PACKAGE LEAFLET

VINCRISTINE KEMEX
VINCRISTINE SULFATE 1 MG

Powder, lyophilized, solution for IV injection
INTRATHECAL ADMINISTRATION IS FATAL

MADE IN ARGENTINA **PRESCRIPTION ONLY MEDICINE**

QUALITATIVE AND QUANTITATIVE COMPOSITION

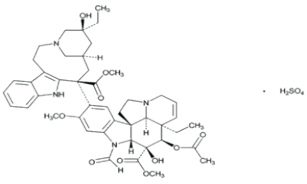
Each vial contains:
Vincristine Sulfate.....1 mg
Mannitol.....10 mg

THERAPEUTIC ACTION
Antineoplastic agent.

INDICATIONS
- Treatment of acute lymphocytic leukemia.
- Treatment of chronic lymphocytic leukemia, chronic myelocytic, for the treatment of acute and chronic lymphoblastic (lymphocytic) leukemia.
- Treatment of neuroblastoma and Wilms tumor.
- Treatment of breast carcinoma, lung carcinoma, ovarian carcinoma, cervical carcinoma, colorectal carcinoma.
- Treatment of Hodgkin's and non-Hodgkin's lymphomas and for the treatment of lymphosarcoma and reticular cell sarcoma.
- Treatment of rhabdomyosarcoma and Ewing's sarcoma.
- Treatment of osteosarcoma.
- Treatment of malignant melanoma.
- Treatment of multiple myeloma.
- Treatment of ovarian germ cell tumors.
- Treatment of mycosis fungoides.
- Treatment of true idiopathic thrombocytopenic purpura (ITP) resistant to the usual treatment of splenectomy and short-term treatment with adrenocorticoids.
- However, although it can raise the platelet count in patients with ITP, Vincristine is recommended only in severe hematological disorders.

PHARMACOLOGY/PHARMACOKINETICS
Physicochemical characteristics:
Origin: Vincristine is a vinca alkaloid.
Molecular weight: 923.4mg/mol
pKa: 5.1 and 7.5 in water.

FORMULA



MECHANISM OF ACTION
Vincristine acts by binding to tubulin and inhibiting the formation of microtubules. This inhibition causes mitosis to arrest at metaphase, through the disruption of mitotic spindle formation; it is cell-cycle specially during the M phase of cell division.
Distribution: Does not cross the blood-brain barrier in significant amounts.
Protein binding: high (75%), binds to various tissues.
Metabolism: hepatic.
Half-life: triphasic.
Alpha phase – 0.07 hours.
Beta phase – 2.27 hours.
Gamma phase – 85 hours.
Excretion: approximately 50% as metabolites.
Primary route: Biliary – about 67%.
Secondary pathway: Renal – about 12%.

DOSAGE
Do not remove cover until the time of injection. IF ADMINISTERED INTRATHECHALLY, CAUSES DEATH. FOR INTRAVENOUS USE ONLY.

Usual Dose for Adults: acute lymphocytic leukemia; neuroblastoma; Wilms tumor; breast, ovarian, cervical carcinoma, Hodgkin's disease and non-Hodgkin's lymphomas, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma, malignant melanoma, ovarian germ cell tumors, mycosis fungoides, idiopathic thrombocytopenic purpura: I.V. 10 to 30 µg (0.01 to 0.03 mg) per kg of body weight, or 400 µg (0.4 mg) to 1.4 mg/m² of body surface area per week as a single dose. A 50% dose reduction is recommended in patients with serum bilirubin concentrations above 3 mg per 100 ml.

Usual pediatric doses: acute lymphocytic leukemia, neuroblastoma, Wilms tumor, Hodgkin's disease and non-Hodgkin's lymphomas, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma, malignant melanoma, ovarian germ cell tumors, idiopathic thrombocytopenic purpura: I.V. 1.5 to 2 mg/m² of body surface once a week as a single dose. For children weighing 10 kg or less, the starting dose is 50 µg (0.05 mg) per kg of body weight I.V. 1 time per week. A 50% dose reduction is recommended in patients with serum bilirubin concentrations above 3 mg per 100 ml.

