 mmol/l).

Patients with Renal Impairment
In patients with renal impairment, particularly in patients with severe renal impairment, decreased renal excretion may result in increased plasma levels of cyclophosphamide and its metabolites. This may result in increased toxicity and should be considered when determining the dosage in such patients. (See section 4.4). A dose reduction of 50% for a glomerular filtration rate below 10 mL/minute is recommended.
Cyclophosphamide and its metabolites are dialyzable, although there may be differences in clearance depending upon the dialysis system being used. In patients requiring dialysis, use of a consistent interval between cyclophosphamide administration and dialysis should be considered. See section 4.4.

Elderly
In elderly patients, monitoring for toxicities and the need for dose adjustment should reflect the higher frequency of decreased hepatic, renal, cardiac, or other organ function, and concomitant diseases or other drug therapy in this population.

Pediatric population
Cyclophosphamide has been administered to children. The safety profile of cyclophosphamide in pediatric patients is similar to that of the adult population.

Dose modification due to myelosuppression
A leukocyte and platelet count should be regularly performed during treatment with cyclophosphamide. It is recommended to adjust the dose, if required, if signs of myelosuppression become evident.

Please refer to the table below. Urinary sediment should also be checked regularly for the presence of erythrocytes.

Leukocyte count/µl	Platelet count/µl	Dosage
>4,000	>100,000	100% of the planned dose
2,500-4.000	50,000-100,000	50 % of the planned dose
<2,500	<50,000	Omit until values normalize or decide individually

In combination therapy further dose reductions may have to be considered.

Administration
Cyclophosphamide is inert until activated by enzymes in the liver. However, as with all cytotoxic agents, it is recommended that reconstitution should be performed by trained personnel, in a designated area.

Precautions to be taken before manipulating or administering the product
Those handling the preparation should wear protective gloves. Care should be taken to avoid splashing material into the eyes. The material should not be handled by women who are pregnant or who are breast-feeding.
The rules and regulations for handling cytostatic in general should be observed when reconstituted or handling Cyclophosphamide. To the extent possible, reconstitution should be performed in a safety hood with laminar air flow. The person handling the product must wear a protective mask and protective gloves. In case of spills, the area must be washed abundantly with water. If Cyclophosphamide powder for injection and infusion is stored (e.g., during transport) at a temperature higher than the maximum allowed, cyclophosphamide may melt. Injection vials containing molten cyclophosphamide can be identified with the naked eye. Cyclophosphamide is a white powder. Fused Cyclophosphamide is a clear or yellowish viscous liquid (usually as drops in the corresponding vials). Injection vials containing molten cyclophosphamide cannot be reused.
The choice of solvent for reconstituting Cyclophosphamide containing cyclophosphamide depends on the route of administration to be used.

Infusion
If the solution is to be used for IV infusion, Cyclophosphamide (containing cyclophosphamide) is reconstituted by adding sterile water for injection or 0.9% sterile sodium chloride solution.
Reconstituted Cyclophosphamide should be further diluted in 5% dextrose or 0.9% sodium chloride solution prior to infusion.
The following amounts of water for injection or 0.9% sodium chloride are added to the vials containing Cyclophosphamide lyophilized powder for injection and infusion: for 200 mg vial add 10 ml; for 1,000 mg vial add 50 ml.
The injection of the solvent into the injection vial creates an abnormally high pressure, which disappears as soon as the second sterile needle is inserted into the rubber stopper of the injection vial. The powder dissolves easily when the injection vial is shaken vigorously to produce a clear solution. If the powder does not dissolve immediately, it is advisable to let the solution settle for a few minutes. The solution should be administered as soon as possible after reconstitution.
After reconstitution the solution is clear and colorless to pale yellow in appearance.

Direct injection
If the solution is to be used for direct injection, Cyclophosphamide (containing cyclophosphamide) is reconstituted by adding 0.9% sterile sodium chloride solution.
Please note that only Cyclophosphamide Kemex reconstituted in 0.9% sterile sodium chloride solution is suitable for bolus injection.
Cyclophosphamide Kemex (containing cyclophosphamide) reconstituted in water is hypotonic and should not be injected directly.
For detailed instruction on reconstitution please refer to section 6.6.

Intravenous use
Intravenous administration should preferably be conducted as an infusion.
To reduce the likelihood of adverse reactions that appear to be administration rate-dependent (e.g., facial swelling, headache, nasal congestion, scalp burning), cyclophosphamide should be injected or infused very slowly. Duration of the infusion (ranging from 30 minutes to 2 hours) should be appropriate for the volume and type of carrier fluid to be infused.
Before intravenous use, the substance must be completely dissolved.

4.3. Contraindications
Cyclophosphamide Kemex is contraindicated in patients who have:
- History of severe hypersensitivity reactions to it, any of its metabolites, or to other components of the product.
acute infections
- Bone marrow aplasia or bone marrow depression prior to treatment
- Urinary tract infection
- Acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy
- Urinary outflow
- Obstruction
- Breastfeeding (see section 4.6).

Cyclophosphamide should not be used in the management of non-malignant disease, except for immunosuppression in life-threatening situations.

4.4. Special warnings and precautions for use
Warnings

Anaphylactic Reactions, Cross-sensitivity with Other Alkylating Agents
Anaphylactic reactions including those with fatal outcomes have been reported in association with cyclophosphamide. Possible cross-sensitivity with other alkylating agents has been reported.

