AUSTRALIAN PRODUCT INFORMATION
ONCASPAR® (pegaspargase) powder for solution for injection/infusion

1 NAME OF THE MEDICINE

Pegaspargase.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ONCASPAR (pegaspargase) is a modified version of the enzyme asparaginase. Pegaspargase, the active substance, is a covalent conjugate of *Escherichia coli* (*E. coli*) derived asparaginase with monomethoxypolyethylene glycol (mPEG) using a succinimidyl-succinate linker.

L-asparaginase is a tetrameric enzyme that is produced endogenously by *E. coli* and consists of identical 34.5 kDa subunits. Approximately 69 to 82 molecules of mPEG are linked to L-asparaginase; the molecular weight of each mPEG molecule is about 5 kDa. ONCASPAR activity is expressed in Units. One unit is defined as the quantity of enzyme required to liberate 1 µmol ammonia per minute at pH 7.3 and 37 °C.

Each vial contains 3,750 U pegaspargase. After reconstitution, 1 mL of solution contains 750 U pegaspargase (750 U/mL). The potency of this product should not be compared to any other pegylated or non-pegylated protein of the same therapeutic class.

For the full list of excipients, see section 6.1 - *List of excipients*.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

Appearance

Lyophilised white to off-white powder. After reconstitution, the solution is clear, colourless and free from visible particles. 1 mL of solution contains 750 U pegaspargase.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ONCASPAR is indicated as a component of antineoplastic combination therapy in patients with Acute Lymphoblastic Leukaemia (ALL).

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be prescribed by physicians and administered by health care personnel experienced in the use of antineoplastic products. The product should only be given in a clinical setting where appropriate resuscitation equipment is available. Patients should be closely monitored and carefully observed for any adverse reactions throughout the administration period (see also section 4.4 - *Special warnings and precautions for use*). As a routine precautionary measure patients should be monitored for one hour after administration.

ONCASPAR does not contain antimicrobial preservative. It is for single use in one patient only. Discard any unused solution.

Recommended premedication

Premedicate patients with paracetamol, an H-1 receptor blocker (e.g. diphenhydramine), and an H-2 receptor blocker (e.g. famotidine) 30-60 minutes prior to administration of ONCASPAR to decrease the risk and severity of both infusion and hypersensitivity reactions (*see section 4.4 – Special warnings and precautions for use*).

Dosage

Patients ≤ 21 years of age

The recommended dose for paediatric patients with a body surface area (BSA) <0.6 m² and infants <1 year of age is 82.5 U (equivalent to 0.1 mL)/kg body weight every 14 days.

The recommended dose for paediatric patients with a BSA >0.6 m^2 and ≤ 21 years of age is 2,500 U (equivalent to 3.3 mL)/m^2 BSA every 14 days.

Patients > 21 years of age

The recommended dose for adult patients > 21 years of age is 2,000 U (equivalent to 2.67 mL)/m^2 BSA every 14 days.

For patients ≥ 65 years of age, the recommended dose has not been established.

Refer to local clinical practice guidelines (e.g. EviQ) for further details regarding prevention, management (including potential dose adjustments) and monitoring of side effects in patients receiving ONCASPAR as part of a multicomponent chemotherapy regimen (see also section 4.4 - *Special warnings and precautions for use*).

Method of administration

For intramuscular (IM) or intravenous (IV) administration only.

For smaller volumes, the preferred route of administration is IM.

Instructions for reconstitution of the vial of lyophilised powder

1. Inject 5.2 mL water for injections into the vial using a syringe and 21 gauge needle.
2. Gently swirl the vial until the powder is reconstituted.
3. After reconstitution, the solution should be clear, colourless and free from visible foreign particles. Do not use if the reconstituted solution is cloudy or if a precipitate has formed. Do not shake.
4. The solution should be used as soon as possible following reconstitution. Reconstituted solution must be used within:
   - 6 hours when stored at room temperature
   - 24 hours when stored at 2-8 ºC.

Dilution of the reconstituted ONCASPAR vial prior to administration

For intravenous infusion, dilute ONCASPAR solution with 100 mL sodium chloride 9 mg/mL (0.9 %) or 5 % dextrose, using sterile/aseptic technique. After dilution, administer immediately into

a running infusion of either sodium chloride 9 mg/mL (0.9 %) or 5 % dextrose, respectively. The dose is usually given over a period of 1-2 hours. Do not infuse other drugs through the same intravenous line during administration of ONCASPAR. If storage is necessary, hold at 2-8 ºC for not more than 24 hours or 6 hours at room temperature (not to exceed 25 ºC).