Preparation of the dosage form: Vincristine Kemex 1 mg powder, lyophilized solution for injection is prepared for IV administration by adding 1 ml of sterile water for injection to the 1 mg vial to produce a solution containing 1 mg Vincristine sulfate per ml.

Stability: The reconstituted solution, stored in the refrigerator, is stable for 14 days.

Incompatibilities: Vincristine Kemex 1 mg lyophilized injection should not be diluted in solutions that raise or lower the pH outside the range of 3.5 to 5.5. It should not be mixed in solutions other than 0.9% sodium chloride solution or 5% dextrose solution.

CONTRAINDICATIONS
Vincristine is an extremely toxic drug, with a very low therapeutic index, which means that therapeutic doses are likely to produce symptoms of toxicity. Therefore, this drug should only be used by professionals experienced in administering chemotherapy.
Vincristine produces a series of neurological problems that are aggravated if the patient has previously experienced a neurological condition. Patients with hereditary neurological problems, childhood poliomyelitis or Charcot-Marie-Tooth syndrome should not be treated with Vincristine.
On the other hand, elderly patients are more susceptible to the neurotoxic effects of Vincristine.
Vincristine can cause paralytic ileus, so its administration is contraindicated in patients with previous adynamic ileus.
Vincristine is metabolized by the liver and excreted in the bile. In the presence of any liver or biliary tract disease, doses should be reduced due to increased risk. Alkaline phosphatase elevations are associated with a higher incidence of neurotoxicity.
Although Vincristine rarely causes myelosuppression, it can cause leukopenia, which usually occurs within the first four days. This drug should not be given to patients undergoing radiation therapy, and patients with any active infection should be treated before receiving Vincristine. Patients with a history of varicella zoster, herpes infections, or other viral infections are at increased risk that the infection may reactivate.
Tumor lysis syndrome (hyperuricemia due to massive tumor cell destruction) may occur after Vincristine administration, therefore appropriate precautions (allopurinol treatment and massive hydration) should be taken to avoid hyperuricemia when treating large tumors. size. In these cases, gout or nephrolithiasis can be aggravated. In the treatment of breast cancer, hyperuricemia does not usually represent a problem, but in the case of leukemia, lymphoma or lung cancer, it is recommended to closely monitor the patient, monitoring uric acid levels.
The risk-benefit ratio should be considered when the following medical problems exist: varicella, declared or recent (including recent exposure), herpes zoster (risk of severe generalized disease), gout (or history), kidney stones (or history; risk of hyperuricemia), liver function impairment (dose reduction recommended), infection, leukopenia, neuromuscular disease, Vincristine sensitivity. Caution should also be exercised in patients who have previously received cytotoxic drugs or radiotherapy, and in those with neuromuscular problems who appear to be more susceptible to the neurological effects of Vincristine.

MONITORING.
The following determinations are especially important in patient follow-up (in some patients, other tests may be required, depending on their condition): hematocrit or hemoglobin, platelet count, total count, and, if appropriate, WBC differential (recommended determinations prior to initiation of therapy and at periodic intervals during therapy; frequency varies according to clinical status, agent, dose, and other agents being used concurrently). Serum alanine aminotransferase (ALT (GPT)) and serum aspartate aminotransferase (AST (GOT)), serum bilirubin, serum lactate dehydrogenase (LDH) (recommended measurements prior to initiation of therapy and at periodic intervals during therapy; frequency varies according to clinical status, agent, dose, and other agents being used concurrently). Serum uric acid (recommended determinations prior to initiation of therapy and at periodic intervals during therapy; frequency varies according to clinical status, agent, dose, and other agents being used concurrently).

