

PRODUCT INFORMATION

LEUNASE INJECTION

NAME OF THE MEDICINE

asparaginase (colaspase)

DESCRIPTION

Colaspase is L-asparaginase, or L-asparagine amidohydrolase. It is an enzyme produced from cultures of *Escherichia coli* HAP. Colaspase is a monomer thought to consist of four subunits of molecular weight about 33,000 each, for a unit molecular weight of $133,000 \pm 5,000$.

The lyophilised powder, which consists of white columnar or needle shaped monoclinic crystals, is readily soluble in water, but insoluble in ethanol and other organic solvents.

Aqueous solutions of colaspase are most stable in the pH range 6.5 to 7.5.

PHARMACOLOGY

Colaspase 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 synthesise L-asparagine for their metabolism.

One Kyowa Unit (KU) of colaspase splits 1 μmol of ammonia from L-asparagine in one minute under standard conditions.

PHARMACOKINETICS

Colaspase is not absorbed from the gastrointestinal tract.

Initial plasma levels following single intravenous injection are dose related. Colaspase distributes into a volume slightly larger than that of the plasma. The concentration of colaspase in the lymph reaches a maximum of about 20% of the plasma level at 3 hours after a dose, and in the CSF reaches 0.4 to 1% of plasma levels.

The plasma half-life of colaspase has been found to vary from 8 to 30 hours, and is unaffected by disease state or hepatic or renal function.

The mechanisms of metabolism and excretion of colaspase are unknown. Only traces of colaspase are found in the urine.

INDICATIONS

Treatment of acute lymphoblastic leukaemia, myeloid leukaemia or malignant lymphoma.

CONTRAINDICATIONS

Pregnancy. (See Use in Pregnancy).

Hypersensitivity to colaspase.

Pancreatitis or a history of pancreatitis. Acute haemorrhagic pancreatitis has been reported after colaspase administration.

PRECAUTIONS

Variations in labelled potencies may exist between brands of colaspase due to individual manufacturer's testing methods.

Prior to the start of Leunase therapy, the patient or his/her family should be fully informed about its benefits and risks.

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.

A test dose should always be administered at the start of treatment to check for hypersensitivity (see Dosage and Administration).

Patients who have received a course of Leunase and who are retreated with Leunase have an increased risk of hypersensitivity reactions.

Allergic reactions to Leunase are frequent and may occur during the primary course of therapy or even during skin testing, although the risk is increased after repeated courses of therapy. The risk of reaction is not completely predictable on the basis of the intradermal skin test, though this should always be administered at the start of treatment to check for hypersensitivity (See Dosage and Administration). Leunase should always be administered in hospital and under close supervision for this reason. Facilities for resuscitation should be close at hand during the use of Leunase. Anaphylaxis and death have occurred even in a hospital setting with experienced observers.

Leunase should be given cautiously to patients with impaired renal and/or liver function. Leunase should not be used as the sole induction agent unless combination therapy is deemed inappropriate. Leunase is not recommended for maintenance therapy.

Leunase has been reported to have immunosuppressive activity in animal experiments. Accordingly, the possibility that use of the drug may predispose to infection should be considered and use should be avoided where possible in the presence of infection. Leunase should be administered with care in patients with varicella (fatal systemic disorders may occur). Similarly, the administration of live virus vaccines should be avoided if possible during Leunase therapy.

Since serious coagulopathy such as cerebral hemorrhage, cerebral infarction and pulmonary hemorrhage may occur, patients should be monitored with frequent testing for fibrinogen, plasminogen, antithrombin, protein C, etc. during treatment, and, if any abnormality is noted, appropriate measures such as suspension or discontinuance of administration should be taken.

Posterior Reversible Encephalopathy Syndrome: Posterior Reversible Encephalopathy Syndrome (PRES), a neurological disorder, may occur rarely during treatment with colaspase. 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. Clinical symptoms of PRES include headache, seizures, altered mental status, hypertension and visual disturbances (primarily cortical blindness or homonymous hemianopsia). It is unclear whether the PRES is caused by colaspase, concomitant treatment or the underlying diseases.

Leunase should be ceased if PRES is suspected or diagnosed. PRES is treated symptomatically, including measures to treat any seizures. Discontinuation or dose reduction of concomitantly administered immunosuppressive medicinal products may be necessary.

Use in Pregnancy (Category D)

Contraindicated. Colaspase has been shown to have teratogenic effects on animals.

Use in Lactation

It is not known whether colaspase is excreted in breast milk, nor whether it has a harmful effect on the newborn. Therefore, it is not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

Paediatric Use

Leunase should be administered with care in children while paying special attention to the manifestation of adverse reactions.

Use in the elderly

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

Effect on Laboratory Tests

The fall in circulating lymphoblasts is often marked and may be accompanied by a marked rise in serum uric acid. Development of uric acid nephropathy is a possibility; preventative measures, eg. allopurinol, increased fluid intake or alkalinisation of urine, should be taken. If the patient is already receiving treatment for gout or hyperuricaemia, dosage adjustment may be required.

As a guide to the effects of therapy, peripheral blood count and bone marrow should be monitored frequently. Serum amylase determinations should be frequently obtained to detect early evidence of pancreatitis. If pancreatitis occurs, therapy should be stopped and not reinstated.

Blood sugar should be monitored during therapy because hyperglycaemia may occur.

Interference with thyroid function tests may occur due to decreased serum thyroxine binding globulin.

