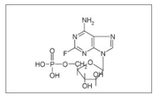
FLUDARABINE KEMEX
Fludarabine 50 mg
Lyophilized for Injection
FOR INTRAVENOUS USE
Rx only

Formula
Each vial contains:
Fludarabine phosphate.....50.00 mg
Mannitol.....50.00 mg
Sodium hydroxide c.s.....pH 7.7

DRUG CATEGORY
Antineoplastic agent

The structural formula is:



WARNING
FLUDARABINA KEMEX (fludarabine phosphate) should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents.
Fludarabine phosphate may severely suppress bone marrow function.
In dose-ranging studies, the administration of high doses of fludarabine phosphate to patients with acute leukemia resulted in severe neurologic effects including blindness, coma, and death. This severe neurologic toxicity was occurred in 36% of patients treated with 96 mg/m²/day for 5-7 days, a dose approximately four times greater than the recommended dose.
This severe neurologic toxicity has been rarely reported (≤ 0.2%) in patients treated at doses within the range of the recommended dose chronic lymphocytic leukemia (CLL).
Cases of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported after one or more cycles of treatment with fludarabine phosphate. Patients treated with fludarabine phosphate should be evaluated and closely monitored for hemolysis.
In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of CLL, an increased incidence of fatal pulmonary toxicity was observed. Therefore, the use of fludarabine phosphate in combination with pentostatin is not recommended.

INDICATIONS
Fludarabina KEMEX is indicated for the initial treatment of B-cell chronic lymphocytic leukemia (CLL) and for the treatment of patients with B-CCL who have not responded to or whose disease has progressed during or after treatment with at least one alkylating agent.
The safety and effectiveness of fludarabine phosphate in patients with previously untreated or non-refractory CLL have not been established.
Fludarabina KEMEX is also indicated for the treatment of patients with stage III and IV low-grade non-Hodgkin lymphoma who have not responded to or whose disease has progressed during or after treatment with at least one alkylating agent.

PHARMACOLOGICAL CHARACTERISTICS AND PROPERTIES
PHARMACOLOGICAL ACTION
Fludarabine phosphate is a fluorinated analog of the antiviral agent vidarabine, 9-ß-D-arabinofuranosyladenine (ara-A), which is relatively resistant to deamination by adenosine deaminase.
Fludarabine phosphate (2F-ara-AMP) is rapidly dephosphorylated to fludarabine (2F-ara-A), which is then phosphorylated intracellularly by the action of desoxycytidine-kinase to the active triphosphate, 2F-ara-ATP. This metabolite inhibits DNA synthesis, via inhibition of ribonucleotide reductase, DNA polymerase α, δ and ε, DNA primase and DNA ligase. Besides, by partially inhibiting RNA-polymerase activity, it reduces protein synthesis.
Although certain aspects of the mechanism of action of 2F-ara-ATP are yet unclear, it is assumed that the effects on DNA, RNA and protein synthesis contribute to inhibition of cell growth, with DNA synthesis inhibition being the dominant factor. In addition, in vitro studies have shown that exposure of lymphocytes to 2 F-ara-A triggers apoptosis. Consequently, hematological tumors are destroyed, but normal lymphocytes are also destroyed.
No clear correlation was found between the pharmacokinetics of 2F-ara-A and the therapeutic efficacy in cancer patients. However, the occurrence of neutropenia and hematocrit changes indicated that the cytotoxicity of fludarabine phosphate inhibits hematopoiesis in a dose-dependent manner.

