CITARABINA KEMEX
CITARABINE (1-beta arabinofuranosyl cytosine)
Lyophilized Powder for Injection
Made in Argentina Under prescription only

Qualitative and Quantitative Formula:
Each vial contains:

CITARABINA KEMEX:	100 mg	500 mg	1 g	2 g
Cytarabine (1-Beta-arabinofuranosyl cytosine)	100 mg	500 mg	1 g	2 g

WARNING
Cytarabine lyophilized powder should only be used by experienced professionals in chemotherapy. Sufficient supportive resources should be available for monitoring drug tolerance and protecting and managing patients experiencing drug toxicity.
The main toxic effect of cytarabine is bone marrow suppression, leading to leukopenia, thrombocytopenia, and anemia. Less severe toxicities include nausea, vomiting, diarrhea, abdominal pain, oral ulceration, and hepatic dysfunction.

THERAPEUTIC ACTION
Antineoplastic.

PHARMACOLOGICAL ACTION
Mechanisms of Action
CITARABINA (Cytarabine) is a specific inhibitor of the S phase of the cell division cycle. Its activity occurs as a result of its activation to cytarabine triphosphate in tissues, and it includes inhibition of DNA synthesis with minimal effect on RNA and protein synthesis.
Other actions
It is a potent immunosuppressant.
Distribution
Only moderate amounts cross the blood-brain barrier with rapid intravenous administration, although concentrations in cerebrospinal fluid reach 40% to 50% of steady-state plasma concentrations after continuous intravenous infusion.
Protein binding: Low (15%)
Metabolism
Rapid deamination in blood and tissues, especially in the liver, but minimal deamination in cerebrospinal fluid (CSF).
Half-life: Varies among individuals and may be related to cytotoxicity.
Alpha phase: 10 to 15 minutes
Beta phase: 1 to 3 hours (around 2 hours after intrathecal administration)
Time to peak concentration: Subcutaneous: 20 to 60 minutes.
Renal elimination: Less than 10% unchanged.

INDICATIONS
*Treatment of acute lymphocytic and myelocytic leukemia
*Treatment of erythroleukemia
*Treatment of chronic myelocytic leukemia
*Treatment of Hodgkin and non-Hodgkin lymphoma
*Treatment of myelodysplastic syndrome

GENERAL INFORMATION ON DOSAGE
It is recommended to use induction therapy in a hospital setting under the supervision of a physician experienced in chemotherapy with antimetabolites. Intrathecal therapy should only be performed by a physician familiar with the procedure.
Various forms of administration are employed, either alone or in combination with other antitumor drugs.
The prescriber may consult medical literature and the manufacturer's information for specific dosage guidance:
*Dosage should be adjusted to meet the individual requirements of each patient, based on clinical response or degree of bone marrow depression.
*Dosage may need to be reduced in patients with renal or hepatic dysfunction, or those experiencing bone marrow depression.
*When administered by rapid intravenous injection, patients typically tolerate higher doses of CITARABINA (Cytarabine) with less hematologic depression compared to slow infusion, although nausea and vomiting may be more severe and persist for several hours after the injection.
*The occurrence of uric acid nephropathy in patients with leukemia or lymphoma can be prevented by adequate oral hydration and, in some cases, administering allopurinol. If serum uric acid concentrations increase, urine alkalization may be necessary.
*An induction regimen may be continued until a response or toxicity occurs, or until it becomes clear that the patient is unresponsive. Bone marrow improvement may take 7 to 64 days; treatment is halted when the bone marrow becomes hypocellular and resumed upon recovery.
*If leukocyte counts fall below 1,000 per cubic millimeter or platelet counts drop below 50,000 per cubic millimeter, therapy may need to be suspended until clear signs of bone marrow recovery appear. The lowest levels of leukocytes and platelets are typically reached after 5 to 7 medication-free days. Therapy can be resumed once adequate leukocyte and platelet levels are achieved.
*In acute leukemia, it can be administered despite the presence of thrombocytopenia and bleeding, as bleeding may cease and platelet counts increase during treatment.
Special caution is advised for patients who develop thrombocytopenia as a result of CITARABINA (Cytarabine) administration.
This may include: extreme care, regular inspection of intravenous puncture sites on the skin and mucous membrane surface for signs of bleeding or hematoma, limiting the frequency of venous punctures or intramuscular injections, urine, vomit, stool, and secretions examination for occult blood, caution in the use of toothbrushes, dental floss, toothpicks, safety razors, and nail clippers, avoiding constipation, and taking precautions to prevent falls and other injuries.
Such patients should avoid excessive alcohol intake and the ingestion of any formula containing acetylsalicylic acid due to the risk of gastrointestinal bleeding. Platelet transfusions may be necessary.
*Patients manifesting leukopenia should be carefully monitored for signs of infection. Antibiotics may need to be administered. In neutropenic patients who develop fever, empiric broad-spectrum antibiotic coverage should be initiated pending results of bacterial cultures and appropriate diagnostic tests.