For instructions on reconstitution of the lyophilised formulation before administration, see Instructions for use, handling and disposal.

Monitoring of asparaginase levels

It is recommended to monitor the trough serum asparaginase activity two weeks after administration of ONCASPAR. If activity falls below 0.1 U/mL, it may be necessary to switch to another asparaginase preparation (see also section 4.4 - *Special warnings and precautions for use-Asparaginase antibodies*).

Instructions for use, handling and disposal

ONCASPAR must be handled and administered with care.

Do not administer if the product, before any manipulation:

- has been frozen
- has been stored at room temperature (not to exceed 25 °C) for more than 48 hours
- has been shaken or vigorously agitated
- has visible foreign matter, or discoloration
- has passed the expiry date.

4.3 CONTRAINDICATIONS

ONCASPAR is contraindicated in patients with:

- history of anaphylactic or severe hypersensitivity reactions to the active substance or to any of the excipients
- history of serious thrombosis during previous asparaginase therapy
- history of pancreatitis including pancreatitis related to previous asparaginase therapy
- history of serious haemorrhagic events during previous asparaginase therapy
- history of severe hepatic impairment.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

It is strongly recommended that every time ONCASPAR is administered to a patient, the name and lot number of the product are recorded in order to link the patient and the lot of the product.

Anaphylaxis and serious hypersensitivity reactions

- Hypersensitivity reactions including life-threatening anaphylaxis, have been observed with ONCASPAR, particularly in patients with known hypersensitivity to *E. coli* derived asparaginase formulations. Other hypersensitivity reactions can include angioedoema, lip swelling, eye swelling, erythema, blood pressure decreased, bronchospasm, dyspnoea, pruritus, and rash.
- Premedicate patients 30-60 minutes prior to administration of ONCASPAR (see section 4.2 - *Dose and method of administration*).

- Because of the risk of allergic reactions ONCASPAR administration should be performed under medical observation. Monitor patients for one hour after administration of ONCASPAR in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (for example, epinephrine, oxygen, intravenous steroids, antihistamines).
- Discontinue ONCASPAR in patients with serious hypersensitivity reactions. Adequate medical treatment and provisions should be available for immediate use in the event of an anaphylactic reaction.

Pancreatic toxicities

Pancreatitis

- Pancreatitis has been reported in patients receiving ONCASPAR. Haemorrhagic or necrotising pancreatitis with fatal outcomes has been reported.
- There is an increased risk of pancreatitis in patients > 10 years of age, with doses greater than the recommended dose, and in the presence of other components of the backbone therapy (such as anthracycline agents, cytarabine and cyclophosphamide).
- If pancreatitis is suspected, ONCASPAR should be discontinued; if pancreatitis is confirmed, ONCASPAR should not be restarted.
- Patients should be informed of the signs and symptoms of pancreatitis, which if left untreated, could be fatal. This includes persistent abdominal pain which can be severe and may radiate to the back.
- Serum amylase and/or lipase measurements should be performed frequently to identify early signs of pancreatic inflammation.
- If treatment is terminated due to pancreatitis, appropriate investigations (e.g. ultrasound) should be performed at least four months following termination of therapy. As the precise pathogenesis is unknown, only supportive measures can be recommended. Disturbances of exocrine pancreatic function can result in diarrhoea.

Hyperglycaemia

- As hyperglycaemia may occur with the use of ONCASPAR, blood and urine glucose levels should be monitored.
- As impaired glucose tolerance may occur with concomitant use of ONCASPAR with prednisone, blood glucose levels should be monitored.