PHARMACOKINETICS
Absorption
After administration of 2F-ara-AMP, the metabolite pharmacokinetics is linear with the dose.
After a single dose infusion of 25 mg/m² 2F-ara-AMP for 30 minutes to patients with CLL, mean peak plasma concentrations of 3.2-3.7 µM were reached at the end of infusion. After the fifth dose, 2F-ara-A levels showed a moderate accumulation with mean peak plasma concentrations of 4.4-4.8 µM at the end of infusion. During a 5-day treatment schedule, 2F-ara-A minimum plasma levels increased about 2 times. 2F-ara-A accumulation after several cycles of treatment can be excluded.
Distribution
Pharmacokinetics studies have shown that 2F-ara-A has a mean volume of distribution (Vss) of 83 L/m² (2.4 L/kg), with a high interindividual variability. In vitro studies with human plasma proteins have shown plasma protein binding of 2F-ara-A is low.
Metabolism
Fludarabine phosphate (2F-ara-AMP) is rapidly transformed in the human body to its principal metabolite, 2F-ara-A. 2F-ara-A is actively transported into leukemic cells where it converts into 2F-ara-ATP, the cytotoxic metabolite. 2F-ara-A-hypoxanthine, which represents the principal metabolite in dogs, has only been found in small quantities in human urine.
Elimination
Elimination is triphasic with an initial half-life of approximately 5 minutes, an intermediate half-life of 1-2 hours, and a terminal half-life of approximately 20 hours.
The mean total plasma clearance is 79 mL/min/ m² (2.2 mL/min/kg).
2F-ara-A elimination is mainly by renal excretion. About 40% to 60% of the administered intravenous dose was excreted in the urine. It is unknown whether the remaining percentage is absorbed or eliminated. Mass balance studies in laboratory animals with H3-F-ara-AMP showed a complete recovery of radiolabelled substances in the urine.
Oral fludarabine
With regard to oral fludarabine, pharmacokinetic studies in cancer patients confirm that single doses of oral fludarabine resulted in a dose-dependent increase in maximum plasma levels (Cmax) and AUC (0-24h).
Bioavailability of oral fludarabine is approximately 51-55% after single or multiple doses, with low intraindividual variation.
Systemic availability, Cmax and time to Cmax slightly increase (<10%) with concomitant food intake. Terminal half-life is unaffected.
These and other pharmacokinetic studies revealed that the daily administration of a 40 mg/m² dose has a similar effect to IV administration.
Pharmacokinetics in Special Populations
Renal Impairment
The total body clearance of the principal plasma metabolite 2F-ara-A shows a correlation with the creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the drug.
Patients with renal impairment demonstrated an increased exposure to 2F-ara-A according to AUC and a decreased clearance of 2F-ara-A, indicating the need for dose reduction. (See Dosage and Administration)
If renal impairment is clinically suspected, or in patients over 70 years old, creatinine clearance should be determined.
Hepatic Impairment
There are no available data concerning the pharmacokinetics of fludarabine in patients with hepatic impairment.
Elderly Patients
There are no pharmacokinetic studies in elderly patients.
Pediatric Patients
There are no pharmacokinetic studies in pediatric patients.

DOSAGE AND ADMINISTRATION
Fludarabina KEMEX lyophilized powder for injection
Instructions for Intravenous Use
FLUDARABINA KEMEX should be prepared for parenteral administration by adding, under aseptic conditions, sterile water for injection. When reconstituted with 2 mL of sterile water for injection, the lyophilized powder should fully dissolved in 15 seconds or less. Each mL of the resulting solution contains 25 mg of fludarabine phosphate, 25 mf of Mannitol, and sodium hydroxide to adjust pH to7.7. The pH range for the final product is 702-8.2. In clinical studies, the product has been diluted in 100 or 125 mL of 5% dextrose injection or 0.9% sodium chloride.
The preparation of FLUDARABINA KEMEX for intravenous use should not be mixed with other drugs. It contains no antimicrobial preservative and it should be used within 8 hours of reconstitution.
Extreme care should be taken to ensure sterility of infusion solutions.
All parenteral drugs should be inspected visually for particulate matter or discoloration before administration.
FLUDARABINA KEMEX should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents.
Handling and disposal
FLUDARABINA KEMEX should not be handled by pregnant women.
Procedures and measures for proper handling and disposal should be observed, in accordance with the guidelines used for cytotoxic drugs.
Any spillage or waste may be disposed of by incineration.
Caution should be exercised in the handling and preparation of FLUDARABINA KEMEX solution.
The use of latex gloves and safety goggles is recommended to avoid exposure in the case of breakage of any vial or accidental spillage. If the solution comes into contact with the skin or mucous membranes, the area should be washed thoroughly with soap and water. In the event of contact with the eyes, flush them thoroughly with water. Exposure by inhalation should also be avoided.
FLUDARABINA KEMEX should only be administered intravenously. No cases have been reported in which extravascular administration led of fludarabine phosphate led to severe local adverse reactions; however, unintentional extravascular administration should be avoided.
Local Tolerability
In accordance with the results obtained in animal studies after the IV administration of fludarabine phosphate, significant reactions of local irritation at the injection site are not to be expected. Even when injections were wrongly given, no significant local irritation was observed after the paravenous, intraarterial and intramuscular administration of an aqueous solution containing 7.5 mg of fludarabine phosphate/mL.
Adults
The recommended dose of FLUDARABINA KEMEX lyophilized powder for injection is 25 mg fludarabine phosphate/m² given daily for 5 consecutive days every 28 days by intravenous route. This is a course of treatment.
Each vial is dissolved with 2 mL of sterile water for injection. Each mL of the resulting solutions contains 25 mg of fludarabine phosphate (See Instructions for Intravenous Use).
The required dose (calculated on the basis of the patient's body surface) is drawn up into a syringe.
For IV bolus injection, this dose is further diluted with 10 mL of 0.9% sodium chloride.
Alternatively, the required dose drawn up into a syringe may be diluted in 100 mL of 0.9% sodium chloride and infused over approximately 30 minutes.
The duration of treatment depends on treatment success and tolerability of the drug.
In patients with CLL, FLUDARABINA KEMEX should be administered up to the achievement of a maximal response (complete or partial remission, generally 6 cycles) and then fludarabine should be discontinued.
In patients with low-grade non-Hodgkin lymphoma, FLUDARABINA KEMEX is also recommended up to the achievement of a maximal response (complete or partial remission). For better efficacy, 2 additional cycles of treatment should be considered. In clinical studies, most patients with low-grade non-Hodgkin lymphoma were treated during 8 cycles at the most.
Children: The safety and effectiveness of fludarabine in children has not been established.

