PRESCRIBING INFORMATION

KIDROLASE 10,000 I.U.

powder for solution for injection

WARNINGS

It is recommended that asparaginase be administered to patients only in a hospital setting under the supervision of a physician who is qualified by training and experience to administer cancer chemotherapeutic agents, because of the possibility of severe reactions, including anaphylaxis and sudden death. The physician must be prepared to treat anaphylaxis at each administration of the drug. In the treatment of each patient the physician must weight carefully the possibility of achieving therapeutic benefit versus the risk of toxicity.

This drug has various toxic properties; therefore, both powder and solution must be handled and administered with care. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Special handling procedures should be reviewed prior to handling and followed diligently.

The following data should be thoroughly reviewed before administering the compound.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition of the powder (for one vial of 100 mg of powder):

L-asparaginase 10,000 I.U.

Glycine 48.6 mg

Sodium hydroxide q.s. pH 6.8 - 7.0

PHARMACEUTICAL FORM

Powder for solution for injection.

CLINICAL DATA

Therapeutic indications

- Acute lymphoblastic leukemia
- Acute myeloblastic leukemia

Dosage and method of administration

After reconstitution with 2.5 ml water for injection:

IV route (through an isotonic glucose or isotonic sodium chloride infusion) or IM route: 500 to 1,000 IU per kg per day in children or 7,500 to 10,000 I.U./m^2/day in adults:

- initial therapy: every day for 6 to 21 days,

- maintenance therapy: once or twice a week,
- reinduction therapy: 3,000 I.U./m^2/day IV x 5 days.

Intradermal skin test

Because of the occurrence of allergic reactions, an intradermal skin test should be performed prior to the initial administration of KIDROLASE and when KIDROLASE is given after an interval of a week or more has elapsed between doses. The skin test solution may be prepared as follows: Reconstitute the contents of a 10,000 I.U. vial with 5.0ml of diluent. From this solution (2,000 I.U./ml) withdraw 0.1 ml and inject it into another vial containing 9.9ml of diluent, yielding a skin test solution of approximately 20.0 I.U./ml. Use 0.1 ml of this solution (about 2.0 I.U.) for the intradermal skin test. The skin test site should be observed for at least one hour for the appearance of a wheal or erythema either of which indicates a positive reaction. An allergic reaction even to the skin test dose in certain sensitized individuals may rarely occur. A negative skin test reactoion does not preclude the possibility of the development of an allergic reaction.

Desensitization

Desensitization should be performed before administering the first dose of KIDROLASE on initiation of therapy in positive reactors, and on retreatment of any patient in whom such therapy is deemed necessary after carefully weighing the increased risk of hypersensitivity reactions. Rapid desensitization of the patient may be attempted with progressively increasing amounts of intravenously administered KIDROLASE provided adequate precautions are taken to treat an acute allergic reaction should it occur. One reported schedule begins with a total of 1 I.U. given intravenously and doubles the dose every 10 minutes, provided no reaction has occurred, until the accumulated total amount given equals the planned doses for that day.

Contraindications

- Known hypersensitivity to the drug or to any of the constituents. In addition, a hypersensitivity reaction occurring during therapy contraindicates the continuation of therapy.
- Hepatic insufficiency, pancreatitis.
- Pregnant and lactating women: see Pregnancy and lactating.
- Yellow fever vaccine

Warnings and special precautions for use

- Allergic reactions to asparaginase are frequent and may occur during the primary course of therapy. They are not completely predictable on the basis of the intradermal skin test. Anphylaxis and death have occurred even in a hospital setting with experienced observers.
- Insulin-dependent diabetes mellitus: this treatment may exacerbate the diabetes.