Coagulopathy

- Serious thrombotic events, including sagittal sinus thrombosis may occur in patients receiving ONCASPAR. ONCASPAR should be discontinued in patients experiencing serious thrombotic events.
- In the presence of corticosteroids, osteonecrosis (avascular necrosis) is a possible complication of hypercoagulability observed in children > 10 years of age with a higher incidence seen in girls (see sections 4.5 - *Interactions with other medicines and other forms of interactions* and 4.8 - *Adverse effects (Undesirable effects)*).
- Increased prothrombin time (PT), increased partial thromboplastin time (PTT), hypofibrinogenemia and antithrombin III decrease may occur in patients receiving ONCASPAR. A baseline coagulation profile should be established and then periodically monitored during

and after treatment; particularly when other medicinal products with coagulation inhibiting pro-coagulant/anticoagulant effects such as, methotrexate, daunorubicin, corticosteroids, acetylsalicylic acid, and non-steroidal anti-inflammatory medicinal products are used concomitantly (see section 4.5 - *Interactions with other medicines and other forms of interactions*).

- When there is a marked decrease in fibrinogen or Antithrombin III (ATIII) deficiency, consider appropriate replacement therapy.

Osteonecrosis

- In the presence of glucocorticoids, osteonecrosis (avascular necrosis) is a possible complication of hypercoagulability observed in children and adolescents with a higher incidence seen in girls (see section 4.5 *Interactions with other medicines and other forms of interactions* and 4.8 - *Adverse effects (Undesirable effects)*). Therefore, close monitoring in children and adolescents is recommended in order to detect any clinical signs/symptoms of osteonecrosis. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment as per standard guidelines of treatment of ALL and supportive care principles.

Hepatic toxicities

- Administration of ONCASPAR with hepatotoxic products can result in severe hepatic toxicity. Caution is required when ONCASPAR is given in combination with hepatotoxic products. Monitor the patient for changes in liver function parameters.
- There may be an increased risk of hepatotoxicity in Philadelphia chromosome positive patients for whom treatment with kinase inhibitors (e.g. imatinib) is combined with asparaginase therapy. There is also an increased risk of hepatic effects (such as increase in transaminases, bilirubin increased, hypofibrinogenemia) among patients > 18 years of age. This should be taken into account when considering the use of ONCASPAR in this patient population.
- Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a rare, life-threatening hepatic condition that can be associated with high-dose chemotherapy.
  Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of hepatic VOD, have been observed in patients treated with ONCASPAR in combination with standard chemotherapy, including during the induction phase of multiphase chemotherapy (see section 4.8 *Adverse effects (Undesirable effects)*).
  Signs and symptoms of VOD include rapid weight gain, fluid retention with ascites, hepatomegaly, thrombocytopenia and rapid increase of bilirubin. The identification of risk factors like pre-existing liver disease or history of VOD is essential for its prevention. Prompt recognition and appropriate management of VOD is imperative. Patients who experience this condition should be treated according to standard medical practice.
- Due to the risk of hyperbilirubinemia, it is recommended to monitor bilirubin levels at baseline and prior to each dose.

Central nervous system toxicities

- Combination therapy with ONCASPAR can result in central nervous system toxicity. Cases of encephalopathy (including reversible posterior leukoencephalopathy syndrome) have been reported. If ONCASPAR is used in association with neurotoxic therapies (such as vincristine and methotrexate), the patient should be closely monitored.

- ONCASPAR may cause central nervous system symptoms manifesting as seizures, confusion, and somnolence.

Myelosuppression

ONCASPAR causes myelosuppression, either directly or indirectly (by altering myelosuppressive effects of other agents such as methotrexate or 6-mercaptopurine). Therefore, use of ONCASPAR could increase the risk of infections in patients.

The peripheral blood count and the patient's bone marrow should be monitored closely. Dose reductions of concurrently administered myelosuppressive agents may be considered.

Asparaginase antibodies

Similar to other protein-based products, anti-drug antibodies can develop with the administration of ONCASPAR (see section 4.8 - *Adverse effects (Undesirable effects)*). The appearance of anti-asparaginase antibodies may be associated with low asparaginase activity levels. As a precaution, measurement of the asparaginase activity level in serum or plasma is recommended. In cases of accelerated reduction of asparaginase activity, switching to an asparaginase preparation derived from another bacterial source may be considered.

Hyperammonaemia

- Asparaginase facilitates the rapid conversion of asparagine and glutamine to aspartic acid and glutamic acid, with ammonia as the shared by-product of both reactions. Intravenous administration of asparaginase may therefore cause serum levels of ammonia to rise sharply following administration.
- The symptoms of hyperammonaemia are often transient in nature and can include nausea, vomiting, headache, dizziness and rash. In severe cases, encephalopathy can develop with or without hepatic impairment, especially in older adults, which can be life-threatening or fatal. If symptoms of hyperammonaemia exist (e.g. nausea, vomiting, lethargy, irritation), ammonia levels should be monitored closely.