WARNINGS
This preparation is for intravenous use only. This drug should be administered by individuals experienced in the administration of Vincristine. Usually the intrathecal administration of Vincristine ends in death. Syringes containing this product must be marked with the auxiliary label that states: INTRATECAL ADMINISTRATION IS FATAL. USE ONLY INTRAVENOUSLY.
Extemporaneous preparation syringes containing this product must be packed in a special wrapping paper that is labeled and indicates: DO NOT REMOVE COVER UNTIL TIME OF INJECTION. INTRATECAL ADMINISTRATION IS FATAL. USE ONLY INTRAVENOUSLY.

1. Treatment of patients after intrathecal administration of Vincristine included immediate removal of spinal fluid and leveling with Ringer's lactose, as with other solutions, and did not prevent ascending paralysis and death. In one case progressive paralysis was arrested in an adult with the following treatment, started immediately after intrathecal injection.As much spinal fluid as can be safely removed through the lumbar access was removed.
2. The subarachnoid space was leveled with Ringer's lactose solution administered continuously through a catheter in the lateral cerebral ventricle at a rate of 150 ml/hour. The fluid was removed through the lumbar access.
3. As soon as frozen plasma was available, 25 ml of it was diluted in 1 l of Ringer's Lactose solution which was administered via a catheter inserted into the lateral cerebral ventricle at a flow rate of 75 ml per hour. The value of the infusion was adjusted to maintain the protein level of 150 mg/dl in the spinal fluid.
4. A 10 g dose of glutamic acid was administered intravenously over 24 hours and then 500 mg three times daily by mouth for one month or until neurological dysfunction stabilized.

The role of glutamic acid in this treatment is uncertain and its use may not be essential.
Pregnancy Category D. Vincristine can cause fetal harm when administered to a pregnant woman. When Vincristine was administered to pregnant rats and hamsters it caused resorption in 23% to 85% of fetuses.
Five monkeys received single doses of Vincristine between days 27 and 34 of their pregnancies, 3 of the fetuses were born normal and 2 of them presented serious and evident malformations. In various animal species Vincristine can induce teratogenesis, as well as death of embryos. There are no well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while receiving it, the potential risk to the fetus should be considered. Women who are likely to become pregnant should be advised to avoid pregnancy.

PRECAUTIONS
Carcinogenicity/Mutagenicity
Secondary diseases are potential delayed effects of many antineoplastic agents, although it is not clear whether these effects are related to their mutagenic or immunosuppressive action. The effect of dose and duration of therapy is also unknown; however, the

risk appears to increase with long-term treatment. Although the information is limited, the available data seem to indicate that the carcinogenic risk is greater with alkylating agents.
Vincristine is associated with an increased risk of developing secondary carcinomas in humans.

Pregnancy/Reproduction
Fertility: In patients receiving antineoplastic therapy, especially with alkylating agents, gonadal suppression may occur resulting in amenorrhea or azoospermia. In general, these effects appear to be related to the dose and duration of therapy and may be irreversible. Predicting the degree of deterioration in testicular or ovarian function is complicated by combination therapy with multiple antineoplastic agents, making it difficult to ascribe effects to individual agents.

Pregnancy: Adequate and well-controlled studies in humans have not been conducted. However, animal studies have shown that Vincristine causes fetal resorption, fetal malformations, and embryonic death, even at doses that are not lethal to the pregnant animal.

First trimester: It is generally recommended that the use of antineoplastics, especially in combination with other drugs, be avoided, when possible, particularly during the first trimester. Although the information is limited, due to the relatively few references to the administration of antineoplastic drugs during pregnancy, the potential mutagenic, teratogenic and carcinogenic effect of these drugs should be considered.
Other hazards to the fetus include adverse reactions seen in adults. In general, the use of contraception is recommended during therapy with cytotoxic drugs.

Lactation: Although very little information is available regarding the excretion of antineoplastic agents in breast milk, due to possible risks to the baby (adverse effects, mutagenicity, carcinogenicity), it is recommended not to breastfeed while Vincristine is being administered. . It is not known whether Vincristine is excreted in breast milk.

Pediatric: Studies to date have not shown pediatric-specific problems that would preclude the use of Vincristine in children.