Myelosuppression, Immunosuppression, Infections
Treatment with cyclophosphamide may cause myelosuppression (anemia, leukopenia, neutropenia and thrombocytopenia) and significant suppression of immune responses, which may result in severe, sometimes fatal, infections, sepsis and septic shock. Infections reported with cyclophosphamide include pneumonias, as well as other bacterial, fungal, viral, protozoal, and parasitic infections.
Latent infections can be reactivated. Reactivation has been reported for various bacterial, fungal, viral, protozoal, and parasitic infections.
Infections occurring during treatment with cyclophosphamide, including neutropenic fever, must be treated appropriately. Antimicrobial prophylaxis may be indicated in certain cases of neutropenia (at the discretion of the managing physician). In case of neutropenic fever, antibiotics and/or antimycotics must be given. Cyclophosphamide must be administered with the necessary caution (or not at all) in patients with severe functional impairment of bone marrow and patients with severe immunosuppression.
Close hematological monitoring is required for all patients during treatment. Hematological parameters must be checked prior to each administration and regularly during treatment. More frequent monitoring may be required if leukocyte counts drop below 3000 cells/microliter (cells/mm^3). Dose adjustment due to myelosuppression is recommended (see section 4.2).
Unless essential, cyclophosphamide should not be administered to patients with a leukocyte count below 2500 cells/microliter (cells/ mm^3) and/or a platelet count below 50,000 cells/microliter (cells/mm^3).
In principle, the fall in the peripheral blood cell and thrombocyte count and the time taken to recover may increase with increasing doses of cyclophosphamide.
The nadirs of the reduction in leukocyte count and thrombocyte count are usually reached in weeks 1 and 2 of treatment. The bone marrow recovers relatively quickly, and the levels of peripheral blood cell counts normalize, as a rule, after approximately 20 days.
Cyclophosphamide treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop a serious infection.
Severe myelosuppression must be expected particularly in patients pre-treated with and/or receiving concomitant chemotherapy and/or radiation therapy.

Urinary Tract and Renal Toxicity
Hemorrhagic cystitis, pyelitis, urethritis, and hematuria have been reported with cyclophosphamide therapy. Bladder ulceration/necrosis, fibrosis/contracture and secondary cancer may develop. Urotoxicity may mandate interruption of treatment. Cases of urotoxicity with fatal outcomes have been reported.
Urotoxicity can occur with short-term and long-term use of cyclophosphamide. Hemorrhagic cystitis after single doses of cyclophosphamide has been reported. Cystectomy may become necessary due to fibrosis, bleeding, or secondary malignancy. Past or concomitant radiation or busulfan treatment may increase the risk for cyclophosphamide-induced hemorrhagic cystitis. Cystitis is, in general, initially abacterial. Secondary bacterial colonization may follow.
Before starting treatment, it is necessary to exclude or correct any urinary tract obstructions. See section 4.3. Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity. Adequate treatment with mesna and/or strong hydration to force diuresis can markedly reduce the frequency and severity of bladder toxicity. It is important to ensure that patients empty the bladder at regular intervals. Hematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist. Severe hemorrhagic cystitis usually requires a discontinuation of the treatment with cyclophosphamide.
Cyclophosphamide has also been associated with nephrotoxicity, including renal tubular necrosis.
Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome resembling SIADH (syndrome of inappropriate secretion of antidiuretic hormone) have been reported in association with cyclophosphamide administration. Fatal outcomes have been reported

Cardiotoxicity, Use in Patients with Cardiac Disease
Myocarditis and myopericarditis, which may be accompanied by significant pericardial effusion and cardiac tamponade, have been reported with cyclophosphamide therapy and have led to severe, sometimes fatal congestive heart failure. Histopathologic examination has primarily shown hemorrhagic myocarditis. Hemopericardium has been reported secondary to hemorrhagic myocarditis and myocardial necrosis. Acute cardiac toxicity has been reported with single doses as low as 20 mg/kg of cyclophosphamide.
Following exposure to treatment regimens that included cyclophosphamide, supraventricular arrhythmias (including atrial fibrillation and flutter) as well as ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported in patients with and without other signs of cardiotoxicity.
The risk of cyclophosphamide cardiotoxicity as a result of treatment with cyclophosphamide, in patients with advanced age, and in patients with previous radiation treatment of the cardiac region and/or previous or concomitant treatment with other cardiotoxic agents. See section 4.5.
Particular caution is required in patients with risk factors for cardiotoxicity and in patients with a pre-existing cardiac disease.

Pulmonary Toxicity
Pneumonitis and pulmonary fibrosis have been reported during and following treatment with cyclophosphamide. Pulmonary veno-occlusive disease and other forms of pulmonary toxicity have also been reported. Pulmonary toxicity leading to respiratory failure has been reported. While the incidence of cyclophosphamide-associated pulmonary toxicity is low, prognosis for affected patients is poor. Late onset of pneumonitis (greater than 6 months after start of cyclophosphamide) appears to be associated with a particularly high mortality. Pneumonitis may develop even years after treatment with cyclophosphamide. Acute pulmonary toxicity has been reported after a single cyclophosphamide dose.

