PRODUCT MONOGRAPH

PrKIDROLASE®
(L-asparaginase)

10,000 IU/Vial
Powder for Solution for Intramuscular injection or Intravenous infusion
OTHER ANTINEOPLASTIC AGENTS
L01XX02

Jazz Pharmaceuticals France SAS
69006 Lyon
France

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RECENT MAJOR LABEL CHANGES

Part I: Health Professional Information

2. Contraindications	Aug, 2019
3. Serious Warnings and Precautions Box	Aug, 2019
7. Warnings and Precautions, General	Aug, 2019
7. Warnings and Precautions, Endocrine and Metabolism	Aug, 2019
7. Warnings and Precautions, Immune	Aug, 2019
7. Warnings and Precautions, Special Populations	Aug, 2019
8. Adverse Drug Reactions	Aug, 2019

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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. Favourable results have sometimes been obtained with L-asparaginase in certain cases of lymphosarcoma, reticulosarcoma, Hodgkin's disease, chronic lymphocytic leukemia and melanosarcoma.

2 CONTRAINDICATIONS

KIDROLASE (L-asparaginase) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

- Severe hepatic impairment
- Current or past severe pancreatitis associated with L-asparaginase therapy
- Current pancreatitis not associated with L-asparaginase therapy
- Patients who have recently been vaccinated against yellow fever (see DRUG INTERACTIONS)
- Patients who are taking phenytoin (see DRUG INTERACTIONS)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Allergic reactions may occur during therapy with KIDROLASE (L-asparaginase)
- 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.
- 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.
- Treatment with L-asparaginase, including KIDROLASE, can cause pancreatitis. Fatal outcome of pancreatitis due to L-asparaginase products, including KIDROLASE, has been reported.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The treatment with KIDROLASE (L-asparaginase) should be initiated and continuously supervised by experienced physicians qualified in cancer chemotherapy.

4.2 Recommended Dose and Dosage Adjustment

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
KIDROLASE 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.

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

4.3 Administration

Administer KIDROLASE 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.

4.4 Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
7 mL capacity vial, containing 10,000 IU L-asparaginase as powder for reconstitution	4mL of Water for Injection	4 mL	When reconstituted with 4 mL the resultant concentration is 2,500 IU per mL.

Reconstitution and dilution should be carried out in controlled and validated aseptic conditions.

Reconstitution for injection
Reconstitute by adding Water for Injection into the vial of L-Asparaginase.
Slowly add the Water for Injection against the inner vial wall, do not squirt directly onto or into the powder. Gently swirl or rotate the vial until the powder is dissolved. Do not shake the vial to prevent foam forming. The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if the solution is clear and free from particles.

Dilution for IV infusion
Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose. Withdraw this amount from the vial using a syringe. Transfer the required amount of the reconstituted solution to an infusion container with either sodium chloride (0.9%) or glucose solution (5%). Discard any unused reconstituted solution left in the vial. Gently invert the infusion container to mix the diluted solution. Do not shake.

The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if the solution is clear and free from particles. The diluted solution ranges in colour from clear light yellow to brown.

4.5 Missed Dose

If a dose is missed or the product had to be temporarily discontinued, dosing should be continued as soon as possible, taking into account the importance of continued asparagine depletion.

5 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.

There is no known antidote for asparaginase overdoses. No data are available on the elimination (peritoneal or by haemodialysis) of the product. Patients who accidentally receive an overdose of L-asparaginase should be monitored closely and receive any appropriate symptomatic and supportive treatment.

For management of a suspected drug overdose, contact your regional Poison Control Centre

6 DOSAGE FORMS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition

Route of Administration	Dosage Form / Strength/ Composition	Non-medicinal Ingredients
Intramuscular injection OR Intravenous infusion	Powder for Solution 10,000 IU *Escherichia coli* L-asparaginase per vial	Glycine Sodium hydroxide (for pH adjustment)

The product contains no preservatives.

Packaging
7 mL colourless glass vial made from Type II glass closed with a bromobutyl stopper and crimped with an aluminium cap stopper.
Pack size: 1 vial per carton

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

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. The incidence of hepatic and pancreatic toxicities and of venous thromboembolic events may be increased in adolescents and young adults compared to children.

Endocrine and Metabolism

Treatment with KIDROLASE may cause glucose intolerance, exacerbate diabetes mellitus and potentially severe hyperglycemia. New onset of glucose intolerance may be irreversible.

In some patients, ketoacidosis has been reported.

