

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. Name of the medicinal product:

**KIDROLASE 10,000 I.U. powder for solution for injection**

### 2. Qualitative and quantitative composition

Composition of the powder (for one vial):

L-asparaginase 10,000 I.U.

For one bottle.

For the complete list of excipients, see section 6.1.

### 3. Pharmaceutical form

Powder for solution for injection.

### 4. Clinical data

#### 4.1. Therapeutic indications

- Acute lymphoblastic leukemia
- Acute myeloblastic leukemia

#### 4.2. Posology and method of administration:

##### Posology

IV route (by infusion of an isotonic glucose or an isotonic sodium chloride solution) or IM route:

500 to 1,000 IU per kg per day in children or 7,500 to 10,000 I.U./m<sup>2</sup>/day in adults:

- initial therapy: every day for 6 to 21 days,
- maintenance therapy: 1 or 2 times per week,
- reinduction therapy: 3,000 I.U./m<sup>2</sup>/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 reaction 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.

### **4.3. Contraindications**

- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Similarly, a hypersensitivity reaction during treatment contraindicates the continuation of treatment.
- Hepatic failure
- pancreatitis (see section 4.4).
- In combination with a live attenuated vaccine and until at least six months after stopping chemotherapy (see section 4.5).

### **4.4 Special Warnings and precautions for use**

Kidrolase should only be used by physicians who specialize in this type of treatment.

Anaphylactic reactions have been observed after using Kidrolase. Administration of this medicinal product must be performed in a healthcare facility, in the presence of trained personnel and the resources necessary to ensure treatment of an anaphylactic reaction that may occur during administration.

Re-administering L-asparaginase after a period of time (for example, between the induction phase and the consolidation phase) may increase the risk of occurrence of an anaphylactic reaction. Close monitoring is recommended in these conditions.

Posterior Reversible Encephalopathy Syndrome (PRES) may occur rarely during treatment with any asparaginase (see section 4.8). This syndrome is characterised in magnetic resonance imaging (MRI) by reversible (from a few days to months) lesions/oedema, primarily in the posterior region of the brain. Symptoms of PRES essentially include elevated blood pressure, seizures, headaches, changes in mental state and acute visual impairment (primarily

cortical blindness or homonymous hemianopsia). 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 or dose reduction of concomitantly administered immunosuppressive medicinal products may be necessary. Expert advice should be sought.

During reinduction, administer corticosteroid therapy for 24 to 48 hours to prevent allergic reactions.

Close monitoring before and during treatment is necessary:

- Blood lipase and blood glucose levels should be monitored to look for pancreatitis or hyperglycaemia. Treatment must be discontinued if there is an increase in blood lipase levels during treatment. This treatment may exacerbate diabetes. Hyperglycaemia can be treated with insulin, if needed.
- Coagulation tests should be performed before treatment and repeated during treatment before each injection of KIDROLASE (at least aPTT, PT, fibrinogen assay, antithrombin III (AT III) assay). Replacement therapy should be performed if fibrinogen is below 1 g/litre or if AT III is below 60%. If the fibrinogen or AT III levels do not increase, or if a significant bleeding disorder appears, it is preferable to temporarily interrupt treatment and it should not be resumed until after laboratory parameters have returned to normal.
- Regular liver function tests will be performed throughout the entire duration of treatment, as will full blood counts.
- Renal function and serum uric acid levels must be monitored.

### **Interaction**

This medicinal product is not recommended with phenytoin or fosphenytoin and methotrexate. In patients treated with phenytoin, administration of an anticonvulsant benzodiazepine should be considered to avoid a risk of seizures related to a reduction of gastrointestinal absorption of phenytoin induced by cytotoxic agents (see section 4.5).

### **4.5. Interactions with other medicinal products and other forms of interaction**

L-asparaginase must not be mixed with other medicinal products before administration.

#### **Contraindicated combinations (see section 4.3):**

##### **Live attenuated vaccines:**

Risk of fatal generalised vaccine disease.

Combination of a cytotoxic agent with a live attenuated vaccine (LAV) is contraindicated during and for at least six months after stopping chemotherapy.

**Combinations that are not recommended (see section 4.4):**

**Phenytoin (and by extrapolation, fosphenytoin)**

Risk of occurrence of seizures due to reduction of gastrointestinal absorption of phenytoin by the cytotoxic agent or risk of increased toxicity or loss of efficacy of the cytotoxic agent due to the increase of its hepatic metabolism by phenytoin or fosphenytoin.

**Methotrexate**

L-asparaginase may reduce or eliminate the effect of methotrexate on malignant cells. Therefore, concomitant administration of L- asparaginase and methotrexate must be avoided.

**Combinations to be used with caution:**

**Vitamin K antagonist**

Increased thrombotic and haemorrhagic risk in cancer. Moreover, possible interaction between VKAs and chemotherapy. INR to be monitored more frequently.