Secondary Malignancies
As with all cytotoxic therapy, treatment with cyclophosphamide involves the risk of secondary tumors and their precursors as sequelae. The risk of urinary tract cancer as well as the risk of myelodysplastic alterations, partly progressing to acute leukemias, is increased. Other malignancies reported after use of cyclophosphamide or regimens with cyclophosphamide include lymphomas, thyroid cancer, and sarcomas.
In some cases, the second malignancy developed several years after cyclophosphamide treatment had been discontinued. Malignancy has also been reported after in utero exposure.
The risk of bladder cancer can be markedly reduced by hemorrhagic cystitis prophylaxis.

Veno-occlusive Liver Disease
Veno-occlusive liver disease (VOLD) has been reported in patients receiving cyclophosphamide, mainly in patients receiving a cytoreductive regimen in preparation for bone marrow transplantation in combination with whole-body irradiation, busulfan, or other agents (see section 4.5). After cytoreductive therapy, the clinical syndrome typically develops 1 to 2 weeks after transplantation and is characterized by sudden weight gain, painful hepatomegaly, ascites, and hyperbilirubinemia/jaundice. However, VOLD has also been reported to develop gradually in patients receiving long-term low-dose immunosuppressive doses of cyclophosphamide.
As a complication of VOLD, hepatorenal syndrome and multiorgan failure may develop. Fatal outcome of cyclophosphamide-associated VOLD has been reported. Risk factors predisposing a patient to the development of VOLD include pre-existing disturbances of hepatic function, previous radiation therapy of the abdomen, and a low performance score.
VOLD incidence has been reported to reduce if a time interval of at least 24 hours is observed between the last administration of busulfan and the first administration of cyclophosphamide (see section 4.2 and 4.5).

Genotoxicity
Cyclophosphamide is genotoxic and mutagenic, both in somatic and in male and female germ cells. Therefore, women should not become pregnant and men should not father a child during therapy with cyclophosphamide.
Women should not become pregnant during the treatment and for a period of 12 months following discontinuation of the therapy.
Men should not father a child during the treatment and for a period of 6 months following discontinuation of the therapy
Animal data indicate that exposure of oocytes during follicular development may result in a decreased rate of implantations and viable pregnancies, and in an increased risk of malformations. This effect should be considered in case of intended fertilization or pregnancy after discontinuation of cyclophosphamide therapy. The exact duration of follicular development in humans is not known but may be longer than 12 months. Sexually active women and men should use effective methods of contraception during these periods of time (see section 4.6.).

Fertility
Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Men treated with cyclophosphamide should be informed about sperm preservation prior to treatment (see section 4.6).

Impairment of Wound Healing
Cyclophosphamide may interfere with normal wound healing.

Precautions
Alopecia
Alopecia has been reported and may occur more commonly with increasing doses. Alopecia may progress to baldness. The hair can be expected to grow back after treatment with the drug or even during continued drug treatment, though it may be different in texture or color.

Nausea and Vomiting
Administration of cyclophosphamide may cause nausea and vomiting. Current guidelines on the use of antiemetics for prevention and amelioration of nausea and vomiting should be considered.
Alcohol consumption may increase cyclophosphamide-induced vomiting and nausea.

Stomatitis
Administration of cyclophosphamide may cause stomatitis (oral mucositis). Current guidelines on measures for prevention and amelioration of stomatitis should be considered.

Paravenous Administration
The cytostatic effect of cyclophosphamide occurs after its activation, which takes place mainly in the liver. Therefore, the risk of tissue injury from accidental paravenous administration is low.
In case of accidental paravenous administration of cyclophosphamide, the infusion should be stopped immediately, the extravascular cyclophosphamide solution should be aspirated with the cannula in place, and other measures should be instituted as appropriate. The area should subsequently be rinsed with physiological saline solution, and the arm or leg should rest.

Use in Patients with Renal Impairment
In patients with renal impairment, particularly in patients with severe renal impairment, decreased renal excretion may result in increased plasma levels of cyclophosphamide and its metabolites. This may result in increased toxicity and should be considered when determining the dosage in such patients. See section 4.2.

Use in Patients with Hepatic Impairment
Severe hepatic impairment may be associated with a decreased effect of cyclophosphamide. This may negatively alter the effectiveness of cyclophosphamide treatment and should be considered when selecting the dose and interpreting response to the dose selected. See section 4.2. Due to the porphyrogenic effect of Cyclophosphamide, patients with acute porphyria should be treated with caution.

Use in Adrenalectomized Patients
Patients with adrenal insufficiency may require an increase in corticoid substitution dose when exposed to stress from toxicity due to cytostatic, including cyclophosphamide.

Use in Patients with Diabetes
Caution is also advised in is patients with diabetes mellitus, since cyclophosphamide may interact with insulin and other hypoglycemic agents (also see section 4.5).

Use in Patients who have recently undergone surgery
In general, cytostatic (among which cyclophosphamide) should not be administered to patients who had a surgery less than 10 days ago.

4.5. Interaction with other medicinal products and other forms of interaction
Cyclophosphamide is inactive, but is metabolized in the liver, mainly by CYP2A6, 2B6, 2C9, 2C19 and 3A4, into two active metabolites.
Planned co-administration or sequential administration of other substances or treatments with cyclophosphamide that could increase the likelihood or severity of toxic effects (by means of pharmacodynamic or pharmacokinetic interactions) requires careful individual assessment of the expected benefit and the risks.
Patients receiving such combinations must be monitored closely for signs of toxicity to permit timely intervention. Patients being treated with cyclophosphamide and agents that reduce its activation should be monitored for a potential reduction of therapeutic effectiveness and the need for dose adjustment.