Use in the elderly (age >65)

There is limited data available for patients older than 65 years.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects on protein-bound drugs

The decrease in serum proteins caused by ONCASPAR can increase the toxicity of other medicinal products that are protein-bound.

Effects on use with other chemotherapeutic agents

Immediately preceding or concomitant treatment with vincristine can increase the toxicity of ONCASPAR and increases the risk of anaphylactic reactions. Therefore, vincristine should be given in a timely manner before administration of ONCASPAR in order to minimise toxicity.

ONCASPAR may affect the action of other chemotherapeutic agents requiring cell division for their effect (i.e. methotrexate, cytarabine). This effect can be either synergistic or antagonistic,

depending on the timing of administration of the agents. Adherence to the treatment schedule is therefore recommended to minimise these potential interactions.

Effects on metabolism and clearance of other drugs

ONCASPAR has the potential to interfere with metabolism and clearance of other medicinal products, based on its effects on protein synthesis and hepatic function, as well as from its combined use with other chemotherapeutic drugs known to interact with CYP enzymes.

Asparaginase may increase the risk of glucocorticoid-induced osteonecrosis in children > 10 years of age, with a higher incidence seen in girls (see sections 4.4 - *Special warnings and precautions for use* and *4.8 - Adverse effects (Undesirable effects)*).

Coagulation effects

The use of ONCASPAR can lead to fluctuating levels of coagulation factors. This could increase the risk of bleeding and/or thrombosis. Caution is needed when anticoagulants such as: coumarin, heparin, dipyridamole, acetylsalicylic acid or nonsteroidal anti-inflammatory drugs are given concomitantly.

Alterations in coagulation parameters (e.g. fall in fibrinogen and ATIII deficiency) can be more pronounced when glucocorticoids, such as prednisone and ONCASPAR are given concomitantly.

Pegaspargase may increase the risk of glucocorticoid-induced osteonecrosis in children and adolescents when both treatments are given simultaneously, with a higher incidence seen in girls, through a potential increase in exposure of dexamethasone (see sections 4.4 - *Special warnings and precautions for use* and 4.8 - *Adverse effects (Undesirable effects)*).

Oral contraceptive effects

An indirect interaction cannot be ruled out between ONCASPAR and oral contraceptives; due to pegaspargase hepatotoxicity that may impair the hepatic clearance of oral contraceptives. Therefore, the combination of ONCASPAR and oral contraceptives is not recommended. A method other than oral contraception should be used in women of childbearing potential (see section 4.5 - *Interactions with other medicines and other forms of interactions*).

Effects on live vaccines

Simultaneous vaccination of live vaccines with ONCASPAR may increase the risk of severe infections attributable to the patient's underlying disease and the usually combined chemotherapy. Vaccination with live vaccines should only be given after consultation with the treating Oncologist. The timing of vaccination after chemotherapy may be dependent on the anti-leukaemic agents used; and might be administered at the earliest, three to six months after the termination of the entire anti-leukaemic treatment.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of pegaspargase on fertility have not been established.

Men and women of childbearing potential should use effective contraception during treatment and for at least 6 months after ONCASPAR discontinuation. Since an indirect interaction between components of the oral contraception and pegaspargase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation. A method other than oral

contraceptives should be used in women of childbearing potential (see section 4.5 - *Interactions with other medicines and other forms of interactions*).

Use in pregnancy

Australian Pregnancy Categorisation (Category D).

There are no adequate data from the use of ONCASPAR and limited data from the use of asparaginase in pregnant women.

No studies of reproductive toxicity were conducted with pegaspargase. Embryotoxicity studies with native L-asparaginase have given evidence of teratogenicity in rats treated from day 6 to 15 of gestation with a No Observed Effect Level (NOEL) for teratogenic effects at 300 U/kg IV. In rabbits doses of 50 or 100 U/kg IV (600 or 1200 U/m^2) on days 8 and 9 of gestation induced congenital malformations in viable foetuses; no NOEL has been determined. Multiple malformations and embryolethal effects were observed with doses in the therapeutic range. Investigations of the effect on fertility and peri- and postnatal development were not conducted.

