40574IG
LUNS-S(5)(10) シンガポール

Antineoplastic enzyme preparation

Leunase® Inj.

L-asparaginase for Injection

Prescription-only drug

Storage	Expiration date
Store in a cold place. [Below 15℃(59℉)]	As indicated on the packaging

CONTRAINDICATIONS
(LEUNASE Inj. 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 Inj. contains 5,000 KU or 10,000 KU of lyophilized L-asparaginase. It is **a white powder to be reconstituted into** an injectable solution before use.

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

2. Product Description

Unit	5,000 KU	10,000 KU
Color	White	White
pH range	6.5 - 7.5	6.5 - 7.5

Stability : Comparatively stable to heat, pH and light in the crystal state.
Stability 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 dose 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 [Azotemia may occur.]
4) Patients with marrow suppression [Administration of LEUNASE may exacerbate marrow suppression.]
5) Patients complicated with infection [Administration of LEUNASE may aggravate infection due to marrow suppression.]
6) Patients with varicella [Fatal systemic disorders may occur.]

2. Important Precautions

1) Since **serious coagulopathy such as cerebral hemorrhage, cerebral 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 increases 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 suppression 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 of 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%).

Table below shows adverse reactions which have been reported in clinical trials and post marketing experience.

	Very Common (10%)	Common (1% to 10%)	Uncommon (0.1% to 1%)	Not known
Hypersensitivity		Rash, Pruritus, Shock	Hypotension	Anaphylaxis
Hepatic	Hyperammonemia, Hypoalbuminemia, Hypofibrinogenemia, Hypoproteinemia, Hypocholesterolemia	Hepatic steatosis, Decreased hepatic function, Increased AST (GOT), Increased ALT (GPT), Hypoprothrombinemia, Decreased in A / G ratio, Increased LDH, Decreased LDH, Increased alkaline phosphatase, Increased gamma-globulin	Hyperfibrinogenemia, Decreased S-GOT	Hepatic function disorder, Hepatic failure
Renal		Edema, Azotemia, Hyperuricemia	Renal function disorder, Increased BUN, Decreased BUN, Hematuria	Proteinuria, Incomplete bladder emptying
Gastrointestinal	Anorexia, Nausea / Retching, Vomiting	Diarrhea, Melena	Hematemesis, Pancreatic necrosis, Increased serum amylase	Pancreatitis acute
Psycho -neurologic		Malaise, Somnolence, Anxiety, Headache, Brain dysfunction, Convulsion	Dizziness	Coma, Consciousness disturbance and disorientation, Organic disorder of brain
Administration site				Administration site reaction (e.g., Induration, Pain, Hemorrhage, Hematoma, Abscess)
Hematology		Thrombocytopenia, Leukocytopenia, Bleeding tendency, Anemia		Coagulopathy such as Cerebral hemorrhage, Cerebral infarction and Pulmonary hemorrhage, Bone marrow suppression
Others	Pyrexia	Abdominal pain, Decrease in body weight, Chilly, General prostration	Chest pain, Back pain, Ophthalmalgia, Flushing, Sneezing	Vascular pain, Abnormal Glucose tolerance, Hyperlipidemia, Sialoadenitis, Parotitis, Infections such as pneumonia and sepsis

Clinical significant adverse reactions

(1) **Shock or anaphylactoid symptoms** may occur. Patients should be carefully observed during treatment, and, if symptoms such as urticaria, angioedema, rigors, vomiting, dyspnea. Clouding of consciousness, convulsions and decreased blood pressure are 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 frequent testing, and appropriate measures such as suspension or discontinuance of administration should be taken if 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, if any abnormality is noted, administration should be discontinued and appropriate measures should be taken.

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

(8) Bone marrow suppression may occur. Patients should be carefully monitored with frequent blood testing. In the event of an abnormality, appropriate measures such as dose reduction or suspension should be taken.

(9) Severe infections such as pneumonia and sepsis may occur. Patients should be carefully monitored and, in the event of an abnormality, appropriate measures should be taken.

4. Use in the Elderly

Since elderly patient 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.[1)]]

6. Pediatric Use

See 2. Important Precautions 5) and 6).

7. Precautions Concerning Use

1) Preparation

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

(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 recommendation in prior to the administration of LEUNASE, since the administration of LEUNASE may cause shock to occur.

(Reconstitute LEUNASE with water for injection (JP), and then dilute a part of the solution with isotonic sodium chloride solution (JP) to make a solution containing 1 to 10 KU of L-asparaginase. Inject 0.1 mL of the solution intracutaneously and observe the patient for about 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.