Interactions negatively affecting the pharmacokinetics of cyclophosphamide and its metabolites
- Reduced activation of cyclophosphamide may alter the effectiveness of cyclophosphamide treatment. Substances that delay activation of cyclophosphamide include:
- Aprepitant
- Bupropion
- Busulfan: decreased elimination of cyclophosphamide and prolonged half-life has been reported in patients who received high-dose cyclophosphamide less than 24 hours after high-dose busulfan. Increased incidence of hepatic veno-occlusive disease and mucositis has been reported with concomitant administration (see section 4.2 and 4.4).
- Ciprofloxacin: when administered prior to treatment with cyclophosphamide (used for conditioning prior to bone marrow transplant), ciprofloxacin may cause regression of the underlying disease.
- Chloramphenicol
- Azole-antimycotics (Fluconazole, Itraconazole): Azole-antimycotics are known to inhibit cytochrome P450 enzymes. Increased amounts of toxic degradation products of cyclophosphamide have been reported in combination with Itraconazole.
- CYP2B6 and CYP3A4 inhibitors (Nevirapin, Ritonavir): co-administration may reduce the efficacy of cyclophosphamide
- Prasugrel
- Sulfonamides, e.g., sulfadiazine, sulfamethoxazole and sulfapyridine
- Thiotepa: a strong inhibition of cyclophosphamide bioactivation by thiotepa in high-dose chemotherapy regimens has been reported when thiotepa was administered 1 hour prior to cyclophosphamide.
- Ondansetron: There have been reports of a pharmacokinetic interaction between ondansetron and high-dose cyclophosphamide resulting in decreased cyclophosphamide AUC.
- Grapefruit (fruit or juice), Rifampicin, St. Johns worth: Co-administration with CYP3A4 Inhibitors or Inducers can reduce the efficacy or increase the toxicity of cyclophosphamide.

- An increase of the concentration of cytotoxic metabolites may occur with:
- Allopurinol: an increase of bone marrow suppression was reported.
- Azathioprine: increased risk of hepatotoxicity (liver necrosis)
- Chloral hydrate
- Cimetidine
- Disulfiram
- Glyceraldehyde
- Protease inhibitors: concomitant use of protease inhibitors may increase the concentration of cytotoxic metabolites. Use of protease inhibitor-based regimens was found to be associated with a higher incidence of infections and neutropenia in patients receiving cyclophosphamide, doxorubicin, and etoposide (CDE) than use of an NNRTI-based regimen. Increased incidence of mucositis is reported in combined therapy of cyclophosphamide (CDE) and saquinavir
- Inducers of human hepatic and extrahepatic microsomal enzymes (e.g., cytochrome P450 enzymes): The potential for hepatic and extrahepatic microsomal enzyme induction must be considered in case of prior or concomitant treatment with substances known to induce an increased activity of such enzymes such as rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort, benzodiazepines and corticosteroids.
- Dabrafenib.

Pharmacodynamic Interactions and Interactions of Unknown Mechanism Affecting the Use of Cyclophosphamide

Combined or sequential use of cyclophosphamide and other agents with similar toxicities can cause combined (increased) toxic effects.

- Increased hepatotoxicity and/or immunosuppression may result from a combined effect of cyclophosphamide and, for example
- ACE inhibitors: ACE inhibitors can cause leukopenia.
- Natalizumab
- Paclitaxel: Increased hepatotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion.
- Thiazide diuretics (e.g., hydrochlorothiazide): An increase of bone marrow suppression was reported.
- Zidovudine
- Clozapine

- Increased cardiotoxicity may result from a combined effect of cyclophosphamide and, for example
- Anthracyclines
- Mitomycin
- Cytarabine
- Pentostatin
- Radiation therapy of the cardiac region or a whole-body irradiation in combination with high doses of cyclophosphamide.
- Trastuzumab

- Increased pulmonary toxicity may result from a combined effect of cyclophosphamide and, for example:
- Amiodarone
- G-CSF, GM-CSF (granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor): reports suggest an increased risk of pulmonary toxicity in patients treated with cytotoxic chemotherapy that includes cyclophosphamide and G-CSF or GMCSF.

- Increased nephrotoxicity may result from a combined effect of cyclophosphamide and, for example:
- Amphotericin B
- Indomethacin: acute water intoxication has been reported with concomitant use of indomethacin.

Other Interactions
Alcohol
A reduced antitumor activity was observed in tumor-bearing animals during ethanol (alcohol) consumption and concomitant oral low-dose cyclophosphamide medication. In some patients, alcohol may increase cyclophosphamide-induced vomiting and nausea.

Etanercept

In patients with Wegener's granulomatosis, the addition of etanercept to standard treatment, including cyclophosphamide, was associated with a higher incidence of non-cutaneous solid malignancies.

Metronidazole
Acute encephalopathy has been reported in a patient receiving cyclophosphamide and metronidazole. Causal association is unclear.
In an animal study, the combination of cyclophosphamide with metronidazole was associated with increased cyclophosphamide toxicity.

Tamoxifen
Concomitant use of tamoxifen and chemotherapy may increase the risk of thromboembolic complications.