Patients must be monitored for developing hyperglycemia and potential complications, especially in patients with uncontrolled diabetes. Administration of insulin and possibly discontinuation of L-asparaginase treatment may be necessary to manage hyperglycemia.

Immune

L-asparaginase has been reported to have immunosuppressive activity in animal experiments. This should be considered because KIDROLASE is used concomitantly with other agents that can reduce immune response and increase the risk for infections.
As with other L-asparaginase preparations, development of specific neutralizing antibodies has been reported with repeated dosing and is associated with reduced L-asparaginase activity. Therefore, monitoring L-asparaginase activity levels in serum or plasma and switching to another asparaginase preparation should be considered.

Monitoring and Laboratory Tests

Patients should be evaluated before initiation of therapy and monitored during therapy for potential toxicities of KIDROLASE and the chemotherapy regimen. This should include laboratory monitoring for pancreatic, hepatic, coagulation, metabolic, hematologic, and renal adverse effects (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic

Pancreatic

Treatment with L-asparaginase, including KIDROLASE, can cause pancreatitis. L-asparaginase induced pancreatitis can be limited to biochemical and/or radiologic manifestations, progress to pancreatitis with clinical symptoms, and can be severe (see ADVERSE REACTIONS). Fatal outcome of pancreatitis due to L-asparaginase products, including KIDROLASE, has been reported.

Patients must be closely monitored for signs and symptoms of pancreatic toxicity and instructed to promptly report potential symptoms of pancreatitis. If pancreatitis is suspected based on clinical symptoms, serum amylase and lipase should be determined. In patients treated with L-asparaginase, increase of serum amylase and lipase may be delayed, mild or absent. Clinical judgment should be used.

KIDROLASE must be permanently discontinued in case of severe pancreatitis (see CONTRAINDICATIONS).

Hyperglyceridemia, if marked, can contribute to the development of pancreatitis (see ADVERSE REACTIONS).

There have been isolated reports of first onset of clinical pancreatitis and detection of pancreatic pseudocyst formation several months after the last administration of L-asparaginase. Patients must be monitored for late-occurring signs of pancreatitis.

Development of chronic pancreatitis as well as persistent pancreatic insufficiency (exocrine insufficiency with, e.g. malabsorption; persistent glucose intolerance / diabetes mellitus) have been reported with L-asparaginase treatment.

Hepatic

Treatment with L-asparaginase, including KIDROLASE, can cause or worsen hepatic injury/dysfunction (including increase in transaminases and bilirubin, hepatic steatosis and hepatic failure). In addition, L-asparaginase reduces hepatic protein synthesis, leading to, e.g. hypoalbuminemia (see Hematologic in this section and ADVERSE REACTIONS).

Patients must be monitored for hepatic dysfunction (see also DRUG INTERACTIONS).

In case of severe hepatic adverse reactions, KIDROLASE should be discontinued until complete or near complete recovery. Treatment must be re-instituted only under very close monitoring.

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, and if the potential benefit outweighs the potential risk.

Neurologic

Central Nervous System (CNS) toxicity, including encephalopathy, seizures and CNS depression, as well as development of the Posterior Reversible Encephalopathy Syndrome (PRES), have been reported in patients treated with protocols that contain L-asparaginase (see ADVERSE REACTIONS).

Posterior Reversible Encephalopathy Syndrome may occur rarely during treatment with any asparaginase Symptoms of PRES include elevated blood pressure, seizures, headaches, changes in mental state and acute visual impairment (primarily cortical blindness or homonymous hemianopsia). Symptoms can be nonspecific, and diagnosis requires confirmation by radiological procedures. It is unclear whether the PRES is caused by asparaginase, concomitant treatment or the underlying diseases. PRES is treated symptomatically, including measures to treat any seizures. Discontinuation of KIDROLASE may be necessary if PRES is suspected or diagnosed. Expert advice should be sought.

Since hyperammonemia, if present, may cause or contribute to CNS toxicity, consider measuring serum ammonia in patients with CNS toxicity. In symptomatic patients initiate treatment as appropriate.

Fatal outcome of L-asparaginase-induced CNS toxicity has been reported.

Renal

Tumour cell destruction can result in hyperuricemia, tumour lysis syndrome and urate nephropathy. Renal impairment may be caused or aggravated by the chemotherapy regimen. Renal function and serum uric acid levels should be monitored and appropriately managed. If necessary, allopurinol should be administered for as long as required.

