

TRANSLATION OF THE FRENCH SUMMARY OF PRODUCT CHARACTERISTICS
Approved by the French Medicines Agency October 22nd, 2004

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

KIDROLASE 10,000 I.U., powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder composition

L-asparaginase (DCI).....10,000 I.U.

Glycine..... 48.6 mg

Sodium Hydroxide..... qs pH=6.8-7.0

For one vial of 100 mg of powder

Solvent composition

Water for injections..... 2.5 ml

For one ampoule

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Acute lymphoblastic leukaemia.
- Leukaemic meningitis.
- Non-Hodgkin's lymphoma.

4.2 Posology and method of administration

IV route (through an isotonic glucose or isotonic sodium chloride infusion) or IM route:

500 to 1,000 I.U. per kg per day in children or 7,500 to 10,000 I.U./m²/day in adults:

- initial therapy: every day for 6 to 21 days;
- maintenance therapy: once or twice a week;
- reinduction therapy: every day for 5 to 15 days.

Intrarachidian route:

50 to 100 I.U. per kg per injection.

4.3 Contraindications

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

4.4 Warnings and special precautions for use

- Insulin-dependent diabetes mellitus: this treatment may exacerbate diabetes.
- For reinduction regimens, corticosteroid premedication should be given for 24 to 48 hours to prevent the occurrence of allergic reactions.
- Blood clotting tests should be carried out before treatment and before each injection of Kidrolase (minimum PTT, KPTT, fibrinogen, anti-thrombin III (AT III)).

Replacement therapy should be instituted if fibrinogen is less than 1 g/L or AT III is less than 60 %. If fibrinogen or AT III levels cannot be increased, the treatment should preferably be suspended temporarily and resumed only when laboratory parameters have returned to normal.

- Hepatic function tests and blood counts should be monitored regularly during therapy.
- Glycaemia and amylasaemia should be monitored throughout treatment. The treatment should be discontinued in case of an amylasaemia level increase.
- Patients should be monitored to detect and prevent hyperuricaemia which can lead to cytolysis.

4.5 Interaction with other medicinal products and other forms of interaction

Common interactions with all cytotoxic agents:

Due to the increased 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 the 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 lethal systemic vaccine disease.
This is even more likely to occur in subjects already immunocompromised by the underlying disease. Use an inactivated vaccine whenever available (poliomyelitis).
- + **Phenytoin, fosphenytoin**
Risk of occurrence of convulsions induced by the decrease in the digestive uptake of phenytoin by the cytotoxic agent or risk of increased 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

- + **Immunosuppressants (cyclosporine, tacrolimus, sirolimus)**
Excessive immunodepression with risk of lymphoproliferation.

4.6 Pregnancy and lactation

Contra-indicated.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

- Hypersensitivity is the most frequent adverse reaction, including urticaria, laryngeal oedema, bronchospasm, hypotension or even true anaphylactic shock. The treatment should be discontinued immediately and withdrawn (see Contraindications).
- Inhibition of protein synthesis:
 - clotting disorders including increased PT and thromboplastin time with hypofibrinogenaemia, decrease in anti-thrombin III, plasminogen and other factors (VII, IX, X and VIII); leading to possible bleeding and thrombotic complications;
 - hypoalbuminaemia;
 - decrease in serum insulin with hyperglycaemia;
 - hypertriglyceridaemia and hypercholesterolaemia;
 - hyperammonaemia, 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.
- Other side effects:
 - potentially fatal acute pancreatitis;
 - cholestatic or cytolytic liver damage with or without steatosis;
 - nausea, vomiting;
 - amenorrhea – azoospermia.

4.9 Overdose

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OTHER ANTINEOPLASTIC

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 proteins; as leukaemic cells cannot synthesize asparagine endogenously, they are dependent on an exogenous source of asparagine for survival. This one being hydrolysed by L-asparaginase, this deficiency involves a destruction of the cells unable to synthesize asparagine endogenously.

Due to this special mechanism of action, cross-resistance with other cytostatic agents is not observed.

5.2 Pharmacokinetic properties

Tissue diffusion of L-asparaginase is low; it has a biphasic half-life ranging from 8 to 30 hours according to the subject; 24 hours after an IV dose of 1,000 I.U. /kg, the plasma concentration is 8 to 20 I.U./ml; after an IM injection, the plasma concentration observed is 50 % lower.

5.3 Preclinical safety data

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

6.2 Shelf life

Before reconstitution: 2 years.

After reconstitution: *see paragraph 6.3 Special precautions for storage.*

6.3 Special precautions for storage

Before reconstitution: store at a temperature between +2°C and +8°C

After reconstitution: 24 hours at a temperature between +2°C and +8°C

6.4 Nature and contents of container

Powder: 7 ml colourless type II glass closed with halogenobutyl rubber stopper.

Solvent: 3 ml colourless type I glass ampoule.

6.5 Instructions for use, handling and disposal

This drug must be handled and prepared with caution. The use of gloves, safety goggles 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.

7. PRESENTATION AND ADMINISTRATIVE IDENTIFICATION NUMBER

311 810.4: 7 ml vial (colourless glass) of powder for solution for injection + 3 ml ampoule (colourless glass) of solvent; box of 1.

552 520.4: 7 ml vial (colourless glass) of powder for solution for injection; box of 10.

8. PRESCRIBING AND DELIVERY CONDITION

List I

9. MARKETING AUTHORISATION HOLDER

Opi

3, allée des Séquoias

69760 LIMONEST

FRANCE

10. DATE OF REVISION OF THE TEXT

October 22nd, 2004