Interactions Affecting the Pharmacokinetics and/or Actions of Other Drugs
Bupropion
Cyclophosphamide metabolism by CYP2B6 may inhibit bupropion metabolism.

Coumarins
Both increased and decreased warfarin effects have been reported in patients receiving warfarin and cyclophosphamide.

Cyclosporine
Lower serum concentrations of cyclosporine have been observed in patients receiving a combination of cyclophosphamide and cyclosporine than in patients receiving only cyclosporine. This interaction may result in an increased incidence of graft versus host disease (GVHD).

Depolarizing muscle relaxants
Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity. Prolonged apnea may occur with concurrent depolarizing muscle relaxants (e.g., succinylcholine, suxamethonium) as a result of a decreased pseudocholinesterase level. If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

Digoxin, β- acetyldigoxin
Impaired absorption of digoxin and β-acetyldigoxin tablets have been reported during a concomitant cytotoxic treatment

Vaccines
The immunosuppressive effects of cyclophosphamide can be expected to reduce the response to vaccination. Use of live vaccines may lead to vaccine-induced infection.
Verapamil
Impaired intestinal absorption of orally administered verapamil has been reported.

Sulfonylurea derivatives
Blood sugar levels may drop, if cyclophosphamide and sulfonylurea derivatives are used concomitantly.

4.6. Fertility, pregnancy and breast-feeding

Women of childbearing potential
Girls treated with cyclophosphamide during pre-pubescence generally develop secondary sexual characteristics normally and have regular menses.
Young women treated with cyclophosphamide during pre-pubescence subsequently have conceived.
Young women treated with cyclophosphamide who have retained ovarian function after completing treatment are at increased risk of developing premature menopause (cessation of menses before age of 40 years).

Pregnancy
There are very limited data from the use of cyclophosphamide in pregnant women. There are reports of serious multiple congenital aberrations after use during the first trimester. Animal studies have shown teratogenicity and other reproduction toxicity (see section 5.3).
Considering the data from human case reports, animal studies and the mechanism of action of cyclophosphamide, its use during pregnancy, in particular during the first trimester, is not recommended.
In each individual case the potential benefit of the treatment should be weighed against the potential risk for the fetus.

Breast-feeding
Cyclophosphamide is excreted into the breast milk and can cause neutropenia, thrombocytopenia, low hemoglobin, and diarrhea in children. Cyclophosphamide is contraindicated during breastfeeding (see section 4.3).

Fertility
Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. In women cyclophosphamide may cause transient or permanent amenorrhea, and in boys treated with cyclophosphamide during pre-pubescence, oligospermia or azoospermia. Men treated with cyclophosphamide may develop oligospermia or azoospermia. Prior to treatment of men with cyclophosphamide, they should be informed of the possibility to store and keep viable sperm collected before treatment.

4.7. Effects on ability to drive and use machines
Patients undergoing treatment with cyclophosphamide may experience undesirable effects (including nausea, vomiting, dizziness, blurred vision, visual impairment) which could affect the ability to drive or use machines. The decision to drive or operate machinery should be made on an individual basis.

4.8. Undesirable effects
The frequency of adverse reactions reported in the table below are derived from clinical trials and from post marketing experience and are defined using the following convention: very common (>1/10), common (> 1/100 to <1/10), uncommon (> 1/1,000 to <1/100), rare (> 1/10,000 to <1/1,000), very rare (< 1/10,000) not known.