Combination chemotherapy
It can be used in combination with other drugs in various regimens. Consequently, the incidence and/or severity of side effects may be altered, and different dosages (generally reduced) may be employed. For example, CITARABINA KEMEX is part of the following chemotherapy combinations:
Cytarabine + doxorubicin
Cytarabine + daunorubicin + prednisolone + mercaptopurine
Cytarabine + thioguanine
Cytarabine + thioguanine + daunorubicin
Cytarabine + doxorubicin + vincristine + prednisolone
Cytarabine + daunorubicin + thioguanine + prednisone + vincristine
Cytarabine + daunorubicin
For dosing and guidelines, please refer to the literature.
For information regarding each drug, consult the corresponding monograph.

PARENTERAL PHARMACEUTICAL FORMS
Usual dose for adults
Acute myelocytic leukemia or erythroleukemia
-Induction therapy: The usual dose of cytarabine in combination with other oncology drugs is 100 mg/m^2 of body surface area by continuous IV infusion for 1 to 7 days or 100 mg/m^2 IV every 12 hours (Days 1-7).
-Maintenance: Subcutaneous, 1 mg/kg of body weight 1 or 2 times per week.
Meningeal leukemia
Intrathecal, 5 to 75 mg/m^2 of body surface area at intervals ranging from once daily for 4 days to once every 4 days. A frequently used dosage is 30 mg/m^2 of body surface area once every 4 days until cerebrospinal fluid measurements are normal, followed by an additional dose.
Usual pediatric doses
See usual dose for adults.
Note: Safety in infants has not been established.

RECONSTITUTION FOR INTRAVENOUS USE
Preparation of the pharmaceutical form
It is reconstituted for intravenous or subcutaneous use by adding 5 ml of sterile water for injection to the 100 mg vial, resulting in a solution containing 20 mg of cytarabine per ml, or by adding 10 ml of sterile water for injection to the 500 mg vial, resulting in a solution containing 50 mg of cytarabine per ml.
The 1 g dose is reconstituted with 10 ml of sterile water for injection, resulting in a solution of 100 mg of cytarabine per ml.
The 2 g dose is reconstituted with 20 ml of sterile water for injection, resulting in a solution of 100 mg of cytarabine per ml.
Caution: It is recommended NOT to use diluents containing benzyl alcohol for the preparation of medications for use in neonates.
Its use has been associated with a potentially fatal toxic syndrome consisting of metabolic acidosis, central nervous system depression, respiratory problems, renal failure, hypotension, and possible seizures and intracranial hemorrhages.
Cytarabine solutions can be further diluted with sterile water for injection, 5% dextrose injection, or 0.98% sodium chloride injection for administration by intravenous infusion.
Do not use diluents containing benzyl alcohol for intrathecal use.

