Revised: Oct 2009 (6th version, Revisions associated with the amendment of the Pharmaceutical Affairs Law)

Standard Commodity Classification No. of Japan
874291

- ANTINEOPLASTIC ENZYME PREPARATION -

LEUNASE® Injection 5000
LEUNASE® Injection 10000

<L-asparaginase for Injection>

Powerful drug and Prescription drug*

Storage
Store in a cold place.

Expiration date
2 years (Do not use after the expiration date indicated on the package.)

	5000K.U. Injection	10000K.U. Injection
Approval No.	21700AMX00049	21700AMX00051
Date of listing in the NHI reimbursement price	December 2005	December 2005
Date of initial marketing in Japan	September 1971	September 1971

* Caution: Use only pursuant to the direction of a physician, etc.

CONTRAINDICATIONS (LEUNASE Injection is contraindicated in the following patients.)
Patients with a history of serious hypersensitivity to any of the components of the product

DESCRIPTION

1. Composition

Each vial of LEUNASE Injection 5000 and 10000 contains the following ingredient. It is an injectable solution to be reconstituted before use.

Brand name		LEUNASE Injection 5000	LEUNASE Injection 10000
Active ingredient	Lyophilized L-asparaginase	5000K.U.	10000K.U.

(One K.U. of L-asparaginase is equivalent to the amount of L-asparaginase that decomposes L-asparagine and produces 1μmole of ammonia per minute at 37°C.)

2. Product description

Brand name	Appearance	pH range	Osmotic pressure ratio
LEUNASE Injection 5000	White powder or porous light mass (lyophilized preparation)	6.5 to 7.5	0.02 (To be reconstituted with 0.5mL of water for injection, JP)
LEUNASE Injection 10000			0.02 (To be reconstituted with 1mL of water for injection, JP)

Stability : Comparatively stable to heat, pH and light in the crystal state.
Stable pH range in aqueous solution is 6.0 to 8.5.

INDICATIONS

Acute leukemia (including blastic crisis in chronic leukemia), malignant lymphoma

DOSAGE AND ADMINISTRATION

The usual dosage is 50 to 200 KU/kg to be administered by intravenous drip infusion every day or every other day. The dosage may be adjusted depending on the age and condition of the patient.

(Preparation)

See 7. Precautions concerning Use.

PRECAUTIONS

1. Careful Administration (LEUNASE should be administered with care in the following patients.)

(1) Patients with pancreatitis or a history of pancreatitis [Exacerbation or recurrence of pancreatitis may occur.]
(2) Patients with hepatic dysfunction [Hyperammonemia is liable to occur.]
(3) Patients with renal dysfunction [Hypernitremia may occur.]
(4) Patients with marrow depression [Administration of LEUNASE may exacerbate marrow depression.]
(5) Patients complicated with infection [Administration of LAUNASE may aggravate infection due to marrow depression.]
(6) Patients with varicella [Fatal systemic disorders may occur.]

2. Important Precautions

(1) Since **serious coagulopathy such as cerebral hemorrhage, cerebral infarction and pulmonary hemorrhage** may occur, patients should be monitored with frequent testing for fibrinogen, plasminogen, AT-III, protein C, etc. during treatment, and, if any abnormality is noted, appropriate measures such as suspension or discontinuance of administration should be taken.
(2) Since **serious acute pancreatitis** may occur, patients should be carefully observed during treatment, and, if symptoms such as abdominal pain, vomiting and in-

creases in pancreatic enzymes including amylase are noted, administration should be discontinued and appropriate measures should be taken.

Since **serious diabetes** may also occur, patients should be carefully observed during treatment, and, if symptoms such as thirst, polydipsia and polyuria are noted, administration should be suspended or discontinued and appropriate measures should be taken.

(3) Since serious adverse reactions such as marrow depression may occur, patient's condition should be carefully monitored with frequent laboratory testing (hematological test, liver function test and renal function test, etc.). If any abnormality is observed, appropriate measures such as reduction of the dosage and suspension of administration should be taken. Additionally, LEUNASE should be administered with care because long-term use of the product may cause enhanced adverse reactions, which may be protracted.

(4) Particular attention should be paid to the occurrence or aggravation of infectious disease and bleeding tendency.