CONTRAINDICATIONS
Hypersensitivity to fludarabine phosphate or any of its components.
Renal impairment with creatinine clearance <30 mL/min.
Hemolytic anemia.
Pregnancy and breastfeeding.

WARNINGS
See the WARNING table at the beginning of this insert.
Neurotoxicity
In dose-ranging studies in patients with acute leukemia, fludarabine phosphate at high doses was associated with severe neurologic effects including blindness, coma and death. These severe neurotoxic effects were observed in 36% of patients treated intravenously with 96 mg/m²/day for 5-7 days, a dose that is approximately four times greater than the recommended dose for the treatment of CLL and low-grade Non-Hodgkin lymphoma.
In patients treated at doses in the range of doses recommended for CLL or low-grade Non-Hodgkin lymphoma, these severe neurotoxicity events occurred rarely (coma, seizures and agitation) or uncommonly (confusion). Patients should be closely observed for signs of neurologic side effects.
The effect of chronic administration of fludarabine phosphate on the central nervous system is unknown. However, patients tolerated the recommended dose in some relatively long studies which describe up to 26 courses of treatment.
Impaired State of Health
In patients with impaired state of health, FLUDARABINA KEMEX should be administered cautiously, once the risk-benefit relation has been carefully assessed. This applies especially to patients with severe impairment of bone marrow function (thrombocytopenia, anemia and granulocytopenia), immunodeficiency or with other history of opportunistic infections.
Myelosuppression
Severe bone marrow suppression, especially with anemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate.
In a Phase I study in solid tumor patients, the mean time to nadir counts was 13 days (range 3-25 days) for granulocytes and 16 days (range 2-32 days) for platelets. Most patients had hematologic impairment at baseline, either due to disease or prior myelosuppressive therapy. Cumulative myelosuppression may be observed. Although chemotherapy-induced myelosuppression is reversible in many cases, fludarabine phosphate administration requires careful hematologic monitoring.
Fludarabine phosphate is a potent antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely monitored for possible signs of hematologic and non-hematologic toxicity. Regular assessment of peripheral blood counts is recommended to detect the development of anemia, neutropenia and thrombocytopenia.
Transfusion of Blood Products
Transfusion-associated graft-versus-host disease (reaction by the transfused immunocompetent lymphocytes to the host) has been reported after transfusion of non-irradiated blood in patients treated with fludarabine phosphate. Because fatal outcome as a consequence of this disease has been reported very frequently, patients who require transfusions and who are or have been treated with FLUDARABINA KEMEX should only received irradiated blood.
Skin Carcinoma
The worsening or flare up of preexisting skin carcinoma has been reported during or after fludarabine phosphate treatment.
Tumor Lysis Syndrome
Tumor lysis syndrome associated with fludarabine phosphate treatment has been reported in patients with large tumor burdens. Since fludarabine phosphate may induce a response in the first week of treatment, precautions should be taken in those patients who are at risk of developing this complication.
Autoimmune Phenomena
During or after fludarabine phosphate treatment, life-threatening and sometimes fatal autoimmune phenomena have been reported to occur (e.g. autoimmune hemolytic anemia, autoimmune thrombocytopenia, thrombocytopenic purpura, pemphigus, Evans' syndrome), irrespective of any history of autoimmune processes or Coombs test result. Most patients developed a recurrence in the hemolytic process when rechallenged with fludarabine phosphate.
Therefore, patients being treated with FLUDARABINA KEMEX should be carefully monitored for signs of autoimmune hemolytic anemia (decreased hemoglobin associated with hemolysis and positive Coombs test). In the case of hemolysis, discontinuation of therapy with FLUDARABINA KEMEX is recommended. For autoimmune hemolytic anemia, the most common treatment measures are irradiated blood transfusion (See Transfusion of Blood Products) and corticosteroids administration.
Contraception
Both women of childbearing potential and fertile men must take contraceptive measures during therapy with FLUDARABINA KEMEX and for 6 months after therapy.
Vaccination
The immunosuppressive properties of fludarabine phosphate impair the success of vaccination and reduce the value of skin tests. Due to the risk of infections, during and after treatment with FLUDARABINA KEMEX vaccination with live vaccines should be avoided.