Geriatric: Although no adequate studies have been conducted in the geriatric population, elderly patients appear to be more susceptible to neurotoxic effects.

Alteration of laboratory values: The following have been selected based on their potential clinical significance.

Physiology / laboratory tests: the concentration of uric acid in the blood and urine may be increased

ADVERSE REACTIONS
Some side effects of antineoplastic therapy are irremediable and represent the pharmacological action of the drug. Some of these (for example, leukopenia and thrombocytopenia) are currently used as indicators of medication effectiveness and facilitate individual dosage titration.
The incidence of side effects is generally dose related and appears to be less at doses below 0.05 mg per kg of body weight per week.
The following side effects/adverse effects have been selected based on their potential clinical significance.

Effects Needing Medical Attention:
Most common effects: autonomic toxicity (constipation, stomach cramps; less commonly, bedwetting, decreased or increased urination, dizziness or dizziness when rising from a lying to sitting position, lack of perspiration, difficult or painful urination). Hyperuricemia or uric acid neuropathy (joint pain, lower back or flank pain; occurs most often during initial treatment of patients with leukemia or lymphoma, as a result of rapid cell destruction leading to elevated uric acid levels). elevated serum). Progressive neurotoxicity (blurred or difficult vision, difficulty walking, drooping eyelids, headache, jaw pain, numbness or tingling in fingers and toes, pain in fingers and toes, pain in the testicles, weakness); it develops after 2 months of treatment and may persist for several days to several months.

Less frequent effects: central nervous system (CNS) toxicity. Hyponatremia or syndrome of inappropriate antidiuretic hormone secretion (SIADH) (agitation, confusion, dizziness, hallucinations, loss of appetite, mental depression, seizures, sleep problems, unconsciousness); extravasation or cellulitis (pain or redness at the injection site).

Rare effects: Leukopenia (usually asymptomatic; rarely, fever or chills, cough or hoarseness, lower back or side pain, painful or difficult urination). Thrombocytopenia (usually asymptomatic; rarely, unusual bleeding or bruising, black-tarry stools, blood in stool and urine, petechiae). Stomatitis (ulcers in the mouth and lips).
NOTE: Leukopenia is usually maximal within 4 days. Although thrombocytopenia is possible, the platelet count varies little and may actually increase in some patients.

Effects that need medical attention only if they continue or are bothersome:
Less frequent effects: swelling, diarrhea, weight loss, nausea and vomiting, skin rash.

Effects Not Needing Medical Attention:
Most frequent effects: hair loss (can be recovered after treatment has ended and possibly during therapy.

OVERDOSE
The adverse effects produced by the use of Vincristine and are related to the dose. Following administration of 10 times the recommended dose to a group of children under 13 years of age, death occurred. In this group of patients, following doses of 3 to 4 mg/m², severe symptoms may appear. Adults may manifest severe symptoms after administration of single doses of 3 mg/m² or more.
Administrations of doses greater than those recommended may manifest exaggerated adverse effects.
Supportive care should include:
1. Prevention of side effects related to inappropriate antidiuretic hormone secretion. Preventive treatment may include fluid restriction and perhaps administration of a diuretic that affects the function of the Loop of Henle and the distal tubule.
2. The administration of anticonvulsants.
3. The use of enemas and cathartics may be necessary in the ileus (decompression of the intestinal tract may be necessary in some instances).
4. Monitoring of the cardiovascular system.
5. Determine daily blood counts to resort to a transfusion if necessary.