**Combinations to take into consideration:**

**Immunosuppressants (cyclosporine, everolimus, tacrolimus, temsirolimus, sirolimus)**

Excessive immunosuppression with a risk of lymphoproliferative syndrome.

**4.6. Fertility, pregnancy and lactation**

The data on use of L-asparaginase in pregnant women are limited. Studies conducted in animals are insufficient for making conclusions about the reproductive toxicity of KIDROLASE (see section 5.3). KIDROLASE is not recommended during pregnancy and in women of childbearing age who do not use contraception.

**Breastfeeding**

It is uncertain whether KIDROLASE is excreted in breast milk. Therefore, breastfeeding is not recommended during treatment with KIDROLASE.

**Fertility**

No fertility data are available.

**4.7. Effects on the ability to drive a vehicle and operate machinery**

Not applicable.

**4.8. Undesirable effects**

The two most common adverse effects are:

- Immediate hypersensitivity reactions, including urticaria, laryngeal oedema, bronchospasm, hypotension and even anaphylactic shock. In case of hypersensitivity reaction, treatment must be immediately and definitively stopped (see section 4.3).
- 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.

Adverse effects are generally reversible.

The adverse effects spontaneously reported as well as those reported in the literature in patients treated with L-asparaginase as part of their chemotherapy protocol are listed in the table below. The adverse effects are classified by system organ class and frequency.

The frequencies below are defined using the following convention:

Very common ( $\geq 1/10$ ); Common ( $\geq 1/100 - < 1/10$ ); Uncommon ( $\geq 1/1,000 - < 1/100$ ); Rare ( $\geq 1/10,000 - < 1/1,000$ ); Very rare ( $< 1/10,000$ ), Not known.

<b>Infections and infestations</b>	
Not known	Infections, Sepsis that may be fatal
<b>Blood system and lymphatic disorders</b>	
Very common	Clotting disorders – prolonged PT and aPTT, abnormal clotting factors (VII, IX, X and VIII), decreased antithrombin III, plasminogen, protein C, protein S and fibrinogen <sup>(1)</sup> ; these disorders may be the cause of haemorrhagic and thrombotic complications.
Not known	Leukopaenia, Neutropaenia, Febrile neutropaenia, Anaemia, Thrombocytopaenia, Bone marrowfailure
<b>Immune system disorders</b>	
Very common	Anaphylactic reactions
Not known	Anaphylactic shock
<b>Metabolism and nutrition disorders</b>	
Common	Hypertriglyceridaemia, High blood amylase levels, High blood lipase levels, Hyperglycaemia, Decrease in insulin levels
Not known	Diabetic ketoacidosis, Hyperammonaemia <sup>(3)</sup> , Hypercholesterolaemia, Hypoalbuminaemia

<b>Psychiatric disorders</b>	
Not known	confusion
<b>Nervous system disorders</b>	
Not known	Clinical signs of metabolic encephalopathy such as consciousness disorders with confusion, Stupor, Episodes of seizures <sup>(2)</sup> , epileptic Seizures <sup>(2)</sup> or Coma.
Rare	Posterior Reversible Encephalopathy Syndrome
<b>Cardiac disorders</b>	
Not known	Myocardial infarction
<b>Vascular disorders</b>	
Very common	Hypotension <sup>(4)</sup>
common	Embolic, venous or more rarely arterial thrombotic events
Not known	Haemorrhage, Hypertension, Flushing <sup>(4)</sup>
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very common	Laryngeal oedema <sup>(4)</sup> , Bronchospasm <sup>(4)</sup> , Dyspnoea <sup>(4)</sup>
<b>Gastrointestinal disorders</b>	
Very common	Nausea, vomiting
Common	Acute pancreatitis, Diarrhoea, Abdominal pain
Very rare	Haemorrhagic or necrotising pancreatitis*
Not known	Fatal pancreatitis*
<b>Hepatobiliary disorders</b>	
Common	Increase in bilirubin ALAT , ASAT, GGT, alkaline phosphatases
Rare	Hepatic failure
Not known	Hepatomegaly, Cholestatic hepatitis, hepatic steatosis, cytolytic hepatitis
<b>Skin and subcutaneous tissue conditions</b>	
Very common	Urticaria, Pruritis, Erythema, Facial oedema, Lip Swelling <sup>(4)</sup>
<b>Renal and urinary disorders</b>	
Not known	Renal failure
<b>Reproductive system and hormonal disorders</b>	
Not known	Amenorrhoea, Azoospermia
<b>General disorders and administration site conditions</b>	
Common	Fever, Chills, Peripheral oedema, Pain

Not known	Fatigue, Malaise, Injection site reaction (including injection site pain, erythema, haematoma or oedema)
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\* See Description of selected adverse effects.