(5) LEUNASE should be administered with care **in children** while paying special attention to the manifestation of adverse reactions.

(6) In case administration of LEUNASE is required in children or patients with reproductive possibility, potential effects on gonad should be considered.

3. Adverse Reactions

Adverse reactions including abnormalities in laboratory data were reported in 128 of 188 (68.1%) patients treated with LEUNASE before approval. A total of 302 patients were investigated before approval and between approval and 1st May 1976. Main reported adverse reactions were nausea in 103 patients (34.1%), vomiting in 89 patients (29.5%), anorexia in 63 patients (20.9%), fever in 43 patients (14.2%), hyperammonemia in 12 of 96 patients (12.5%) and shock in 6 patients (2.0%).

(1) Clinically significant adverse reactions

1) **Shock and anaphylactoid symptoms** may occur. If any of symptoms such as urticaria, angioedema, chills, vomiting, dyspnea, clouding of consciousness, convulsions, and decreased blood pressure is observed, administration should be immediately stopped and appropriate measures should be taken.

2) **Serious coagulopathy such as cerebral hemorrhage, cerebral infarction and pulmonary hemorrhage** (decrease of fibrinogen, decrease of prothrombin, decrease of plasminogen, decrease of AT-III, decrease of protein C, etc.) may develop. Patients should be carefully observed with frequent testing during treatment, and, if any abnormality is noted, appropriate measures such as suspension or discontinuance of administration should be taken.

3) **Serious acute pancreatitis** may occur. Patients should be carefully observed during treatment, and, if symptoms such as abdominal pain, vomiting and increases in pancreatic enzymes including amylase are noted, administration should be discontinued and appropriate measures should be taken.

Diabetes due to pancreatic endocrinopathy (inflammation of Langerhans' islet) may also occur. Patients should be carefully observed during treatment, and, if symptoms such as thirst, polydipsia and polyuria are noted, administration should be suspended or discontinued and appropriate measures should be taken.

4) **Hyperammonemia with consciousness disturbance** may occur. Patients should be carefully observed with regular testing, and appropriate measures such as suspension or discontinuance of administration should be taken if any abnormality is observed.

5) Symptoms such as **coma, consciousness disturbance and disorientation** may occur. Patients should be carefully observed, and appropriate measures such as suspension or discontinuance of administration should be taken if any abnormality is noted.

6) **Serious hepatic damage such as hepatic failure** may occur. Patients should be carefully monitored by hepatic function test. And, if any abnormality is noted, administration should be discontinued and appropriate measures should be taken

7) Extensive **organic disorder of brain**, which resulted in death, has been reported.

(2) Other adverse reactions

Such adverse reactions as listed in the below table may occur. Patients should be carefully observed, and, if any abnormality occurs, appropriate measures such as reduction of the dose and suspension of administration should be taken.

	≧5%	**5% > ≥0.1%**	**Incidence unknown**
Hypersensitivity	Rash		
Hematologic	Thrombocytopenia	Anemia	
Hepatic	Fatty liver		Hepatic function disorder
Renal		Edema, hypernitremia	Albuminuria, diuretic failure
Gastrointestinal	Anorexia, nausea, vomiting, diarrhea		
Psycho -neurologic	Malaise	Somnolence, anxiety, headache	
Others	Fever		Vascular pain, abnormal glucose tolerance, hyperlipaemia, sialoadenitis, parotitis

4. Use in the Elderly

Since elderly patients often have reduced physiological function and, therefore, are particularly susceptible to hepatic disorder, LEUNASE should be administered with caution in elderly patients, paying special attention to the dose and patient's condition.

5. Use during Pregnancy, Delivery or Lactation

(1) Administration of LEUNASE is not recommended in pregnant women or women who may possibly be pregnant. [Animal studies with mice and rats have shown teratogenicity of this drug manifested as exencephalia, anomaly of thoracic vertebra and ribs and delayed ossification.]

(2) Nursing mothers should discontinue breast feeding during treatment. [The safety of LEUNASE in nursing mothers has not been established.]

6. Pediatric Use

See 2. Important Precautions 5) and 6)

7. Precautions concerning Use

(1) Preparation[2)]

1) Reconstitute LEUNASE initially with 2 to 5mL of water for injection, JP (The Japanese Pharmacopoeia), and then dilute the solution with replenisher solution to 200 to 500mL.