Variations in labelled potencies may exist between brands of L-asparaginase due to individual manufacturer's testing methods. LEUNASE should only be used by physicians experienced in the use and management of cytotoxic therapy. It should be used in a hospital environment, where there are adequate facilities to monitor and manage the possible short and longer term complications of therapy.

8. Drug Interactions

When asparaginase is administered immediately prior to or with methotrexate, it may diminish or abolish the cytotoxic effect of methotrexate. However, when administered to leukemia patients 9 to 10 days before or shortly after methotrexate, asparaginase appears to enhance the antitumor effect of methotrexate. Concomitant administration of asparaginase and vincristine may produce cumulative neuropathy. The toxicity seems to be less pronounced when asparaginase is administered after vincristine, instead of before or with the drug. Therefore, asparaginase should be administered after vincristine and prednisone, rather than before or with these drugs. The effects of asparaginase on liver function may interfere with the activation or detoxification of cyclophosphamide, mercaptopurine, and vincristine or may enhance the cytotoxicity of mercaptopurine, methotrexate, and prednisone.

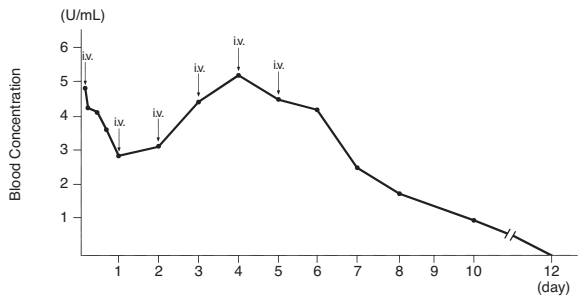
9. Incompatibilities

This product should not be mixed with other drugs.

[PHARMACOKINETICS]

1. Blood concentration[3)]

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



[CLINICAL STUDIES][5)7)]

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

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[8)10)]

L-asparaginase demonstrates antineoplastic sensitivities against lymphoblastoma L 5178Y of mice, lymphoma 6C3HED of mice, and sarcoma Walker 256 of rats.

2. Mechanism of action[5)11)]

L-asparaginase is an enzyme which hydrolyses the amino acid L-asparagine to L-aspartic acid and ammonia, and thus interferes with the growth of certain tumour cells, which unlike healthy cells, are unable to synthesize L-asparagine for their metabolism.

[PHYSICOCHEMISTRY]

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

Non-proprietary name: L-asparaginase

Molecular weight : 141,000 (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.

[HANDLING]

L-asparaginase is a contact irritant. Care should be taken to avoid contact with skin or mucous membranes (especially eyes). If accidental contact occurs, the affected area should be flushed with water for at least 15 minutes.

[PACKAGING]

5,000 KU/vial : Box of 1 vial

10,000 KU/vial : Box of 1 vial

Not all pack sizes may be marketed.

[REFERENCES]

1. Ohguro T. et al.: Yamaguchi Igaku, 18, 271, 1969
2. Nowak-Göttl U. et al.: Haematologic, 81, 127, 1996
3. Fujita H. et al.: Jap. J. Cancer Chemotherapy 1 (2), 215, 1974
4. Negishi T. et al.: Oyo Yakuri (Pharmacometrics), 4 (4), 593, 1970
5. Yamada K. et al.: Saishin Igaku, 25, 1064, 1970
6. Minoshima A. et al.: Shonika (Pediatrics of Japan), 11, 81, 1970
7. Nagamura S. et al.: Jap. J. Cancer Clinics, 10, 1032, 1970
8. Kidd J.G.: Recent Results in Cancer Research; Experimental and Clinical Effects of L-Asparaginase: Springer-Verlag.3, 1970
9. Burchenal J.H. et al.: Recent Results in Cancer Research; Experimental and Clinical Effects of L-Asparaginase: Springer-Verlag.102, 1970
10. Patterson Jr.M.K.: Recent Results in Cancer Research; Experimental and Clinical Effects of L-Asparaginase: Springer-Verlag.22, 1970
11. Broome J.D.: Recent Results in Cancer Research; Experimental and Clinical Effects of L-Asparaginase: Springer-Verlag.15, 1970

Product owner:
Kyowa Kirin Co., Ltd.
1-9-2 Otemachi, Chiyoda-ku, Tokyo

Revision Date: Oct 2019
Version: 4

IG