DATA SHEET

1 PRODUCT NAME

Leunase powder for infusion, 10,000KU.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 10,000 KU of asparaginase (colaspase).

After reconstitution, 1 mL of solution contains 2,000KU of asparaginase (colaspase).

Asparaginase (colaspase) is L-asparaginase, or L-asparagine amidohydrolase. It is an enzyme produced from cultures of *Escherichia coli* HAP. Asparaginase (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 ± 5,000.

3 PHARMACEUTICAL FORM

Leunase is a 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 Leunase are most stable in the pH range 6.5 to 7.5.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Asparaginase (colaspase) is indicated for the treatment of acute lymphoblastic leukaemia, myeloid leukaemia or malignant lymphoma.

4.2 DOSE AND METHOD OF ADMINISTRATION

Asparaginase (colaspase) 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.

Test Dose

Before treatment is started a test dose of 1 to 10 KU of asparaginase (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.

Dose

The usual dosage range for asparaginase (colaspase) 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.

Precautions to be taken before handling or administering the medicine

Asparaginase (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.

Method of administration

Reconstitute by adding 5mL of water for injections to a vial containing 10,000 KU of asparaginase (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 asparaginase (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.

For instructions on reconstitution and dilution of the medicine before administration, see section 6.6.

4.3 CONTRAINDICATION

Pregnancy. (See section 4.6).

Hypersensitivity to asparaginase (colaspase).

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

Asparaginase (colaspase) 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 section 4.2).

Patients who have received a course of asparaginase (colaspase) and who are retreated with asparaginase (colaspase) have an increased risk of hypersensitivity reactions.

Allergic reactions to asparaginase (colaspase) 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 section 4.2). Asparaginase (colaspase) 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 asparaginase (colaspase). Anaphylaxis and death have occurred even in a hospital setting with experienced observers.

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

Asparaginase (colaspase) 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. Asparaginase (colaspase) 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 asparaginase (colaspase) 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.

Use in Lactation

It is not known whether asparaginase (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

Asparaginase (colaspase) 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, asparaginase (colaspase) 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 alkalisation 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 reinstituted.

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.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Asparaginase (colaspase) 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 asparaginase (colaspase) 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 asparaginase (colaspase) must be used with either vincristine or prednisone, it should be given after the other treatment in order to reduce the risk of interaction.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Use in Pregnancy (Category D)

Contraindicated. Asparaginase (colaspase) has been shown to have teratogenic effects on animals.

Breast-feeding

It is unknown whether asparaginase (colaspase) is excreted into human breast milk. Because potential serious adverse reactions may occur in nursing infants, Asparaginase (colaspase) should be discontinued during breast-feeding.

Fertility

No human data on the effect of asparaginase (colaspase) on fertility are available.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Asparaginase (colaspase) has moderate influence on the ability to drive and use machines, especially through its potential effects on the nervous and gastrointestinal systems (see section 4.8).

4.8 UNDESIRABLE EFFECTS

a. Summary of the safety profile

The primary toxicity of asparaginase (colaspase) results from immunologic reactions caused by exposure to the bacterial protein. Hypersensitivity reactions range from transient flushing or rash and urticaria to anaphylaxis.

Most serious side effects of asparaginase (colaspase) include severe hypersensitivity reactions such as anaphylactic shock (rare), fatal hyperthermia (rare), or haemorrhagic pancreatitis (rare). Extensive organic disorder of brain (not known), which resulted in death, has been reported.

Leukoencephalopathy such as posterior reversible encephalopathy syndrome (PRES) has been reported, although the causal relationship between asparaginase (colaspase) and leukoencephalopathy has not been clear.

A range of nervous system disorders have been reported, including somnolence, anxiety, headache (common); severe depression, stupor, coma, seizures, EEG changes, Parkinson-like syndrome (rare); confusion, consciousness disturbance, disorientation (not known). 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.

Most frequently (very common) observed side effects of asparaginase (colaspase) include hypersensitivity reactions (see also section 4.4), nausea, vomiting, fever, and weight loss.

b. Tabulated summary of adverse reactions

The following adverse reactions have been accumulated from clinical trials with asparaginase (colaspase) as well as post-marketing experience with other E. coli-derived asparaginase preparations in children and adults.

The adverse drug reactions are presented in the following table by system/organ class, and are ranked by frequency, using the following convention:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare < 1/10,000
Not known cannot be estimated from the available data

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

System organ class	**Frequency and symptom**
Infections and infestations	**Not known** Severe infections such as pneumonia and sepsis.
Blood and lymphatic system disorders	**Rare** Intracranial thrombosis or haemorrhage, peripheral venous thrombosis, fatal bleeding associated with hypofibrinogenaema, bone

	marrow depression. **Not known** Serious coagulopathy such as cerebral hemorrhage, cerebral infarction and pulmonary hemorrhage. Decrease in platelets, and depression of various other clotting factors (particularly Factors V, VIII, VII and IX and plasminogen), haemorrhagic diathesis. Hyperlipidaemia.
Immune system disorders	**Very common** Hypersensitivity Reactions, see section 4.4. **Not known** Shock or anaphylaxis, Sialoadenitis, parotitis.
Endocrine disorders	**Common** Pancreatitis, hyperglycaemia.
Metabolism and nutrition disorders	**Not known** Glucose tolerance abnormal.
Psychiatric disorders	**Common** Anxiety.
Nervous system disorders	**Common** Headache, somnolence. **Rare** Severe depression, stupor, coma, seizures, EEG changes, Parkinson-like syndrome. **Not known** Headache, confusion, consciousness disturbance, disorientation, consciousness disturbance. Extensive organic disorder of brain. Leukoencephalopathy such as posterior reversible encephalopathy syndrome (PRES).
Vascular disorders	**Not known**