PRECAUTIONS
Pregnancy
Fludarabine phosphate has been shown to be teratogenic and/or embryotoxic in animal studies
Preclinical studies in rats have demonstrated that fludarabine phosphate passes through the placental barrier.
A case of fludarabine phosphate use during early pregnancy leading to skeletal and cardiac malformations in the newborn has been reported.
FLUDARABINA KEMEX should not be used during pregnancy.
Women of childbearing potential should be advised to avoid becoming pregnant and to inform their treating physician immediately if this occurs.
Breastfeeding
It is unknown whether this drug is excreted in breast milk.
However, there is evidence from preclinical data that fludarabine phosphate and its metabolites transfer from maternal blood to milk. Therefore, breastfeeding should be interrupted during FLUDARABINA KEMEX therapy.
Use in Pediatrics
The safety and effectiveness of FLUDARABINA KEMEX in children have not been established.
Use in Geriatrics
Because there are limited data concerning the use of fludarabine phosphate in patients over 75 years old, caution should be exercised in the administration of this drug in these patients.
In patients over 70, creatinine clearance should be measured.
Renal and Hepatic Impairment
The total body clearance of the principal plasma metabolite 2F-ara-A shows a correlation with the creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the drug.
Patients with renal impairment demonstrated an increased total body exposure (AUC of 2F-ara-A). Limited clinical data are available in patients with impaired renal function (creatinine clearance below 70 mL/min).
Therefore, if renal impairment is clinically suspected, or in patients over 70 years old, creatinine clearance should be determined. If creatinine clearance is between 30 and 70 mL/min, dose should be reduced by up to 50%, and hematologic parameters should be carefully monitored to assess toxicity. FLUDARABINA KEMEX is contraindicated if creatinine clearance is <30 mL/min.
There are no available data concerning the use of fludarabine phosphate in patients with hepatic impairment. In these patients, FLUDARABINA KEMEX should be used with caution and administered if the expected benefit outweighs any potential risk.
Carcinogenesis, Mutagenesis and Impairment of Fertility
Fludarabine phosphate has shown to cause DNA damage in a sister chromatid exchange test, chromosomal aberrations in an in vitro cytogenetic assay, and to increase the micronucleus rate in the in vivo mouse micronucleus test. However, fludarabine phosphate has shown not to cause gene mutations and not to be mutagenic in the dominant lethal test in male mice. Thus, the mutagenic potential has been demonstrated in somatic cells but not in germ cells.
The presumption that this is a tumor-inducing substance is based on the known effect of fludarabine phosphate on DNA and mutagenicity studies. No animal study has been conducted specifically concerning the tumorigenicity issue, since the presumption of an increased risk of secondary tumors due to fludarabine phosphate treatment can be exclusively verified from epidemiological data.
Embryotoxicity
Embryotoxicity studies in animals have shown that fludarabine phosphate is potentially teratogenic. In view of the small exposure margin between teratogenic doses in animals and human therapeutic doses as well as in analogy to other antimetabolites which are assumed to interfere with the differentiation process, the therapeutic use of fludarabine phosphate is associated with a relevant risk of teratogenic effects in humans. (See Pregnancy and Breastfeeding)

DRUG INTERACTIONS
In a clinical study using fludarabine phosphate in combination with pentostain (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL), an unacceptably high incidence of fatal pulmonary toxicity was observed. Therefore, the use of FLUDARABINA KEMEX in combination with pentostatin is not recommended.
The therapeutic efficacy of FLUDARABINA KEMEX may be reduced by dipyridamole and other inhibitors of adenosine uptake.