Sensitivity/Resistance

Administration of KIDROLASE can cause hypersensitivity reactions (infusion/injection reactions), including reactions presenting as anaphylaxis. Reactions have occurred following the first or subsequent administrations.
Hypersensitivity Reactions include

- Reactions limited to the area at or near the site of IM or IV administration, and
- Other reactions, including reactions with symptoms consistent with an anaphylactic reactions, and reactions accompanied by fever.

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 to 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).

Hypersensitivity reactions can begin during or immediately following administration. In the majority of patients, local and non-local reactions occur within the first 24 hours. Later onset of reactions has been reported two days or later after IM administration.
Once a patient has received L-asparaginase as part of a treatment regimen, retreatment with the same agent at a later time (e.g. use during a later consolidation phase) is associated with an increased risk of hypersensitivity and anaphylactic reactions.

Sexual Health

Reproduction
Women of childbearing potential must avoid pregnancy during cancer chemotherapy and for a period of time thereafter.

Men are advised not to father a child during cancer chemotherapy and for a period of time thereafter.

Refer to current practice guidelines for the duration to avoid conceiving following treatment with KIDROLASE.

7.1 Special Populations

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 unless the potential benefit to the patient outweighs the risk to the fetus or breast feeding child.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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 based on the collective clinical experience with KIDROLASE.

The two most common adverse effects are:

- Immediate hypersensitivity reactions, including urticaria, laryngeal oedema, bronchospasm, hypotension and even anaphylactic shock. In case of a hypersensitivity

reaction, treatment must be immediately and definitively stopped (see CONTRAINDICATIONS).

- Thromboembolic events resulting from the effects of asparaginase on clotting protein synthesis, are the second most common class of adverse effects. They may be fatal or result in sequelae based on their location. The disease itself and the presence of a central venous catheter contribute to increasing thromboembolic risk (see WARNINGS AND PRECAUTIONS, Hematologic).

Adverse effects of a clinical or biological nature observed in the course of clinical trials as well as those reported in the literature in patients treated with L-asparaginase can be classified as follows:

Cardiovascular

- Myocardial infarction
- Hypotension and flushing (these symptoms are commonly associated with hypersensitivity reactions)
- embolism, venous thrombosis, arterial thrombosis, haemmorrhage including fatal outcomes, hypertension,

Endocrine and Metabolism

- hypoalbuminemia;
- decrease in serum insulin with hyperglycemia, diabetic ketoacidosis;
- hypertriglyceridemia, hyperamylasaemia, hyperlipasaemia, hyperglycemia, 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 KIDROLASE on endogenous asparagin and glutamine.

Gastrointestinal

Nausea and vomiting generally appear at the beginning of treatment. They may be due directly to the drug itself or be secondary to elevation of BUN and blood uric acid. These adverse 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.

Hematologic

Thromboembolic events resulting from the effects of asparaginase on clotting protein synthesis are the second most common class of adverse effects. They may be fatal or result in sequelae based on their location. The disease itself and the presence of a central venous catheter contribute to increasing thromboembolic risk (see WARNINGS AND PRECAUTIONS, Hematologic).

Coagulation disorders includeincluding increases in Prothrombin Time (PT) and Thromboplastin Time with hypofibrinogenemia, decreases in antithrombin III, plasminogen and other clotting 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.

Coagulopathy, antithrombin III decreases, plasminogen, Protein C, Protein S, and fibrinogen resulting from the inhibition of protein synthesis were observed.

Bone marrow failure 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.

- Resulting from bone marrow depression.
- Leukopenia, neutropenia, febrile neutropenia, anaemia, thrombocytopenia.

Hepatic/Biliary/Pancreatic

Abnormalities of hepatic function are quite frequent and may, warrant interruption of treatment. Most characteristics are the following:

- Haemorrhagic pancreatitis, necrotising pancreatitis, pancreatitis including fatal outcomes, and lethal acute pancreatitis (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- Hypocholesterolemia, hypoalbuminemia, increase of blood alkaline phosphatase and ALT (SGOT) levels.
- Liver enzyme increased. 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 regresses 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.
- Hepatic failure, hepatomegaly, hepatitis cholestatic, and hepatitis.
- Blood bilirubin increased.

To mitigate these adverse 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 any patient whose lab values are abnormal.

Immune

- Infections including bacterial, viral, fungal and opportunistic infections.
- Sepsis including fatal outcomes.

Investigations

- Weight loss

Neurologic

A posterior reversible encephalopathy syndrome (PRES) has been observed during therapy with asparaginase-containing regimens (see WARNINGS AND PRECAUTIONS, Neurologic).

