PRODUCT MONOGRAPH

PrKIDROLASE®
(L-asparaginase)

Powder for Solution 10,000 IU/Vial

Antileukemic Agent

EUSA Pharma SAS
69760 Limonest
France

Control No. 120402

Canadian Distributor:
CGF Pharmatec
3516 Griffith
Montreal, Québec H4T 1A7

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PART I: HEALTH PROFESSIONAL INFORMATION

PrKIDROLASE®
(L-asparaginase)

SUMMARY PRODUCT INFORMATION

<table>
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<th>Route of Administration</th>
<th>Dosage Form/Strength</th>
<th>Clinically Relevant Nonmedicinal Ingredients</th>
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<td>Intramuscular or intravenous infusion (see Dosage and Administration)</td>
<td>10 000 International Units per vial</td>
<td>Glycine and sodium hydroxide</td>
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INDICATIONS AND CLINICAL USE

KIDROLASE® (L-asparaginase) is indicated mainly to induce remissions in acute lymphoblastic leukemia. Remissions have also been obtained in cases of acute myeloblastic and acute myelomonocytic leukemia although these forms are less sensitive to the action of the enzyme. Favorable results have sometimes been obtained with L-asparaginase in certain cases of lymphosarcoma, reticulosarcoma, Hodgkin's disease, chronic lymphocytic leukemia and melanosarcoma.

CONTRAINDICATIONS

Patients with known hypersensitivity to L-asparaginase or to any of the constituents of KIDROLASE®; a hypersensitivity reaction occurring during therapy contraindicates the continuation of treatment.

Patients with hepatic insufficiency, pancreatitis.
Pregnant or lactating women: L-asparaginase has been shown in animals to possess embryotoxic and teratogenic activity; therefore, it should not be used in pregnant patients or lactating women.

Patients who have recently been vaccinated against yellow fever.

Patients who are taking phenytoin (see DRUG INTERACTIONS)

**WARNINGS AND PRECAUTIONS**

<table>
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<tr>
<th>WARNING</th>
<th>ALLERGIC REACTIONS MAY OCCUR DURING THERAPY WITH KIDROLASE® (L-ASPARAGINASE), ESPECIALLY IN PATIENTS WITH KNOWN HYPERSENSITIVITY TO THE OTHER FORMS OF L-ASPARAGINASE.</th>
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<tr>
<td>WARNING</td>
<td>IN VIEW OF THE UNPREDICTABILITY OF ADVERSE REACTIONS, KIDROLASE® SHOULD BE USED BY PHYSICIANS EXPERIENCED IN CANCER CHEMOTHERAPEUTIC AGENTS ONLY IN A SETTING WHERE FULL RESUSCITATION FACILITIES ARE IMMEDIATELY AVAILABLE.</td>
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<tr>
<td>WARNING</td>
<td>KIDROLASE® HAS AN ADVERSE EFFECT ON LIVER FUNCTION IN SOME PATIENTS. THERAPY WITH KIDROLASE® MAY INCREASE PRE-EXISTING LIVER IMPAIRMENT CAUSED BY PRIOR THERAPY OR UNDERLYING DISEASE. IN THE TREATMENT OF EACH PATIENT, THE PHYSICIAN MUST WEIGH CAREFULLY THE POSSIBILITY OF ACHIEVING THERAPEUTIC BENEFIT VERSUS THE RISK OF TOXICITY.</td>
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**General**

KIDROLASE® (L-asparaginase) may be used for maintenance or reinduction treatment; however, if a relapse occurs during maintenance treatment with KIDROLASE®, reinduction should be attempted with another agent.

L-asparaginase may induce allergic reactions. Since the intradermal test is unreliable in detecting the sensitivity of the patients - reactions have been observed after a negative intradermal test and vice-versa - and these reactions regress rapidly with I.V. corticotherapy, it is advisable to administer corticosteroids for a day or 2 before initiating reinduction treatment. Furthermore, at the time of injection, the appropriate material required to treat anaphylactic shock should be readily available.
When intermittent administration has been used, anaphylactic reactions L-asparaginase were 3 times more frequent when administered I.V. than when injected I.M. Consequently, the I.M. route is recommended for intermittent administration. (See Dosage and Administration).