INTERACTIONS WITH OTHER MEDICINES

Leunase may interact with some antitumour agents and therefore should be used in combination regimes only by physicians familiar with the benefits and risks of a given regimen.

Increased toxicity may be associated with administration of Leunase concurrently with or immediately before a course of vincristine (neuropathy and disturbance erythropoiesis) and prednisone (hyperglycaemic effects).

For this reason it is suggested that if Leunase must be used with either vincristine or prednisone, it should be given after the other treatment in order to reduce the risk of interaction.

Leunase has been shown in tissue culture and animal studies to decrease the effect of methotrexate and hence methotrexate should not be used with Leunase therapy when plasma asparagine levels are below normal.

ADVERSE EFFECTS

Serious or Life Threatening Reactions

Rarely fatal hyperthermia, anaphylactic shock or haemorrhagic pancreatitis may occur.

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

Allergic Reactions

(See **PRECAUTIONS**)

Biochemical abnormalities

Increase in AST, ALT, alkaline phosphatase, serum bilirubin, BUN; decrease in serum lipoprotein, serum albumin, serum fibrinogen and serum cholesterol; serum and urine acetone, serum thyroxine binding globulin; hyperglycaemia; less commonly, increase in blood ammonia.

Dermatological

Urticaria, rash, exanthema and hives are signs of hypersensitivity reactions. If they occur, treatment should be stopped.

Endocrine

Pancreatitis, hyperglycaemia, sialoadenitis, parotitis.

Gastrointestinal

Nausea, vomiting and anorexia are common side effects, diarrhoea and abdominal cramps are less common. Stomatitis.

General

Fever, chills, weight loss, malabsorption syndrome, respiratory distress, malaise.

Genitourinary

Disturbances in renal function may appear (proteinuria, oedema). Hypoalbuminuria, hyperuricaemia and uric acid nephropathy. Acute renal failure and incomplete bladder emptying have been reported to occur.

Haematological

Decrease in platelets, and depression of various other clotting factors (particularly Factors V, VIII, VII and IX and plasminogen), haemorrhagic diathesis may appear, rarely intracranial thrombosis or haemorrhage or peripheral venous thrombosis have occurred, fatal bleeding associated with hypofibrinogenaemia has occurred, transient bone marrow depression.

Hepatic

Liver dysfunction, fatty liver.

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

Musculoskeletal

Arthralgia.

Metabolism and nutrition disorders

Hyperlipidaemia.

Nervous system

Somnolence, anxiety, headache, confusion, consciousness disturbance, disorientation; rarely, severe depression, stupor, coma, seizures, EEG changes, Parkinson-like syndrome. CNS effects are more common in adults where their incidence may approach 30 to 60%.

Patients should be carefully observed, and appropriate measures such as suspension or discontinuance of administration should be taken if any abnormality is noted.

Leukoencephalopathy such as posterior reversible encephalopathy syndrome has been reported, although the causal relationship between Leunase and leukoencephalopathy has not been clear.

Infection

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.

DOSAGE AND ADMINISTRATION

Caution

Colaspase 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.

The usual dosage range for Leunase is 50 to 200 KU/kg bodyweight daily or every alternate day, given intravenously. Dosage should be individualised based on the clinical response and tolerance of the patient. Specialist texts should be consulted for recommended dosing schedules (including sequence of administration), when used alone or in combination.

Test Dose

Before treatment is started a test dose of 1 to 10 KU of colaspase in 0.1 mL of distilled water should be injected subcutaneously and the injection site observed for several hours for evidence of primary hypersensitivity. Serious allergic reactions can occur following administration of a test

dose; patients should be observed in a hospital setting. A negative skin reaction does not preclude the development of an allergic reaction.

Intravenous administration

Reconstitute by adding 5mL of water for injections to a vial containing 10,000 KU of colaspase and shake gently to dissolve. Only a clear solution should be used. Direct reconstitution with normal saline should be avoided because it may cause the solution to become turbid due to salting out.

The dose required should then be removed from the resulting solution, containing 2,000 KU of colaspase per mL, and further diluted in 200 to 500 of either normal saline or 5% glucose w/v before use. This product should not be mixed with other drugs. Infusion should be slow, over the 2 to 4 hours. Discard any unused portion of solution. To reduce microbiological hazard reconstitution and further dilution should occur just prior to dosing and infusion should commence as soon as practicable and certainly be completed within 24 hours.

Toxicity

See following table.

Leunase Toxicity		Mouse		Rat		Guinea Pig	
		Male	Female	Male	Female	Male	Female
Acute toxicity	IV	95.7	75.0	33.3	42.5	15.0	15.0
LD ₅₀	IP	240.0	183.7	36.1	46.0	89.8	89.8
(x 10 ⁴ KU/kg)	SC	210.0	190.0	36.1	54.2		

PRESENTATION AND STORAGE CONDITIONS

Vials, 10,000 KU: 1s.

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Leunase must be used immediately after reconstitution.

Only clear solutions should be used.

Discard any unused portion of solution.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park, NSW 2113
AUSTRALIA

sanofi-aventis new zealand limited
Level 8,
56 Cawley Street
Ellerslie, Auckland
NEW ZEALAND

POISON SCHEDULE OF THE MEDICINE (MEDICINE CLASSIFICATION)

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE ARTG

21 October 1991

DATE OF MOST RECENT AMENDMENT

04 November 2016