2) Direct reconstitution with isotonic sodium chloride solution, JP should be avoided because it may cause the solution to become turbid due to salting out.

(2) Precautions during administration

1) Intradermal test is recommended in prior to the administration of LEUNASE, since the administration of LEUNASE may cause shock to occur.

Reconstitute 5000 K.U. of LEUNASE with 2mL of water for injection, and then dilute the solution with isotonic sodium chloride solution to make a 5mL solution. Take 0.1mL of the solution and dilute with isotonic sodium chloride solution to make a 1mL solution. Inject 0.1mL of the solution intracutaneously (dosage: 10 K.U.),[3)] and observe the patient for 15 to 30 minutes for confirming that no abnormality occurs.

2) LEUNASE should be used immediately after reconstitution.

(3) Route of administration

LEUNASE should not be administered by other routes than intravenous drip infusion.

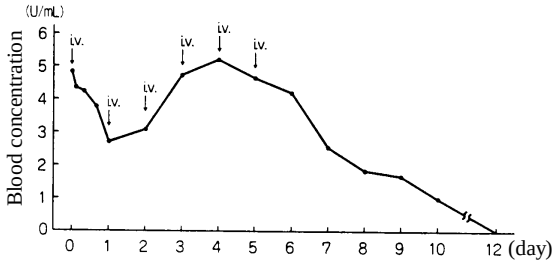
(4) Other precautions

It has been reported that LEUNASE has a higher potency than other L-asparaginase preparations manufactured and used in other countries[4)]. Attention should, therefore, be paid to the dosage in case this product is used in consultation with therapies prevailing in other countries.

PHARMACOKINETICS

1. Blood concentrations[5)]

Blood concentration of L-asparaginase changed as indicated in the below when it was administered intravenously for 6 consecutive days in lymphosarcoma patients at a dose of 11,000 KU (200 KU/kg):



2. Distribution (data from study in rats)[6)]

The concentration of L-asparaginase detected 15 minutes after intravenous administration of 2,500 KU/kg of L-asparaginase in rats was highest in the liver followed by spleen, lung, kidney, stomach and then by small intestine.

3. Excretion (data from study in rats)[6)]

When L-asparaginase was intravenously administered in rats at a dose as large as 50,000 to 100,000 KU/kg, only 0.014 to 0.032% of the dose was collected in urine within 24 hours after administration, indicating very little excretion of unchanged active substance. No activity was detected in urine after administration at a small dose.

CLINICAL STUDIES[7)~9)]

The results of clinical studies conducted at 36 institutions in Japan mainly in the patients with tumors in hematopoietic organs are summarized in the below table.

Cases which were judged as "complete remission" or "partial remission" by multiple Japanese evaluation criteria concerning therapeutic effects in acute leukemia and malignant lymphoma were evaluated as responded.

Disease	Type	Response rate (responded/treated)	
Acute leukemia	Lymphocytic leukemia	75.0%	(51/68)
	Myelocytic leukemia	40.8%	(29/71)
	Others	44.4%	(4/9)
Malignant lymphoma	Hodgkin's disease	36.4%	(4/11)
	Reticulosarcoma	53.8%	(7/13)
	Lymphosarcoma	68.9%	(13/19)
Total		56.5%	(108/191)

PHARMACOLOGY

1. Antineoplastic activity[10)-12)]

L-asparaginase demonstrates antineoplastic activities against lymphoblastoma L5178Y of mice, lymphoma 6C3HED of mice and sarcoma Walker 256 of rats.

2. Mechanism of action[7)13)]

L-asparaginase exerts its antineoplastic activity by decomposing L-asparagine in blood and thereby depriving asparagine requiring tumor cells of nutrients.

PHYSICOCHEMISTRY

L-asparaginase is a protein composed of four subunits containing 321 amino acids each.

Nonproprietary name : L-asparaginase (JAN)
Molecular weight : 141,000 (by Yhantis method)
Description : L-asparaginase occurs as a white cylinder or needle crystal of monoclinic system.
Solubility : It is very soluble in water but practically insoluble in methanol, acetone or chloroform.

PACKAGING

LEUNASE Injection 5000: Boxes of one vial
LEUNASE Injection 10000: Boxes of one vial

REFERENCES

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