Guidelines for handling and disposal of CITARABINA.
There is growing concern and evidence suggesting that personnel involved in the preparation and administration of parenteral antineoplastic drugs may be at risk due to the potential teratogenicity, mutagenicity, and/or carcinogenicity of these drugs, although the actual risk is unknown.

* Use a biological safety cabinet during the reconstitution and dilution of the parenteral medication, and wear disposable gloves and masks.
* Employ proper techniques to prevent contamination of the medication, work area, and operator during the transfer from one container to another.
* Carefully and correctly dispose of needles, vials, ampoules, and unused medication.

PRECAUTIONS
Carcinogenicity
Secondary malignancies are possible long-term effects of many antineoplastic drugs, although it is unclear whether the effect is related to their mutagenic or immunosuppressive action. The dose and duration of treatment's effect are also unknown, although the risk appears to increase with long-term use. Although information is limited, available data suggests that the risk of carcinogenesis is higher with alkylating agents.
Antimetabolites have been shown to be carcinogenic in animals and may be associated with an increased risk of secondary carcinomas in humans, although the risk seems to be lower than with alkylating agents.
Mutagenicity
CITARABINA KEMEX can cause chromosomal abnormalities in humans.
Reproduction and Pregnancy:
Fertility
In patients undergoing antineoplastic therapy, especially with alkylating agents, gonadal suppression leading to amenorrhea or azoospermia may occur. These effects generally appear to be dose and duration-dependent and may be irreversible. Predicting the degree of testicular or ovarian dysfunction is complicated by the frequent use of combinations of various antineoplastic drugs, making it difficult to assess the effects of each drug separately. CITARABINA KEMEX has been associated with reversible toxicity in germ cells in humans.
Pregnancy
Although no studies have been conducted in humans, the risk-benefit relationship should be evaluated since CITARABINA KEMEX is teratogenic in rats and mice. Cases of trisomy, limb and ear malformation, and splenic malformation (specifically splenomegaly) have been reported in newborns whose mothers received CITARABINA KEMEX during pregnancy. Knowledge of several normal newborns whose mothers received treatment with Citarabine also exists.
First trimester: Avoidance of antineoplastic use, especially combination chemotherapy, is generally recommended during this period if possible. Although information is limited due to few examples of antineoplastic administration during pregnancy, the potential mutagenic, teratogenic, and carcinogenic risks of this medication should be considered in the risk-benefit assessment.
Other risks to the fetus include adverse reactions observed in adults.
Lactation
While very little information is available regarding excretion in breast milk, breastfeeding is not recommended while receiving treatment with CITARABINA KEMEX due to the risk to the infant.
Pediatrics
Although adequate and well-controlled studies have not been conducted in the pediatric population, the response to this medication is not expected to be affected in this age group.
Geriatrics
Although adequate and well-controlled studies have not been conducted in the pediatric population, it is not expected that the response to this medication will be affected at this age.
Dentistry
The bone marrow depressant effects can lead to increased microbial infections, delayed healing, and gingival bleeding. Dental work should ideally be completed before the start of therapy and continued once blood counts have returned to normal values. Patients should be instructed on proper oral hygiene and the careful use of toothbrushes, dental floss, and toothpicks. It may cause stomatitis, which can be associated with significant discomfort.

INTERACTIONS WITH MEDICATIONS AND/OR RELATED PROBLEMS
The following interactions have been selected on the basis of their potential clinical significance. Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication:
* Allopurinol or Colchicine or Probenecid or Sulfinpyrazone:
Cytarabine may increase the concentration of uric acid in the blood. It may be necessary to adjust the dosage of antigout medications to control hyperuricemia and gout.
* Cyclophosphamide:

Concurrent use of Cytarabine with Cyclophosphamide (at high-dose therapies) in the preparation of patients undergoing bone marrow transplantation has been reported to increase the risk of cardiomyopathy followed by death.
* Medications causing blood dyscrasias:
The leukopenic or thrombocytopenic effects of Cytarabine may be aggravated by concurrent use of other treatments that cause bone marrow depression. Dosage adjustment based on routine hematological monitoring is recommended.
* Methotrexate:
Administration of Cytarabine within 48 hours before or 10 minutes after the initiation of Methotrexate therapy may lead to synergism of cytotoxic effects. However, the evidence is not conclusive, and dosage adjustment based on routine hematological monitoring is recommended.
* Bone marrow depressants:
Radiation therapy (concurrent use may increase the bone marrow depressant effects of these medications and radiation therapy, dosage reduction may be necessary).
* Live virus vaccines:
Due to suppressed normal defense mechanisms, simultaneous use with live virus vaccines may enhance vaccine virus replication, increase vaccine side effects, and/or decrease patient antibody response to the vaccine. Immunization of these patients should be approached with caution after careful review of the patient's hematological status and only with the knowledge and consent of the physician overseeing the Cytarabine treatment.
The time interval between discontinuation of immunosuppressive medications and recovery of vaccine response capability depends on the intensity and type of immunosuppressive medication used, underlying disease, and other factors. It is estimated to range from 3 months to 1 year.
Patients with leukemia in remission should not receive live virus vaccines until at least 3 months after the last chemotherapy. In addition, immunization with oral poliovirus vaccines should be postponed in individuals in close contact with the patient, especially family members.

INTERFERENCES WITH DIAGNOSIS
With physiological values
Serum alkaline phosphatase concentrations
Serum aspartate aminotransferase (AST/SGOT) concentrations
Blood and urine uric acid concentrations (may increase)

CONTRAINDICATIONS
It should not be used when the following conditions exist:
- Existing or recent varicella (chickenpox)
- Herpes zoster (risk of severe disseminated disease). The risk-benefit ratio should be evaluated in the following clinical cases:
- Bone marrow depression, gout, history of kidney stones
- Liver dysfunction
- Infection
- Renal dysfunction
- Infiltration of tumor cells in the bone marrow
- Caution should also be exercised in patients who have previously received cytotoxic drug treatment or radiotherapy
- Patients who have shown previous hypersensitivity to cytarabine
Patient Monitoring
The following are of particular importance:
- Blood urea nitrogen (BUN)
- Hematocrit
- Platelet count
- Serum alanine aminotransferase (ALT/SGPT)
- Serum aspartate aminotransferase (AST/SGOT)
- Serum bilirubin
- Serum creatinine
- Serum lactate dehydrogenase (LDH)
- Uric acid
- Total and differential white blood cell count (determinations should be performed before initiating therapy and at periodic intervals during therapy, frequency varies according to clinical status, drug dosage, and other concurrently used medications)
- Bone marrow aspiration (recommended every 2 weeks until remission occurs)