	Vascular pain.
Gastrointestinal disorders	**Very common** Nausea, vomiting. **Common** Diarrhoea. **Uncommon** Abdominal cramps. **Not known** Stomatitis.
Hepatobiliary disorders	**Common** Hepatic steatosis. **Not known** Liver dysfunction, fatty liver. Serious hepatic damage such as hepatic failure. 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.
Skin and subcutaneous tissue disorders	**Common** Urticaria, rash, exanthema and hives are signs of hypersensitivity reactions. If they occur, treatment should be stopped.
Musculoskeletal and connective tissue disorders	**Common** Arthralgia.
Renal and urinary disorders	**Common** Azotaemia. **Not known** Disturbances in renal function (proteinuria, oedema). Hypoalbuminuria, hyperuricaemia and uric acid nephropathy. Hyperammonemia with consciousness disturbance. Acute renal

	failure and incomplete bladder emptying.
General disorders and administration site conditions	**Very common** Fever, weight loss. **Common** Malaise, oedema. **Not known** Malabsorption syndrome, chills, respiratory distress. Administration site reaction (e.g., induration, pain, haemorrhage, haematoma, abscess).
Investigations	**Common** 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; **Uncommon** Increase in blood ammonia.

c. Description of selected adverse reactions

d. Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

No case of asparaginase overdose with clinical symptoms has been reported. There is no specific antidote. Treatment is symptomatic and supportive.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents; Other antineoplastic agents.

ATC code: L01XX02.

Asparaginase (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 asparaginase (colaspase) splits 1 µmol of ammonia from L-asparagine in one minute under standard conditions.

5.2 PHARMACOKINETIC PROPERTIES

Asparaginase (colaspase) is not absorbed from the gastrointestinal tract.

Initial plasma levels following single intravenous infusion are dose related. Asparaginase (colaspase) distributes into a volume slightly larger than that of the plasma. The concentration of asparaginase (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 asparaginase (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 asparaginase (colaspase) are unknown. Only traces of asparaginase (colaspase) are found in the urine.

5.3 PRECLINICAL SAFETY DATA

Toxicity

See following table.

Asparaginase (colaspase) 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		

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

None.

6.2 INCOMPATIBILITIES

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 SHELF LIFE

Unopened vials

2 years. Store at 2°C to 8°C (Refrigerate. Do not freeze). Do not use after the expiration date indicated on the package.

Reconstituted and diluted solution

Asparaginase (colaspase) must be used immediately after reconstitution.

Only clear solutions should be used.

Discard any unused portion of solution.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

None. For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER AND SPECIAL EQUIPMENT FOR USE, ADMINISTRATION OR IMPLANTATION

Vials, 10,000 KU: 1s.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Only Medicine.

8 SPONSOR

sanofi-aventis new zealand limited
Level 8,
56 Cawley Street
Ellerslie, Auckland
NEW ZEALAND
Toll Free Number (medical information 0800 283 684)

9 DATE OF FIRST APPROVAL

16 February 1978

10 DATE OF REVISION OF THE TEXT

02 August 2017

11 SUMMARY TABLE OF CHANGES

Format changed in accordance with the updated data sheet SPC-style format

Below highlights all differences between the current and the new formatted Datasheet document

SECTION	ADDITIONAL TEXT ADDED / CHANGES
Throughout the data sheet	Replaced Leunase with asparaginase (colaspase), apart from Sections 1 and 3, as per guidelines. Active substance name has been changed from colaspase to asparaginase (colaspase) as per Changed Medicine Notification. In text references have been updated to the relevant data sheet sections. Where appropriate, replaced injection with infusion as per Changed Medicine

	Notification.
1 PRODUCT NAME	Leunase powder for infusion, 10,000KU
2 QUALITATIVE AND QUANTITATIVE COMPOSITION	One vial contains 10,000 KU of asparaginase (colaspase). After reconstitution, 1 mL of solution contains 2,000KU of asparaginase (colaspase).
3 PHARMACEUTICAL FORM	Added product name, as per NZ datasheet guidelines.
4.1 THERAPEUTIC INDICATIONS	Asparaginase (colaspase) is indicated for the
4.2 DOSE AND METHOD OF ADMINISTRATION	For instructions on reconstitution and dilution of the medicine before administration, see section 6.6
4.6 FERTILITY, PREGNANCY AND LACTATION	Added sections on breast feeding and fertility.
4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES	Updated.
4.8 UNDESIRABLE EFFECTS	Added safety profile. Undesirable effects have been organised in a tabulated summary and updated using data from company core data sheet. Paragraphs introducing the table have been added. Reporting of suspected adverse reactions section has been added as per the guidelines. sialoadenitis, parotitis moved from infections and infestations to Immune system disorders
4.9 OVERDOSE	No case of asparaginase overdose with clinical symptoms has been reported. There is no specific antidote. Treatment is symptomatic and supportive.
5.1 PHARMACODYNAMIC	Pharmacotherapeutic group: Antineoplastic

PROPERTIES	agents; Other antineoplastic agents. ATC code: L01XX02.
6.1 LIST OF EXCIPIENTS	None.
6.2 INCOMPATIBILITIES	This medicine must not be mixed with other medicines except those mentioned in section 6.6.
6.3 SHELF LIFE	Unopened vials 2 years. Store at 2°C to 8°C (Refrigerate. Do not freeze). Do not use after the expiration date indicated on the package. Reconstituted and diluted solution
6.4 SPECIAL PRECAUTIONS FOR STORAGE	None. For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING	Any unused medicine or waste material should be disposed of in accordance with local requirements.
8 SPONSOR	Toll Free Number (medical information 0800 283 684)
9 DATE OF FIRST APPROVAL	16 February 1978
10 DATE OF REVISION OF THE TEXT	02 August 2017