ADVERSE EFFECTS
TOXIC REACTIONS
The most common adverse effects include myelosuppression (neutropenia, thrombocytopenia and anemia), fever and chill, and infection, including pneumonia. Other frequently reported effects are edema, malaise, fatigue, weakness, peripheral neuropathy, visual disorders, anorexia, nausea, vomiting, diarrhea, stomatitis, and skin rash.
The most frequently reported adverse effects and those reactions most clearly related to the drug will be described hereinafter on the basis of the affected system. Their frequencies (common > 1%, uncommon < 1% and > 0.1%) are based on data from clinical trials, irrespective of the causal relation with fludarabine phosphate. The rare adverse events (< 0.1%) were identified especially from post-marketing reports.
Body as a Whole
Fever, chills, infection, malaise, weakness and fatigue have been commonly reported.
Hematopoietic System
Hematologic events (neutropenia, thrombocytopenia and anemia) have been reported in most patients with CLL treated with fludarabine phosphate. Myelosuppression may be severe and cumulative. The prolonged effect of fludarabine phosphate on the decrease in T-lymphocytes may lead to an increased risk of opportunistic infections, including those due to latent viral reactivation, e.g. progressive multifocal leucoencephalopathy.
In rare instances the myelodysplastic syndrome has been reported in patients treated with fludarabine phosphate. Most of these patients also received previous, concomitant or subsequent alkylating or irradiation therapy.
Monotherapy with fludarabine phosphate has not been associated with an increased risk of developing myelodysplastic syndrome.
Clinically significant autoimmune phenomena have been rarely reported (See Warnings).
Metabolic and Nutritional Disorders
Tumor lysis syndrome has been reported in some patients with CLL treated with fludarabine phosphate. This syndrome may include hyperuricemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperkalemia, hematuria, (urate) crystalluria, and acute renal failure. The onset of this syndrome may be heralded by flank pain and hematuria.
Edema has been frequently reported.
Changes in hepatic and pancreatic enzyme levels are not common.
Nervous System
Coma, seizures and agitation have rarely occurred, and confusion was uncommon.
Peripheral neuropathy has been commonly observed.
Senses
Visual disturbances are commonly reported events. In rare instances, optic neuritis, optic neuropathy and blindness have been reported.
Respiratory System
Pneumonia is commonly reported. Pulmonary hypersensitivity reactions (pulmonary infiltrates/pneumonitis/fibrosis) associated with dyspnea and cough are uncommon.
Gastrointestinal System
Gastrointestinal disturbances such as nausea and vomiting, anorexia, diarrhea and stomatitis are common events. Gastrointestinal bleeding, mainly related to thrombocytopenia, is uncommon.
Cardiovascular System
Heart failure and arrhythmia have been rarely reported.
Urogenital System
Hemorrhagic cystitis has been rarely reported.
Skin and Appendages
Skin rush has been frequently reported. In rare cases Stevens-Johnson syndrome or toxic epidermal necrolysis (Lyell's syndrome) may develop.

ANTIDOTES AND ANTAGONISTS
There is no known antidote or antagonist.

OVERDOSAGE
Symptoms
High doses of fludarabine phosphate have been associated with an irreversible central nervous system toxicity characterized by delayed blindness, coma and death. In addition, high doses have also been associated with severe thrombocytopenia and neutropenia due to myelosuppression.
Treatment
There is no known specific antidote for fludarabine phosphate overdosage. Treatment consists in discontinuing the drug and providing supportive therapy.
In the event of an overdose attend the nearest hospital or contact the Center for Toxicology.
Hospital de Niños Ricardo Gutiérrez.
Mark 011 if you live in the interior
(011) 4821-6666
Sánchez de Bustamante 1399 Capital Federal.
Specialty for adults:
Hospital Posadas.
Mark 011 if you live in the interior
(011) 4654-6648

STORAGE
As a solid lyophilized powder stored in glass containers, FLUDARABINA KEMEX is stable for 24 months at refrigerator temperature of 2-8 °C. It is recommended to use FLUDARABINA KEMEX within 8 hours after reconstitution. FLUDARABINA KEMEX does not contain any antimicrobial preservatives. The necessary precaution must be observed to guarantee the sterility of the prepared solutions.

HOW SUPPLIED
FLUDARABINA KEMEX Lyophilized powder for injection 50 mg in cartons containing: 1 and 5 vials.

"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 55080
Laboratorio Kemex S.A.–Nazarre 3446– Capital federal (C1417DXH)
Technical Director: Dr. Natalia Alonso – Pharmacist
Made in Argentina

kemex laboratorio

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