At the beginning of treatment, monitoring of blood uricemia should be performed and, if necessary, allopurinol should be administered for as long as required.

Hepatic function tests and blood counts should be monitored regularly during therapy.

**Endocrine and Metabolism**
Treatment with KIDROLASE® may exacerbate diabetes mellitus. Hyperglycemia has been observed in a number of patients; therefore, glycemia should receive particular attention during treatment, especially in patients with uncontrolled diabetes.

Amylasemia should also be monitored throughout treatment. Treatment should be discontinued in case of an increase in amylasemia levels.

**Hematologic**
Cerebral thrombosis and hemorrhage have been observed in patients treated with KIDROLASE®. In some of these patients, events may have been attributable to coagulation disorders such as increases in Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT), hypofibrinogenemia, decreases in antithrombin III, plasminogen and other coagulation factors (VII, IX, X, VIII).

Blood clotting tests (aPTT, KPTT, Fibrinogen and AT III levels) should be carried out before treatment and before each injection of KIDROLASE® (L-asparaginase). Replacement therapy should be instituted if fibrinogen is less than 1g/L or ATIII less than 60%. If fibrinogen and AT III cannot be increased, treatment should preferably be suspended and resumed only when the laboratory parameters have returned to normal.
Neurologic
Cerebral thrombosis has been observed in patients treated with KIDROLASE® (see above under Hematologic).

Special Populations
Pregnant Women – See Contraindications
Nursing Women – See Contraindications

Monitoring and Laboratory Tests – see General and Hematologic

ADVERSE REACTIONS
Clinical trials with KIDROLASE® (L-asparaginase) were conducted prior to 1970, and some patient subpopulations participating in those trials might have differed from the patients for whom KIDROLASE® is used today. Furthermore, some of the concomitant chemotherapeutics would have been different than would be administered to those patients today, and the survival rates would have been very different for some of the subpopulations of patients in the clinical trials that were conducted. All of these factors would have an influence upon the adverse event profile. Therefore, the adverse reaction profile observed in those studies might have differed from what would be observed now in any recent clinical trial, including the frequencies of these adverse events. However, the following information represents the best possible understanding of the Adverse Reactions that have been observed during 35 years of clinical experience with KIDROLASE®.

Hypersensitivity reactions are the most frequent and may include urticaria, laryngeal oedema, bronchospasm, hypotension or even true anaphylactic shock. If these reactions occur, discontinue treatment immediately (see Contraindications).

Side effects of a clinical or biological nature observed in the course of clinical trials with L-asparaginase can be classified as follows:
- Hypersensitivity reactions
Within one-half to one hour following the injection of L-asparaginase, cases of hypersensitivity reactions have been observed. These consisted of cutaneous manifestations, oedema or, in a small number of patients, an anaphylactic reaction. The latter can be seen after the first injection but it occurs mainly between the 5th and the 9th administration.

- Digestive problems
  Nausea and vomiting generally appear at the beginning of treatment. It may be due directly to the drug itself or be secondary to elevation of BUN and blood uric acid. These side effects are rather frequent but rarely severe enough to necessitate withdrawal of treatment.
  Diarrhea and abdominal pain have been observed infrequently but the precise cause is unknown.
  In rare instances, intestinal perforation has occurred although it has been impossible to establish the exact relationship with L-asparaginase.

- Disturbances of hepatic function
  Abnormalities of hepatic function are quite frequent and may, in some cases, even warrant interruption of treatment. Most characteristics are the following: hypocholesterolemia, hypoalbuminemia, increase of alkaline phosphatase and ALT (SGOT) levels. A weak elevation of the AST (SGPT) and an increase in beta and gammaglobulins shown by protein electrophoresis have also been noted. Cholestatic or hepatocellular liver injury with or without steatosis has also been reported. However, while L-asparaginase hepatotoxicity is in most cases mild and regressive, it can in rare instances induce jaundice which may be severe enough to cause death in those patients who are often in rather poor general condition.
  To prevent these side effects, it is recommended that hepatic function tests be performed at least once a week during L-asparaginase therapy and that the treatment be stopped should any significant changes occur.
  Furthermore, before attempting reinduction with KIDROLASE®, hepatic function should be checked to avoid giving L-asparaginase to a patient already showing abnormal values.