- Once a patient has received KIDROLASE as part of a treatment regimen, retreatment with this agent at a later time is associated with increased risk of hypersensitivity reactions.
- For reinduction regimens, corticosteroid premedication should be given for 24 to 48 hours to prevent the occurrence of allergic reactions.
- In patients found by skin testing to be hypersensitive to asparaginase, and in any patient who has received a previous course of therapy with asparaginase, therapy with this agent should be instituted or reinstituted only after successful desensitization, and then only if in the judgment of the physician the possible benefit is greater than the increased risk. Desensitization itself may be hazardous (See DOSAGE AND ADMINISTRATION, intradermal Skin Test). In view of the unpredictability of the adverse reactions to asparginase, it is recommended that this proceduct be used in a hospital setting. Asparaginase has an adverse effect on liver function in the majority of patients. Therapy with asparaginase may increase pre-existing liver impairment caused by prior therapy on the underlying disease. Because of this there is a possibility that asparaginase may increase the toxicity of other medications.
  The administration of KIDROLASE *intravenously concurrently with or immediately before* a course of vincristine and prednisone may be associated with increased toxicity (See DOSAG AND ADMINISTRATION, *Recommended Induction Regimen*).
- This drug has various toxic properties, therefore, both powder and solution must be handled and administered with care (See boxed warning and DIRECTIONS FOR RECONSTITUTION, *Special handling*). KIDROLASE may be irritating to eyes, skin, and the upper respiratory tract. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided.
  Appropriate protective equipment should be worn when handling KIDROLASE. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part should be washed immediately with soap and water. Medical attention should be sought. If inhaled, remove from exposure and seek medical attention (See DIRECTIONS FOR RECONSTITUTION, *Special Handling*). Asparaginase has been reported to have immunosuppressive activity in animal experiments. Accordingly, the possibility that use of the drug in man may predispose to infection should be considered. Asparaginase toxicity is reported to be greater in adults than in pediatric patients.
- Blood clotting tests should be carried out before treatment and before each injection of Kidrolase (minimum PTT, KPTT, fibrinogen, anti-thrombin III (ATIII)). Replacement therapy should be instituted if fibrinogen < 1g/L or ATIII< 60%. If fibrinogen or ATIII levels cannot be increased, the treatment

should preferably be suspended temporarily and resumed only when laboratory parameters have returned to normal.
- Hepatic function tests, blood counts and bone marrow tests should be monitored regularly during therapy.
- Glycemia and amylasemia should be monitored all along therapy. The treatment should be withdrawn in case of amylasemia level increase.
- Patients should be monitored to detect and prevent cytolysis which can lead to hyperuricemia.

Interactions with other drugs and other forms of interaction

Common interactions with all cytotoxic agents:
Due to the risk of thrombosis in tumoral diseases, anticoagulant treatments are frequently administered. If it is decided to treat the patient with oral anticoagulants, the high within-patient variability of coagulability in the course of these diseases and potential interaction between oral anticoagulants and anticancer chemotherapy require an increase in the INR testing frequency.

Contra-indicated associations:
Yellow fever vaccine: risk of lethal systemic vaccine disease.

Associations to be avoided:
-Attenuated live vaccines (other than yellow fever):
Risk of possibly fatal disseminated disease. This is even more likely to occur in subjects already immunosuppressed by the underlying disease. Use an inactivated vaccine when available (poliomyelitis).
- Phenytoin, fosphenytoin
Risk of occurrence of convulsions induced by the decrease in digestive uptake of phenytoin by the cytotoxic agent or risk of increase toxicity or diminished efficacy of the cytotoxic agent due to the increase of its liver metabolism by phenytoin.

Associations requiring precautions for use:
Phenytoin (in case of prior chemotherapy treatment)
Risk of occurrence of convulsions induced by the decrease in the digestive uptake of phenytoin by the cytotoxic agent.
Temporarily associate an anticonvulsive benzodiazepine.

Associations to be taken into consideration
- Immunosuprresants (cyclosporine, tacrolimus, sirolimus)
Excessive immunodepression with risk of lymphoproliferation

Other Drug interactions
Tissue culture and animal studies indicate that ASPARAGINASE can diminish or abolish the effect of methotrexate on malignant cells. This effect on methotrexate

activity persists as long as plasma asparagine levels are suppressed. These results would seem to dictate against the clinical use of methotrexate with ASPARAGINASE, or during the period following ASPARAGINASE therapy when plasma asparagine levels are below normal.

Drug/Laboratory Test Interactions
L-asparaginase has been reported to interfere with the interpretation of thyroid function tests by producing a rapid and marked reduction in serum concentrations of thyroxine-binding globulin within two days after the first dose. Serum concentrations of thyroxine-binding globulin returned to pretreatment values within four weeks of the last of L-asparaginase.

Pregnancy and breast-feeding
This drug is contra-indicated during pregnancy and for nursing mothers.

Pediatric Use
Asparaginase toxicity is reported to be greater in adults than in pediatric patients.

Adverse effects
* Hypersensitivity is the most frequent adverse reaction, such as urticaria, laryngeal edema of the larynx, bronchospasm, hypotension or even true anaphylactic shock. If these reactions occur, the treatment should be discontinued immediately and withdrawn (see Contraindications).