- 1- Resulting from the inhibition of protein synthesis.
- 2- Seizures may be associated with cases of thrombosis or metabolic encephalopathy.
- 3- Resulting from excessive ammonia production by the action of L-asparaginase on endogenous asparagine and glutamine.
- 4- These symptoms are commonly associated with hypersensitivity reactions.

#### Description of selected adverse effects

Pancreatic disorders – Acute pancreatitis occurs in less than 10% of cases. Isolated cases of pseudocyst formation have been reported up to 4 months after the last administration of treatment; relevant exams (e.g. ultrasound) may be considered after the last administration of treatment. Very rare cases of haemorrhagic or necrotising pancreatitis occur and may be fatal. L-asparaginase may affect endocrine function. Hyperglycaemia is the most commonly reported adverse effect and it is easy to control it by administering insulin. Rare cases of diabetic ketoacidosis have been reported.

Nervous system disorders and cardiac disorders observed on Kidrolase are often the result of a thromboembolic event or may be promoted by the concomitant prescriptions of cancer drugs.

In rare cases, a posterior reversible encephalopathy syndrome (PRES) has been observed during therapy with asparaginase-containing regimens. (For information on precautions for use, see section 4.4).

#### Paediatric population

The frequency, type and severity of adverse effects should be the same in children and adults.

#### Other special populations

No special patient populations have been identified in which the tolerability profile of the medicinal product is expected to be different from the profile defined above.

#### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: (<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il> ).

#### **4.9. Overdose**

No cases of overdose have been reported with *E. coli* asparaginase. In case of an overdose, the patient must necessarily be placed under medical observation. There is no known antidote for asparaginase overdoses. No data are available on the elimination (peritoneal or by haemodialysis) of the product.

### **5. Pharmaceutical properties**

#### **5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: OTHER ANTINEOPLASTIC AGENT

ATC Code: L01XX02

L-asparaginase is a protein enzyme extracted from *Escherichia coli* cultures. It destroys asparagine by hydrolysis. This amino acid is a basic component of cellular protein; leukemia cells, which cannot synthesise this amino acid themselves, must use extracellular asparagine.

Given that extracellular asparagine is hydrolysed by L- asparaginase, this deficiency leads to the destruction of cells that are unable to endogenously synthesise asparagine.

Given this particular mechanism of action, there is no cross-resistance with other cytostatic agents.

#### **5.2. Pharmacokinetic properties**

Asparaginase is poorly distributed in tissue; its half-life is biphasic and varies between 8 and 30 hours, depending on subjects; 24 hours after IV injection of 1,000 IU/kg, the plasma level is between 8 and 20 IU/mL; after IM injection, the plasma level observed is 50% lower.

#### **5.3 Preclinical safety data**

The following effects have been observed in animals after intravenous injection, leading to exposure rates similar to those observed in clinical practice: reversible hepatotoxicity, resorption and significant foetal abnormalities in New Zealand white rabbits, delayed growth and development, but also malformations of rat embryos treated *in vitro*.

### **6. Pharmaceutical data**

#### **6.1 List of excipients**

Glycine

Sodium hydroxide

#### **6.2 Incompatibilities**

See section 4.5

#### **6.3. Shelf-life**

Before reconstitution: The expiry date of the product is indicated on the packaging materials.

After reconstitution: The physical and chemical stability of the reconstituted solution has been demonstrated for 24 hours at a temperature between 2°C and 8°C. However, from a microbiological perspective, the product should be used immediately. If it is not used immediately, shelf life and storage conditions after reconstitution and before use are the sole responsibility of the user and should not exceed 24 hours at a temperature between 2°C and 8°C. Reconstitution should be performed in strict aseptic conditions.

#### **6.4. Special precautions for storage**

Before reconstitution: Store in a refrigerator (between 2°C and 8°C).

After reconstitution: Do not freeze.

For storage conditions of the medicinal product after reconstitution, see section 6.3.

#### **6.5 Nature and contents of the container**

7 ml colorless type II glass bottle closed with a bromobutyl stopper.

#### **6.6 Special precautions for disposal and handling**

This medicinal product must be handled and prepared with caution. The use of gloves, safety goggles and a mask is recommended.

In case of skin contact with the concentrate or solution for infusion, the product should be removed immediately and completely using soap and water.

In case of contact with a mucous membrane with the concentrate or solution for infusion, it must be immediately rinsed thoroughly with water.

Do not mix with other medicinal products.

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

### **7. Manufacturer and Marketing authorization holder (MAH):**

**Manufacturer:** Jazz pharmaceuticals France S.A.S, CITY ONE, 84 QUAI CHARLES DE GAULLE 69006 LYON, France.

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

The content of this leaflet was approved by the Ministry of Health in January 2018 and updated according to the guidelines of the Ministry of Health in January 2018.