- Inhibition of protein synthesis and Metabolic disturbances
  - clotting disorders including increases in Prothrombin Time (PT) and
Thromboplastin Time with hypofibrinogenemia, decreases in antithrombin III, plasminogen and other factors (VII, IX, X and VIII) leading to possible bleeding and thrombotic complications. In consideration of coagulation changes during L-asparaginase treatment, hemostatic function should be checked periodically.

- hypoalbuminemia;
- decrease in serum insulin with hyperglycemia;
- hypertriglyceridemia and hypercholesterolemia;
- hyperammoniemia, sometimes associated with clinical signs of metabolic encephalopathy such as consciousness disorders with confusion, stupor or coma, resulting from excessive ammonia production induced by the action of KIDROLOUS® on endogenous asparagin and glutamine.

- Hematologic risks

Bone marrow aplasia is exceptional with L-asparaginase and its hematological toxicity is not increased by its association with other antileukemic drugs; nevertheless, the usual blood and bone marrow determinations should be done.

- Other side effects

- in rare instances, central nervous system disturbances appearing mostly in adults and consisting of mild depression associated with personality disorders, disorientation, delusion, convulsions and pseudo-parkinsonism;
- renal failure;
- septicemia during a period of bone marrow aplasia;
- fever due either to the disease itself or to the treatment;
- less frequently, weight loss, hyperglycemia, acute pancreatitis including fatalities and respiratory distress with retrosternal pressure;
- cerebral thrombosis;
- amenorrhea, azoospermia.

**DRUG INTERACTIONS**

**Drug-Drug Interactions**

*Interactions common to all cytotoxic agents:* Due to the increased risk of thrombosis in tumoral diseases, anticoagulant treatment is frequently administered. If oral
anticoagulants are given, the high within-patient variability of coagulability in the course of the disease and the potential interaction between oral anticoagulants and anticancer chemotherapy require that INR (or PT) testing be done frequently.

**Contra-indicated:**
- **Yellow fever vaccine** because of the risk of lethal systemic vaccine disease.
- **Phenytoin, fosphenytoin:** Risk of convulsions induced by the decrease in the digestive uptake of phenytoin by cytotoxic agents or risk of increased toxicity or diminished efficacy of cytotoxic agents due to the induction of its liver metabolism.

**Associations to be avoided:**
- **Attenuated live vaccines** (other than Yellow fever vaccine) because of the risk of fatal disseminated disease. This is even more likely to occur in subjects already immunocompromised by their disease. Use an inactivated vaccine when available (i.e. poliomyelitis vaccine).

**Associations to be used with precaution:**
- **Phenytoin** (when used prior to chemotherapy): in patients already receiving phenytoin, consideration should be given to temporarily associate an anticonvulsant benzodiazepine to avoid the risk of convulsions caused by the decrease in digestive uptake of phenytoin induced by cytotoxic agents.
- **Immunosuppressants** such as cyclosporin, tacrolimus or sirolimus could cause excessive immunodepression with risk of lymphoproliferation.

**Drug-Food Interactions and Drug-Herb Interactions** have not been studied

**Drug-Laboratory Interactions**
None have been observed

**DOSAGE AND ADMINISTRATION**

Administer KIDROLASE® (L-asparaginase) either intramuscularly, or intravenously into the tubing of a running infusion of an isotonic glucose solution or of normal saline which does not contain a preservative.

Dissolve the enzyme with 4 mL of sterile water for injection (per vial of 10,000 International Units). Rotate gently, do not shake.
- **Daily administration**
  Daily administration is the most usual method and the least likely to cause side effects. The dosage varies from 200 to 1,000 I.U. per kg per day for 28 consecutive days. After this period, if complete remission is obtained, maintenance therapy is instituted, otherwise induction treatment is continued for another 14 days.