- In pediatric patients with advanced leukemia, a lower incidence of anaphylaxis has been reported with intramuscular administration, although there was a higher incidence of milder hypersensitivity reactions than with intravenous administration.
- Fatal hyperthermia has been reported.

* Inhibition of protein synthesis:
-Clotting disorders including increased PT and thromboplastin time with hypofibrinogenemia, decrease in anti-thrombin III, plasminogen and other factors (VII, IX, X and VIII), leading to possible bleeding and thrombolic complications;
- Hypoalbuminaemia
- Decrease in serum insulin with hyperglycemia; glucosuria and polyuria.
- Inhibition of lipoprotein lipase activity; increase in serum triglycerides and cholesterol.
- Decrease in brain concentrations of L-asparagine or L-glutamine, resulting in hyperammonaemia with clinical signs of metabolic encephalopathy such as consciousness disorders with confusion, stupor or coma in some patients.

* Some patients have shown central nervous system effects consisting of depression, somnolence, fatigue, coma, confusion, agitation and hallucinations varying from mild to severe. Rarely, a Parkinson-like syndrome has occurred, with tremor and a progressive increase in muscular tone. These side effects

usually have reversed spontaneously after treatment was stopped. Therapy with ASPARAGINASE is associated with an increase in blood ammonia during the conversion of asparagine to aspartic acid by the enzyme. No clear correlation exists between the degree of elevation of blood ammonia levels and the appearance of CNS changes.

* Other adverse effects:

- Acute pancreatitis, including fatalities.

- Cholestatic or hepatocellular liver injury with or without steatosis.

- A variety of liver function abnormalities have been reported, including elevations of SGOT, SGTP, alkaline phosphatase, bilirubin (direct and indirect), and depression of serum albumin, cholesterol (total and esters), and plasma fibrinogen. Increases and decreases of total lipids have occurred. Marked hypoalbuminemia associated with peripheral edema has been reported. However, these abnormalities usually are reversible on discontinuance of therapy and some reversal may occur during the course of therapy. Fatty changes in the liver have been documented by biopsy. Malabsorption syndrome has been reported.

- Rarely, transient bone marrow depression has been observed, as evidenced by a delay in return of hemoglobin or hematocrit levels to normal in patients undergoing hematologic remission of leukemia.

- Marked leukopenia has been reported.

- Nausea - vomiting, chills, fever, anorexia, abdominal cramps, weight loss.

- Amenorrhea, azoospermia,

- Headache and irritability may occur and usually are mild.

- Azotemia, usually pre-renal, occurs frequently. Acute renal shut down and fatal renal insufficiency have been reported during treatment. Proteinuria has occurred infrequently.

Overdosage

The acute intravenous LD_{50} of ASPARAGINASE for mice was about 500,000 I.U./kg and for rabbits about 22,000 I.U./kg.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

OTHER ANTINEOPLASTIC
(L: Antineoplastics and immunomodulators)
ATC Code: L01XX02

L-asparaginase is a protein enzyme extracted from *Escherichia coli* which degrades asparagine by hydrolysis.
This amino acid is one of the basic constituents of cellular protein. As leukemic cells cannot synthesized aspargine endogenously, they are dependent on an exogenous source of aspargine for survival. Depletion of aspargine by treatment with L-asparaginase results in the death of cells unable to synthesize aspargine endogenously. Due to this special mechanism of action, cross-resistance with other cytostatic agents is not observed.

Pharmacokinetic properties

Tissue diffusion of L-asparaginase is low. It has a biphasic half-life ranging from 8 to 30 hours according to subject. 24 hours after an IV dose of 1,000 I.U./kg, plasma concentrations were 8 to 20 IU/mL, while plasma concentrations after an IM injection were 50% lower.

PHARMACEUTICAL DATA

Shelf-life

Before reconstitution: 2 years.
After reconstitution: see Special precautions for storage.

Special precautions for storage

Before reconstitution: store at a temperature between 2°C and 8°C.
After reconstitution: the reconstituted solution may be kept for 24 hours at a temperature between 2°C and 8°C.

Instructions for use/handling

This drug must be handled and prepared with caution. The use of gloves, safety glasses and a mask is recommended.
In case of contact of the solution for dilution or the infusion solution with the skin, wash immediately and thoroughly with soap and water.
In case of contact of the solution for dilution or the infusion solution with mucous membranes, wash immediately with copious amounts of water.
Do not mix with other drugs.

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Importer: CTS Ltd., 4 Haharash Street, Hod Hasharon

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