Due to teratogenicity shown in animal studies with native L-asparaginase, ONCASPAR should not be used during pregnancy.

Use in lactation

It is not known whether pegaspargase is excreted into breast milk. Potential risk to newborns/infants breast feeding cannot be excluded. Therefore, as a precautionary measure, breast feeding should be discontinued during treatment with ONCASPAR and not resumed until after treatment with ONCASPAR has ceased.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The following adverse reactions have been reported in patients treated with ONCASPAR along with other chemotherapeutic agents: somnolence, confusion, dizziness, syncope, seizure. Patients should not drive or operate machinery while receiving ONCASPAR if they experience these or other CNS-related events (see section 4.4 - *Special warnings and precautions for use*).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

The adverse reactions described in this section are gathered from a combination of adverse reactions from clinical trial data and post-marketing experience with ONCASPAR in ALL patients.

The safety profile for ONCASPAR is based on randomised, controlled, prospective, open label, multicenter studies using ONCASPAR at a dose of 2500 U/m^2 administered intravenously (IV) as a first line treatment of ALL during the Induction phase (studies DFCI 001-011 and AALL07P4) (see section 5.1 - *Pharmacodynamic properties-Clinical Trials*).

In addition, the safety profile includes data from other ONCASPAR pharmacokinetic studies using the intramuscular (IM) route of administration (studies CCG-1962 (see section 5.1 - *Pharmacodynamic properties-Clinical Trials*) and CCG-1991), as well as other post-marketing studies from the literature were also considered to determine the safety profile.

Study CCG-1991 was a randomised, multifactorial design study in which 2,957 subjects aged 1 to <10 years with newly diagnosed standard risk ALL were administered ONCASPAR 2,500 U/m^2 as a component of various multi-agent chemotherapy regimens using the IM route of administration.

The most common adverse reactions with ONCASPAR (observed in at least 2 studies with a frequency of > 10 %) included: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hypofibrinogenemia, activated partial thromboplastin time prolonged, hypertriglyceridemia, hyperglycaemia, febrile neutropenia.

The most severe adverse reactions with ONCASPAR (Graded 3 or 4) consistently reported in all studies and observed in studies DFCI 11-001 and AALL07P4 with a frequency of > 5 % included: anaphylactic reaction, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hypoalbuminemia, febrile neutropenia, blood fibrinogen decreased, hyperglycaemia, lipase increased, pancreatitis, hypoglycaemia, embolism, activated partial thromboplastin time prolonged, hypersensitivity.

Adverse reactions that were reported in studies DFCI 11-001 and AALL07P4 are presented in Table 1.

Table 1: Adverse Reactions Observed with ONCASPAR In at Least One Subject in Each of the Studies DFCI 11-001 and AALL07P4

System Organ Class	**Preferred Term**	**DFCI 11-001** **ONCASPAR 2,500 U/m^2 N=119 N (%)**	**AALL07P4** **ONCASPAR 2,500 U/m^2 N=52 n (%)**
Blood and Lymphatic System Disorders	Febrile neutropenia	18 (15.1)	8 (15.4)
Gastrointestinal Disorders	Pancreatitis	20 (16.8)	4 (7.7)
	Ascites	1 (0.8)	1 (1.9)
Hepatobiliary Disorders	Blood bilirubin increased	28 (23.5)	22 (42.3)
Immune system disorders	Anaphylactic reaction	1 (0.8)	10 (19.2)
	Hypersensitivity	7 (5.9)	3 (5.8)
Infections and infestations	Sepsis	3 (2.5)	1 (1.9)
Investigations [§]	Hypoalbuminemia	96 (80.7)	1 (1.9)
	Alanine aminotransferase increased	62 (52.1)	10 (19.2)
	Aspartate aminotransferase increased	47 (39.5)	6 (11.5)
	Hypertriglyceridemia	43 (36.1)	6 (11.5)
	Blood fibrinogen decreased	30 (25.2)	3 (5.8)
	Lipase increased	28 (23.5)	5 (9.6)
	Amylase increased	20 (16.8)	2 (3.8)
	Activated partial thromboplastin time prolonged	12 (10.1)	9 (17.3)
	International normalised ratio Increased	6 (5.0)	4 (7.7)
	Hypokalemia	1 (0.8)	6 (5.0)