- **Intermittent administration**
  L-asparaginase may also be administered intermittently with 3 injections per week for 4 weeks using the following dosage schedule:

  - 400 I.U./kg on Monday and Wednesday,
  - 600 I.U./kg on Friday.

  After this period, maintenance therapy is instituted if complete remission is obtained; otherwise, the treatment is continued for another 14 days.

  When intermittent administration has been used, anaphylactic reactions with L-asparaginase were 3 times more frequent when administered I.V. than when injected I.M. Consequently, the I.M. route is recommended for intermittent administration.

- **Polychemotherapy**
  When L-asparaginase is used in association with other antileukemic drugs, full doses, as stated above, should be administered.

  N.B.- The choice of dose and method of administration is made according to the particular circumstances governing each case.
OVERDOSAGE

Two cases of accidental overdosage were reported where children received an injection representing 10 times the normal daily dose. No clinical signs were observed but, in one case, there was an increase in aspartic and glutamic acid plasma levels.

Patients who receive accidentally an overdose of L-asparaginase should be monitored closely for hyperammoniaemia and, if present, receive appropriate corrective treatment.

ACTION AND CLINICAL PHARMACOLOGY

L-asparaginase exerts an antitumor activity which is directly related to its catalytic action upon the hydrolysis of the extracellular L-asparagine into L-aspartic acid and ammonia. This action is exerted on certain neoblastic cells which are unable to synthesize the L-asparagine needed for their own growth and which must rely upon the extracellular L-asparagine supply to assure their development.

At high dosages, L-asparaginase also shows a marked immunosuppressive effect which has been measured in various in vivo and in vitro tests. Both cell mediated and humoral immunities are affected by this inhibitory effect.

STORAGE AND STABILITY

The product, in powder form, in unopened vials, is stable for up to 24 months at 2 °C to 8 °C.

KIDROLASE® (L-asparaginase) contains no preservative. Reconstitution should be done under strict aseptic conditions. Reconstituted product when not refrigerated should be used immediately (within 3 hours). If not and storage is required, keep refrigerated (2 °C to 8 °C) and use within 72 hours.
DOSAGE FORMS, COMPOSITION AND PACKAGING

Vials of 10,000 International Units.

Non-medicinal ingredients: glycine and sodium hydroxide.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

L-asparaginase or L-asparagine-amido-hydrolase EC 3.5.1.1. type EC 2, a protein of undetermined constitution, is an enzyme isolated from Escherichia coli.

Its molecular weight is approximately 139,000; it is a white, or almost white, slightly hygroscopic powder which is practically insoluble in methanol, acetone, ether and chloroform but soluble in water. Enzymatic titration shows that L-asparaginase has an activity of approximately 200 units/mg.

DETAILED PHARMACOLOGY

- General Pharmacology
  L-asparaginase does not have any apparent effect on the principal body functions. In the pentobarbital anesthetized dog, L-asparaginase, at a dose of 5,000 U/kg I.V. produces no effect on the ECG, the cardiac rhythm, the blood pressure, the respiratory system or the autonomic nervous system.

  In addition, 5 injections (2-1/2 days apart) of 12,000 U/kg I.V. failed to produce any significant changes in the thromboelastogram and thrombocyte count in the mouse.

- Antitumor activity
  The activity of L-asparaginase has been tested on various tumors, lymphosarcomas and leukemias of animals. One study carried out on 109 leukemias in the mouse revealed that X-ray-induced and spontaneous leukemias are especially responsive to L-asparaginase while those which are viral-induced or caused by chemical agents, are only slightly or not responsive at all.
In addition, experiments with 2 sensitive tumor systems, EARAD-1 leukemia and C57B1/Rho leucosarcomatosis, have demonstrated that the effect of L-asparaginase varies with the number of grafted tumor cells.

Furthermore, in EARAD-1 leukemia, it has been shown that the antitumor activity of the enzyme depends on the dose injected, but that it is not influenced by the parenteral route used.