ADVERSE EFFECTS
The incidence of adverse effects (except for nausea and vomiting) is higher with continuous intravenous administration than with rapid intravenous administration.
Acute pancreatitis has been reported in patients previously treated with asparaginase.
Brain dysfunction (confusion, fatigue, memory loss) Cerebellar dysfunction (speech problems, difficulty standing or walking, tremors).
Gastrointestinal ulcers (peritonitis)
Pulmonary edema
Liver damage with hyperbilirubinemia, intestinal necrosis, necrotizing colitis.
Skin rash and/or skin eruption leading to desquamation. Fatal cardiomyopathy.
Sudden respiratory distress syndrome progressing to pulmonary edema and cardiomegaly.
Peripheral sensory and motor neuropathies.
The following adverse effects have been selected based on their potential clinical significance:
*These indicate the need for medical attention:
- Very frequent incidence, occurring in 15 to 100% of patients.
Leukopenia or infection: (usually asymptomatic; less frequently, fever or chills, cough or hoarseness, side or back pain, pain or difficulty urinating).
Stomatitis: mouth ulcers and on the lips.
Thrombocytopenia: (usually asymptomatic, less frequently, unusual bleeding and bruising, constipation and black stools, blood in urine and stools, and petechiae).
Note: In leukopenia, the level of leukocytes declines in two initial phases within the first 24 hours, reaching a nadir on days 7 to 9, followed by a brief rise until day 12, and a profound drop with a nadir on days 15 to 24. Levels rapidly increase toward the baseline in the following 10 days.
With thrombocytopenia, platelet count notably decreases during the 5 days following the dose, reaching a nadir on days 12 to 15, and then gradually increases toward the baseline in the next 10 days.
-Less frequent incidence: Occurs in 10% or less of patients:
Central nervous system, cerebellar, or cerebral toxicity. In high-dose therapies, (numbness or tingling in hands, feet, or face, unusual fatigue).
Hyperuricemia or uric acid nephropathy (joint pain, lower back or side pain, swelling of feet or lower legs).
Note: Hyperuricemia or uric acid nephropathy commonly occur during the initial treatment of leukemia or lymphoma as a result of rapid cell breakdown, leading to elevated serum uric acid concentrations.
-Rare incidence: Occurs in 2% or less of patients: Cellulitis or thrombophlebitis: (pain at the injection site).
Drug reaction: bone or muscle pain, chest pain, fever, hypersensitivity or general discomfort or weakness, redness of the eyes, skin rash.
Esophagitis: (difficulty swallowing).
Gastrointestinal bleeding: (black and tarry stools).
Hepatotoxicity: (yellow eyes or skin).
Megaloblastic anemia: (fainting, irregular heartbeats, unusual fatigue, weakness).
Pulmonary edema or interstitial pneumonitis: (cough, difficulty breathing). Urinary retention: (decreased urination).
Note: Drug reaction generally occurs 6 to 12 hours after administration and can be prevented or managed with steroid treatment.
*These indicate the need for medical attention only if they persist or become bothersome:
-Very frequent incidence: Occurs in 15 to 100% of patients: Loss of appetite, nausea, and vomiting.
Note: Nausea and vomiting occur more frequently with large intravenous doses than with infiltration.
-Less frequent or rare incidence: Occurs in 10% or less of patients: Diarrhea, dizziness, headache.
*These do not indicate the need for medical attention:
-Less frequent or rare incidence:
Hair loss.
Note: Complete alopecia is more common with high-dose therapies.
These indicate the need for medical attention if they occur after discontinuation of the medication:
Bone marrow depression (black stools, blood in urine or stools), cough or hoarseness, fever or chills, back pain, pain while urinating and defecating, unusual bleeding.
Patient observations:
The patient should be advised regarding the following:
Proper use of medication.
Be cautious with combination therapy, take each medication at the right time. It is important to drink plenty of fluids to increase urine production and aid in the excretion of uric acid.
Nausea and vomiting are common side effects, but it is important to continue with the medication despite gastric discomfort.
Precautions during its use:
* Close monitoring of the patient by the physician is important.
* Avoid immunizations unless approved by the physician, including family members.
* Avoid contact with individuals with bacterial or viral infections, especially when blood count is low.

SIDE EFFECTS
It may cause blood-related problems, so it is important to discuss them with the doctor. The doctor, as well as the nurse, can assist in managing the effects. Hair loss is possible, but it will grow back after the treatment is completed.

STORAGE
Store between 15 - 30 °C and protected from light. After reconstitution, it is stable for 48 hours at room temperature and 7 days under refrigeration. Once diluted, it is stable for 7 days at room temperature and under refrigeration.

PRESENTATION
- CIRATABINA KEMEX 100 mg - 500 mg - 1 g - 2 g: Package containing 1 ampoule vial.
INCOMPATIBLE WITH FLUOROURACIL AND METHOTREXATE SOLUTIONS.

"This medication should be administered by prescription only and should not be repeated without a new medical prescription."
KEEP MEDICATIONS OUT OF REACH OF CHILDREN.

MEDICINAL SPECIALTY AUTHORIZED BY THE MINISTRY OF HEALTH
CERTIFICATE No. 49,179

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