Organ System Class	Recommended MedDRA term	Frequency
Infections and infestations	Infections 1	Common
	Pneumonia2	Uncommon
	Sepsis1	Uncommon
Neoplasms, benign and malignant and unspecified (including cysts and polyps)	Acute leukemia 3	Rare
	Myelodysplastic syndrome	Rare
	Secondary malignancies	Rare
	Bladder cancer	Rare
	Ureteric cancer	Rare
	Tumor lysis syndrome	Very rare
	Non-Hodgkin's lymphoma	Not known
	Sarcoma	Not known
	Renal cell carcinoma	Not known
	Renal pelvis cancer	Not known
	Thyroid cancer	Not known
Blood and lymphatic system disorders	Myelosuppression4	Very common
	Leukopenia	Very common
	Neutropenia	Very common
	Febrile neutropenia	Common
	Thrombocytopenia	Uncommon
	Anemia	Uncommon
	Disseminated intravascular coagulation	Very rare
	Hemolytic uremic syndrome	Very rare
	Agranulocytosis	Not known
	Lymphopenia	Not known
	Hemoglobin decreased	Not known
Immune system disorders	Immunosuppression	Very common
	Anaphylactic/Anaphylactoid reaction	Uncommon
	Hypersensitivity reaction	Uncommon
	Anaphylactic shock	Very rare
e disorders	SIADH (syndrome of inappropriate antidiuretic hormone secretion)	Rare
Metabolism and nutrition disorders	Anorexia	Uncommon
	Dehydration	Rare
	Hyponatremia	Very rare
	Blood glucose increased	Not known
	Blood glucose decreased	Not known
Psychiatric disorders	Confusional state	Very rare
Nervous system disorders	Peripheral neuropathy	Uncommon
	Polyneuropathy	Uncommon
	Neuralgia	Uncommon
	Convulsion	Rare
	Dizziness	Rare
	Dysgeusia	Very rare
	Hypogeusia	Very rare
	Paresthesia	Very rare
	Neurotoxicity5	Not known
	Reversible posterior leukoencephalopathy	Not known
	Syndrome6	
	Encephalopathy	Not known
Eye disorders	Blurred vision	Rare
	Visual impairment	Rare
	Conjunctivitis	Very rare
	Eye oedema 7	Very rare
	Lacrimation increased	Not known
Ear and labyrinth disorders	Deafness	Uncommon
	Tinnitus	Not known
Cardiac disorders	Cardiomyopathy	Uncommon
	Myocarditis	Uncommon
	Heart failure 8	Uncommon
	Tachycardia	Uncommon
	Ventricular arrhythmia	Rare
	Supraventricular arrhythmia	Rare
	Ventricular fibrillation	Very rare
	Angina	Very rare
	Myocardial infarction	Very rare
	Pericarditis	Very rare
	Atrial fibrillation	Very rare
	Ventricular tachycardia	Not known
	Cardiogenic shock	Not known
	Pericardial effusion	Not known
	Bradycardia	Not known
	Palpitations	Not known
	Electrocardiogram QT prolonged	Not known
Vascular disorders	Flushing	Uncommon
	Hemorrhage	Rare
	Thromboembolism	Very rare
	Hypertension	Very rare
	Hypotension	Very rare
	Pulmonary embolism	Not known
	Venous thrombosis	Not known
	Vasculitis	Not known
	Peripheral ischemia	Not known
Respiratory, thoracic and mediastinal disorders 89	Acute respiratory distress syndrome (ARDS)	Very rare
	Chronic pulmonary interstitial fibrosis,	Very rare
	Pulmonary oedema	Very rare
	Bronchospasm	Very rare
	Dyspnea	Very rare
	Hypoxia	Very rare
	Cough	Very rare
	Nasal congestion	Not known
	Oropharyngeal pain	Not known
	Rhino rhea	Not known
	Sneezing	Not known
	Pulmonary veno-occlusive disease	Not known
	Obliterative bronchiolitis	Not known
	Alveolitis allergic	Not known
	Pneumonitis	Not known
	Pleural effusion	Not known
Gastrointestinal disorders	Mucosal inflammation	Common
	Enterocolitis hemorrhagic	Very rare
	Acute pancreatitis	Very rare
	Ascites	Very rare
	Stomatitis	Very rare
	Diarrhea	Very rare
	Vomiting	Very rare
	Constipation	Very rare
	Nausea	Very rare
	Abdominal pain	Not known
	Parotid gland inflammation	Not known
	Gastrointestinal hemorrhage	Not known
	Cecities	Not known
	Colitis	Not known
	Enteritis	Not known
Hepatobiliary disorders	Hepatic function abnormal	Common
	Hepatitis	Rare
	Veno-occlusive liver disease	Very rare
	Hepatomegaly	Very rare
	Jaundice	Very rare
	Cholestatic hepatitis	Not known
	Hepatotoxicity 10	Not known
Skin and subcutaneous tissue disorders	Alopecia 11	Very common
	Rash	Rare
	Dermatitis	Rare
	Nail discoloration	Rare
	Skin discoloration 12	Rare
	Stevens-Johnson syndrome	Very rare
	Toxic epidermal necrolysis	Very rare
	Radiation erythema	Very rare
	Pruritus (including itching due to inflammation)	Very rare
	Erythema multiforme	Not known
	Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)	Not known
	Urticaria	Not known
	Erythema	Not known
	Facial swelling	Not known
	Hyperhidrosis	Not known
Musculoskeletal and connective tissue disorders	Rhabdomyolysis	Very rare
	Cramps	Very rare
	Scleroderma	Not known
	Muscle spasms	Not known
	Myalgia	Not known
	Arthralgia	Not known
Renal and urinary tract disorders	Cystitis	Very common
	Microhematuria	Very common
	Hemorrhagic cystitis	Common
	Macrohematuria	Common
	Suburethral hemorrhage	Very rare
	Bladder wall oedema	Very rare
	Bladder fibrosis and sclerosis	Very rare
	Renal impairment	Very rare
	Blood creatinine increased	Very rare
	Renal tubular necrosis	Very rare
	Renal tubular disorder	Not known
	Nephropathy toxic	Not known
	Hemorrhagic urethritis	Not known
	Bladder contracture	Not known
	Nephrogenic diabetes insipidus	Not known
	Atypical urinary bladder epithelial cells	Not known
	Blood urea nitrogen increased	Not known
Pregnancy, puerperium and perinatal conditions	Premature labor	Not known
Reproductive system and breast disorders	Impairment of spermatogenesis	Common
	Ovulation disorder (rarely irreversible)	Uncommon
	Amenorrhea 13	Rare
	Azoospermia/asperima 13	Rare
	Oligospermia 13	Rare
	Infertility	Not known
	Ovarian Failure	Not known
	Oligomenorrhea	Not known
	Testicular atrophy	Not known
Congenital, familial and genetic disorders	Intra-uterine death	Not known
	Fetal malformation	Not known
	Fetal growth retardation	Not known
	Fetal damage	Not known
	Carcinogenic effect on offspring	Not known
General disorders and administrative site conditions	Fever	Very common
	Chills	Common
	Asthenia	Common
	Malaise	Common
	Chest pain	Rare
	Headache	Very rare
	Multiorgan failure	Very rare
	Injection/infusion site reactions (Thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema)	Very rare Uncommon Uncommon
Investigations	Blood lactate dehydrogenase increased	Uncommon
	C-reactive protein increased	Uncommon
	ECG changes	Very rare
	Decreased LVEF	Uncommon
	Weight gain	Not known
	Lower levels of female sex hormones	Not known
	Blood estrogen level decreased	
	Blood gonadotropin level increased	