- **Immunosuppressive activity**
  In several in vivo and in vitro tests, L-asparaginase exerts a marked inhibitory effect on the manifestations of humoral immunity (antibody production) and of cellular immunity (blast transformation of lymphocytes). In certain other immunological reactions where the participation of both immunological systems is possible, the action of L-asparaginase varies; it does not prolong the survival time of a skin homograft in the mouse but seems to impede the rejection of a non-histocompatible leukemia. It has a marked inhibiting effect in the rat on 2 pathologies which strongly resemble auto-immune diseases: adjuvant-induced arthritis and experimental allergic encephalomyelitis.

- **Antiviral activity**
  L-asparaginase has been shown to exert an antiviral effect on 3 DNA viruses: vaccina virus, myxoma virus and Herpes simplex. This effect seems to be associated with an action of the enzyme on a cellular reactions requiring L-asparagine and essential to the replication of the DNA molecule.

**TOXICOLOGY**

- **Acute Toxicity**
  The acute toxicity of L-asparaginase in the mouse and in the rat when administered by the I.V. route is rather low, the LD_{50} in both species being above 200,000 U/kg; in the cat and the dog, the LD_{50} is in the range of 50,000 U/kg while in the rabbit, the LD_{50} of the enzyme is about 800 U/kg. The greater toxicity of L-asparaginase in the
rabbit is probably due to a greater dependency of this species on L-asparaginase rather than to a toxic effect of the enzyme.

- **Subacute Toxicity**
  In the mouse, the subacute LD$_{50}$ of L-asparaginase administered by the I.V. route for 5 consecutive days is approximately 300,000 U/kg I.V. per day. At a daily dose of 25,000 U/kg I.V., the animals became emaciated, but this more or less normalized after treatment was stopped. Two subacute toxicity studies have been done in the rat. In the first of these, daily dosages of 200, 800 and 3,000 U/kg I.P. were administered over a period of 14 weeks.

L-asparaginase did not cause any deaths among the animals; however, a mild periportal steatosis, which was not dose related, was observed in the liver, and a few animals showed changes in the epithelial cells in the testicles or a hypertrophy of the cortex of the thymus with proliferation of the large and medium thymocytes and a decrease in the number of small thymocytes. In the second study, daily doses of 0, 200, 1,000 and 5,000 U/kg I.P. were administered for a period of one month. The only difference observed among the test animals, when compared with the control group, was a curtailment of weight gain at the 2 higher dosages.

In the rabbit, the subacute LD$_{50}$ was calculated 7 and 20 days after the end of a 5-day treatment period with L-asparaginase were respectively 1,150 and 760 U/kg I.V. per day.

A dog injected with 10,000 U/kg I.V. per day for 9 consecutive days responded with anorexia, weight loss, salivation and vomiting. Blood was also observed in the stools and there was a temporary decrease in the red cells.

By contrast, 6 dogs were treated at doses of 0, 200, 800 or 3,000 U/kg I.V., 5 days a week for 13 weeks, and no changes in the hemogram or urinalysis were noted. Vomiting occurred a few hours after the injection in animals receiving the highest dosages. At autopsy, atrophy of the thymus was observed and in one dog treated at
the highest dose, a slight fatty infiltration and diffusion of hepatocytes could be seen in the liver.

In the monkey, five injections of 800 or 1,200 U/kg I.V. were given weekly for 4 weeks. At the end of the first week of treatment, the animals treated at the lower dose showed a weight loss accompanied by decreases in the number of reticulocytes and in hematocrit and serum-cholesterol levels. Transitory increases of BSP retention and SGOT levels were also observed. At the end of the treatment, thrombocyte levels were elevated and there was a fatty infiltration of the hepatic cells.

TERATOGENICITY

Investigations of teratogenic activity were conducted in the rabbit and the rat; in both species, L-asparaginase was administered I.V. during the gestation period (on the 8th and 9th day in the rabbit and from the 6th to the 15th day in the rat).

These studies show that:

- in the pregnant rabbit, L-asparaginase exerts significant embryotoxic and teratogenic activities at a daily dose of 50 U/kg I.V.;

in the pregnant rat, a daily dose of 300 U/kg I.V. demonstrates a rather clear embryotoxic activity while a teratogenic effect is observed at a dose of 1,000 U/kg I.V. per day.

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