In the event of an overdose, go to the nearest hospital or contact the poison centers:
Hospital de Niños Dr. Ricardo Gutiérrez: Phone #.: (011) 4962-9247/9248/9212
Hospital Dr. Juan P. Garrahan: Phone #: (011) 4941-6191/6012
Hospital Dr. Juan A. Fernández: Phone #: (011) 4808-2600/2650
Hospital Dr. A. Posadas Phone #: (011) 4469-9200/9300
La Plata: Cátedra de Farmacologia, Facultad de Ciencias Médicas, Universidad Nacional de la Plata: Phone #: (0121) 440117
Rosario: Cátedra de Farmacologia, Facultad de Ciencias Médicas, Universidad Nacional de Rosario: Phone #: (0341) 460077
Córdoba: Subsecretaría de Programación Sanitaria, Ministerio de Salud de la Pcia. de Córdoba: Phone #: (0351) 4604351

INTERACTION WITH OTHER DRUGS.
Drug Interaction and/or Related Problems: The following drug interaction and/or related problems have been selected based on their potential clinical significance. Combinations containing any of the following drugs, depending on the amount present, may also interact with this drug:
- Allopurinol, colchicine, probenecid, sulfinpyrazone: vincristine can raise the concentration of uric acid in the blood, it may be necessary to adjust the doses of antigout agents to control hyperuricemia and gout; Allopurinol is preferred to prevent or reverse vincristine-induced hyperuricemia because of the risk of uric acid nephropathy with uricosuric antigout agents.
- Asparaginase: its joint use can produce additive neurotoxicity; if vincristine is used in conjunction with asparaginase, toxicity appears to be less pronounced when asparaginase is given after vincristine, rather than before or at the same time.
- Bleomycin: the sequential administration of vincristine before bleomycin stops the cells in mitosis, so that they are more susceptible to bleomycin; it is often used for therapeutic advantage.
- Blood dyscrasia (caused by drugs): the leukopenic and/or thrombocytopenic effects of vincristine may be increased with concurrent use or recent therapy if these drugs cause the same effects; dose adjustment of vincristine, if necessary, should be based on blood counts.
- Other bone marrow depressants or radiotherapy: simultaneous use can increase the bone marrow depressant effects of these drugs and radiotherapy; although the myelosuppressive effects of vincristine are modest.
- Doxorubicin: the joint use with vincristine and prednisone can increase the myelosuppressive effects, it is recommended to avoid their combination.
- Other neurotoxic drugs, or spinal cord irradiation: joint use can produce additive neurotoxicity.
- Killed Virus Vaccines: Because normal defense mechanisms may be suppressed by vincristine therapy, the patient's antibody response to the vaccine may be diminished. The interval between discontinuation of immunosuppressive drugs and recovery of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppressive drug used, the underlying disease, and other factors; and it is estimated that it varies between 3 months and 1 year.
- Live virus vaccines: because the normal defense mechanisms may be suppressed by vincristine therapy, concurrent use with a live virus vaccine may enhance the replication of the vaccine virus, may increase the side effects / adverse effects of the vaccine virus, and/or may decrease the patient's antibody response to the vaccine; immunization of these patients should be undertaken only with extreme caution after careful review of the patient's hematologic status and only with the knowledge and consent of the physician in charge of vincristine therapy. The interval between discontinuation of immunosuppressive drugs and recovery of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppressive drug used, the underlying disease, and other factors; and it is estimated that it varies between 3 months and 1 year. Patients with leukemia in remission should not receive live virus vaccines until at least 3 months after their last chemotherapy. Immunization with oral poliovirus vaccine should be delayed in persons in close contact with the patient, especially family members.

PHARMACEUTICAL FORM
Package containing 1 vial, 10 ml

STORAGE CONDITIONS: Keep this product in a refrigerator (2 °C to 8 °C) and protected from light.

KEEP OUT OF THE REACH OF CHILDREN.

"THIS MEDICINE MUST BE USED EXCLUSIVELY UNDER PRESCRIPTION AND CANNOT BE REPEATED WITHOUT A NEW PRESCRIPTION."

Medicinal specialty authorized by the Ministry of Health (ANMAT).
Certificate No. 56,972
Technical Director: Natalia Alonso – Pharmacist.
Laboratory Kemex S.A. – Nazarre 3446/54 - (C1417DXH) –City of Buenos Aires. Argentina.
Phone number: 011-4138-1000
farmacovigilancia@kemexlab.com
www.kemexlab.com

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