1 An increased risk for and severity of pneumonias (including fatal outcomes), other bacterial, fungal, viral, protozoal, and parasitic infections; reactivation of latent infections, including viral hepatitis, tuberculosis, JC virus with progressive multifocal leukoencephalopathy (including fatal outcomes), *pneumocystis jiroveci*, herpes zoster, *strongyloides*, sepsis and septic shock (including fatal outcomes).
2 including fatal outcomes
3 including acute myeloid leukemia, acute promyelocytic leukemia
4manifested as Bone marrow failure, Pancytopenia, Neutropenia, Agranulocytosis, Granulocytopenia, Thrombocytopenia (complicated by bleeding), Leukopenia, Anemia
5 manifested as myelopathy, peripheral neuropathy, polyneuropathy, neuralgia, dysesthesia, hypoesthesia, paresthesia, tremor, dysgeusia, hypogeusia, parosmia.
6 manifested as headache, altered mental functioning, seizures and abnormal vision from blurriness to vision loss
7 Observed in connection with an allergic reaction
8 Including fatal outcomes
9 While the incidence of cyclophosphamide-associated pulmonary toxicity is low, prognosis for affected patients is poor.
10 Hepatic failure, Hepatic encephalopathy, Ascites, Hepatomegaly, Jaundice, Blood bilirubin increased, Hepatic enzymes increased (ASAT, ALAT, ALP, gamma-GT)
11 May progress to baldness
12 Of the palms and heels
13 Persistent

Remark
Certain complications such as thromboembolism, disseminated intravascular coagulation, and hemolytic uremic syndrome may occur because of the underlying disorders, but the frequency of these complications may increase due to chemotherapy with cyclophosphamide.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the ANMAT webpage or via email to farmacovigilancia@kemexlab.com.

4.9. Overdose
Serious consequences of overdosage include manifestations of dose dependent toxicities such as myelosuppression, urotoxicity, cardiotoxicity (including cardiac failure), veno occlusive hepatic disease, and stomatitis. See section 4.4.
Patients who received an overdose should be closely monitored for the development of toxicities, and hepatotoxicity, in particular.
There is no specific antidote for an overdosage of cyclophosphamide.
Cyclophosphamide and its metabolites are dialyzable. Therefore, rapid hemodialysis is indicated when treating any suicidal or accidental overdose or intoxication. Overdosage should be managed with supportive measures, including appropriate, state-of-the-art treatment for any concurrent infection, myelosuppression, or other toxicity, should it occur. Cystitis prophylaxis with mesna can help to prevent or reduce urotoxic effects in case of cyclophosphamide overdosage.

IN THE EVENT OF AN OVERDOSE, GO TO THE NEAREST HOSPITAL OR CONTACT A POISON CONTROL CENTER:
Hospital de Niños Dr. Ricardo Gutiérrez: Phone # +54 11 4962-6666/2247
Hospital Pedro de Elizalde: Phone # +54 11 4300-2115 / 4362-6063
Hospital Dr. Juan A. Fernández: Phone # +54 11 4808-2655
Hospital Dr. A. Posadas: Phone # +54 11 4654-6648/4658-7777/ 0800-3330160

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic Properties
Pharmacotherapeutic group: Antineoplastic and Immunomodulating Agents; Antineoplastic agents. Alkylating agents. Nitrogen mustard analogues.
ATC code: L01AA01.

Cyclophosphamide has been demonstrated to have a cytostatic effect in many tumor types.
Cyclophosphamide engages probably to the S-or G2-phase of the cell cycle.
It remains to be shown whether the cytostatic effect is entirely dependent on the alkylation of DNA or other mechanisms such as inhibition of chromatin transformation processes or inhibition of DNA polymerases play a role. The metabolite acrolein has no antineoplastic activity, but is responsible for the adverse urotoxic effect.
The immunosuppressive effect of cyclophosphamide is based on the fact that cyclophosphamide has an inhibitory effect on B-cells, CD4 + T-cells and to a lesser extent on CD8 +-T-cells. In addition, it is assumed that cyclophosphamide has an inhibitory effect on the suppressor that regulate the IgG2 class of antibodies.
Cross-resistance, especially with structurally related cytotoxic agents, e.g., Ifosfamide, as well as other alkylating agents, cannot be excluded.
Cyclophosphamide is administered as an inactive prodrug that is activated in the liver.

5.2. Pharmacokinetic Properties
Cyclophosphamide is administered as an inactive prodrug that is activated in the liver.

Absorption
Cyclophosphamide is quickly and almost completely absorbed from parenteral sites.

Distribution
Less than 20% of cyclophosphamide is bound to plasma proteins. The protein binding of the metabolites of cyclophosphamide is higher but less than 70%. To what extent the active metabolites protein bound, is not known. Cyclophosphamide is about in the cerebrospinal fluid and the mother's milk. Cyclophosphamide and metabolites can pass through the placenta.