Encephalopathy can be a consequence of hyperammonemia, 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 KIDROLASE on endogenous asparagine and glutamine. Seizures may be associated with cases of thrombosis or metabolic encephalopathy.

Psychiatric

- In rare instances, confusional state, central nervous system disturbances appearing mostly in adults and consisting of mild depression associated with personality disorders, disorientation, delusion, convulsions and pseudo-parkinsonism have been reported.

Renal

- Renal failure

Respiratory

- Retrosternal pressure
- Laryngeal oedema, brochospasm, dyspnoea: these symptoms are commonly associated with hypersensitivity reactions.

Sensitivity/Resistance

The hypersensitivity reactions are the most frequent undesirable effects. 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. Immediate hypersensitivity reactions include urticaria, laryngeal oedema, bronchospasm, hypotension and even anaphylactic shock. The anaphylactic reaction can be seen after the first injection but it occurs mainly between the 5th and the 9th administration. In case of a hypersensitivity reaction, treatment must be immediately and definitively stopped (see CONTRAINDICATIONS).

Sexual Health

Reproduction

- Amenorrhoea, azoospermia

Skin

- Urticaria, pruritus, erythema, facial oedema, lip swelling, these symptoms are commonly associated with hypersensitivity reactions.
- Pyrexia, chills, oedema peripheral, pain, fatigue, malaise, injection site reaction

9 DRUG INTERACTIONS

9.1 Serious Drug interactions Box

Serious Drug Interactions

Patients receiving other agents which have potential life threatening interactions with KIDROLASE should be taken into consideration when administering KIDROLASE (Drug-Drug Interactions below).

- Yellow fever vaccine
- Phenytoin
- Fosphenytoin
- Attenuated live vaccines
- Methotrexate
- Cytarabine
- Vincristine

9.2 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.

Contraindicated:
- 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.
- Methotrexate, cytarabine: Non-clinical data indicate that prior or concurrent administration of L-asparaginase attenuates the effect of methotrexate and cytarabine. Administration of L-asparaginase after methotrexate or cytarabine results in a synergistic effect. The extent to which these affect the overall effectiveness of established treatment protocols is not known.
- Vincristine: Administration of L-asparaginase concurrently with or immediately before administration of vincristine may be associated with increased toxicity and increased risk of anaphylaxis.
- Immunosuppressants such as cyclosporin, tacrolimus or sirolimus could cause excessive

immunodepression with risk of lymphoproliferation.

9.3 Drug-Food Interactions

Interactions with food have not been established.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

L-asparaginase exerts an antitumour 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.

10.2 Pharmacodynamics

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.

11 STORAGE, STABILITY AND DISPOSAL

Unopened product in powder form
Is stable for up to 24 months at 2°C to 8°C.

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.

Diluted product
The diluted product for IV infusion should be used immediately. If this is unavoidable the solution should be stored at a temperature between 2°C and 8°C, and used within 72 hours when diluted with Sodium Chloride 0.9% or 24 hours when diluted with a glucose solution (5%).

KIDROLASE (L-asparaginase) contains no preservative. **Reconstitution and dilution should be done under strict aseptic conditions.**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Caution should be exercised when handling and preparing KIDROLASE solution. The use of gloves, safety glasses and mask is recommended. If the solution comes into contact with the skin, the area should be washed thoroughly with soap and water. In the event of contact with a mucous membrane, rinse them thoroughly with copious amount of water.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

- Proper name: Escherichia coli L-asparaginase
- Common Name (BAN): L-asparaginase
- Chemical Name: L-asparagine-amido-hydrolase
- Molecular Weight: Its molecular weight is approximately 141,000 Da
- Physiochemical properties
  - Physical Form: White crystalline powder.
  - Specific Activity: Enzymatic titration shows that L-asparaginase has an activity of approximately 200 units/mg.
- Solubility: practically insoluble in methanol, acetone, ether and chloroform but soluble in water.

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.

14 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.

Antitumour activity

The activity of L-asparaginase has been tested on various tumours, 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 tumour systems, EARAD-1 leukemia and C_{57}B1/Rho leucosarcomatosis, have demonstrated that the effect of L-asparaginase varies with the number of grafted tumour cells.

Furthermore, in EARAD-1 leukemia, it has been shown that the antitumour 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.

15 NON-CLINICAL 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-asparagine 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 dose 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 LD50=s 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.

16 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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