Metabolism
Cyclophosphamide is activated in the liver to the active metabolites 4-hydroxy-cyclophosphamide and aldofosfamide (tautomeric form of 4-hydroxy-cyclophosphamide) through phase I metabolism by cytochrome P450 (CYP) enzymes. Different CYP isozymes contribute to the bioactivation of cyclophosphamide, including CYP2A6, 2B6, 2C9, 2C19 and 3A4, 2B6 in which the exhibits highest 4-hydroxylase activity. Detoxification is done mainly through glutathione-S-transferases (GSTA1, GSTP1) and alcohol dehydrogenase (ALDH1, ALDH3). Two to four hours after administration of
cyclophosphamide, the plasma concentrations of the active metabolites are maximal, after which a rapid decrease of plasma concentrations takes place.

Elimination
The plasma half-life of cyclophosphamide is about 4 to 8 hours in adults and children. The plasma half-lives of the active metabolites are not known. Following high-dose IV administration within the framework of allogeneic bone marrow transplantation, the plasma concentration of pure cyclophosphamide follows linear first- order kinetics. Compared with conventional cyclophosphamide therapy, there is an increase in inactive metabolites, indicating saturation of activating enzyme systems, but not of the stages of metabolism leading to inactive metabolites.
During the course of high-dose cyclophosphamide therapy over several days, there is a decrease in the areas under the plasma concentration-time curve of the parent compound, probably due to auto-induction of microsomal metabolism activity.
Cyclophosphamide and its metabolites are primarily excreted by the kidneys.

5.3. Preclinical Safety Data
Acute toxicity
The acute toxicity of cyclophosphamide is relatively low. This was demonstrated in studies on mice, guinea pigs, rabbits and dogs.
Chronic toxicity
Chronic administration of toxic doses led to hepatic lesions manifested as fatty degeneration followed by necrosis. The intestinal mucosa was not affected. The threshold for hepatotoxic effects was 100 mg/kg in the rabbit and 10 mg/kg in the dog.
Mutagenicity and carcinogenicity
The mutagenic effects of cyclophosphamide have been demonstrated in various in-vitro and in-vivo tests. Chromosome aberrations following administration of cyclophosphamide have also been observed in humans. The carcinogenic effects of cyclophosphamide have been demonstrated in animal studies on rats and mice.
Teratogenicity
The teratogenic effects of cyclophosphamide have been demonstrated in various animals (mice, rats, rabbits, rhesus monkeys and dogs). Cyclophosphamide can cause skeletal, tissue as well as other malformations.

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients

CYCLOPHOSPHAMIDE KEMEX 200 mg
Mannitol

CYCLOPHOSPHAMIDE KEMEX 1000 mg
Mannitol

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
2 years.
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C for the reconstituted solution and for the diluted solution.
From a microbiological point of view, the reconstituted and diluted solution should be used immediately, unless reconstitution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C- 8°C.

6.4. Special precautions for storage
Do not store above 25°C. For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5. Nature and content of containers
Cyclophosphamide Kemex Powder for Solution for Injection is available in the following pack sizes:
Cyclophosphamide Kemex 200 mg Powder for Solution for Injection – 1, 5, 6, 25, 50 and 100 vials, being the last three for exclusive use in hospitals.
Cyclophosphamide Kemex 1000 mg Powder for Solution for Injection – 1, 6, 25, 50 and 100 vials, being the last three for exclusive use in hospitals.

6.6. Special precautions for disposal and other handling
For each 100 mg of cyclophosphamide, 5 ml of solvent must be added for reconstitution.
The choice of diluent for reconstituting Cyclophosphamide containing cyclophosphamide depends on the route of administration to be used. See form of administration.

Infusion
If the solution is to be used for IV infusion, Cyclophosphamide Kemex (containing cyclophosphamide) is reconstituted by adding sterile water for injection or 0.9% sterile sodium chloride solution.

Intravenous Use
Intravenous administration should preferably be conducted as an infusion.

Infusion
Reconstituted Cyclophosphamide Kemex should be further diluted in 5% dextrose or 0.9% sodium chloride injection prior to infusion.

Direct Injection
Please note that only Cyclophosphamide Kemex reconstituted in 0.9% sterile sodium chloride solution is suitable for bolus injection.

Cyclophosphamide Kemex (containing cyclophosphamide) reconstituted in water is hypotonic and should not be injected directly.

Disposal of unused medication and all materials that have been in contact with it will be done in accordance with local regulations.

STORE AT A TEMPERATURE BETWEEN 15 °C TO 25 °C
PROTECT FROM LIGHT IN ITS ORIGINAL PACKAGING
KEEP OUT OF THE REACH OF CHILDREN.
IF YOU HAVE ANY QUESTIONS, CONTACT YOUR DOCTOR
"This medicine must be used exclusively under a medical prescription and cannot be repeated without a new prescription"

7. MARKETING AUTHORIZATION HOLDER
Laboratorio Kemex S.A. – Nazarre 3446/54 - (C1417DXH) –Ciudad Autónoma de Buenos Aires. Argentina.
Technical Director: Natalia Alonso – Pharmacist.

8. MARKETING AUTHORIZATION NUMBER(S)
Medicinal specialty authorized by the Health Ministry (ANMAT).
Certificate No. 55,159

9. DATE OF REVISION OF THE TEXT
11/2016
farmacovigilancia@kemexlab.com

05093.00

kemex laboratorio