System Organ Class	Preferred Term	DFCI 11-001 ONCASPAR 2,500 U/m² N=119 N (%)	AALL07P4 ONCASPAR 2,500 U/m² N=52 n (%)
Metabolism and Nutrition Disorders	Hyperglycaemia	26 (21.8)	22 (42.3)
Nervous system disorders	Syncope	2 (1.7)	1 (1.9)
	Seizure	1 (0.8)	1 (1.9)
Vascular disorders	Embolism*	14 (11.8)	1 (1.9)

* The following adverse reactions were observed in DFCI 11-001: Pulmonary embolism (1.7 %), venous thrombosis (1.7 %), venous thrombosis limb (0.8 %), thrombophlebitis superficial (0.8 %).
§ The disparity in the reported ADR frequencies may be attributed primarily to differences in the study design (e.g. enrolment criteria, chemotherapy regimen, differences in laboratory / AE data collection, and dictionaries used to collect safety data).

Study CCG-1962, was a multi-centre randomised study of ONCASPAR compared with native *E. coli* asparaginase as part of antineoplastic combination therapy in children aged 1 through 9 years with newly diagnosed untreated standard-risk acute lymphoblastic leukaemia. Detailed safety information was collected for pre-specified adverse reactions identified as asparaginase-induced adverse reactions and for Grade 3 and 4 non-haematologic adverse reactions according to the Children's Cancer Group (CCG) Toxicity and Complication Criteria. The per-patient incidence for these selected adverse reactions occurring at a severity of Grade 3 or 4 is presented in Table 2 below.

Table 2: Per-Patient Incidence of Selected Grade 3 And 4 Adverse Reactions in Study CCG-1962

	ONCASPAR (n=58)	**Native *E. coli* asparaginase** (n=59)
Abnormal Liver Tests	3 (5 %)	5 (8 %)
Elevated Transaminases[1]	2 (3 %)	4 (7 %)
Hyperbilirubinemia	1 (2 %)	1 (2 %)
Hyperglycaemia	3 (5 %)	2 (3 %)
Central Nervous System Thrombosis	2 (3 %)	2 (3 %)
Coagulopathy[2]	1 (2 %)	3 (5 %)
Pancreatitis	1 (2 %)	1 (2 %)
Clinical Allergic Reactions to Asparaginase	1 (2 %)	0

[1] Aspartate aminotransferase, alanine aminotransferase.
[2] Prolonged prothrombin time or partial thromboplastin time; or hypofibrinogenaemia.

Table 3 describes adverse reactions reported with ONCASPAR in the clinical program and during post-marketing experience. The frequency of side effects is defined by 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), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse Reactions Reported With ONCASPAR Therapy (In The Clinical Program And During Post-Marketing Experience)

MedDRA Standard System Organ Class	**Adverse Reaction**
Blood and lymphatic system disorders	*Very Common*: Febrile neutropenia *Common*: Anaemia, coagulopathy, thrombosis *Not known:* Bone marrow failure
Gastrointestinal disorders	*Very common*: Pancreatitis, diarrhoea, abdominal pain, nausea *Common*: Vomiting, stomatitis, ascites *Rare:* Pancreatitis necrotising, pancreatitis haemorrhagic *Not known:* Pancreatic pseudocyst, parotitis*
General disorders and administration site conditions	*Not known:* Pyrexia
Hepatobiliary disorders	*Common:* Hepatotoxicity, fatty liver *Rare:* Hepatic cell necrosis, jaundice, cholestasis, icterus and hepatic failure with fatal outcome
Immune system disorders	*Very common*: Hypersensitivity, urticaria, rash, anaphylactic reactions *Not known:* Anaphylactic shock
Infections and infestations	*Common*: Infections, sepsis
Investigations	*Very Common*: Weight decreased, hypoalbuminaemia, alanine aminotransferase increased, aspartate aminotransferase increased, hypertriglyceridaemia, blood fibrinogen decreased, amylase increased, lipase increased, activated partial thromboplastin time prolonged, blood bilirubin increased, antithrombin III decreased****, neutrophil count decreased**** *Common:* Prothrombin time prolonged. international normalised ratio increased, hypokalaemia, blood cholesterol increased, hypofibrinogenaemia, gamma-glutamyl transferase increased, hyponatremia, platelet count decreased *Not known:* Blood urea increased, anti-pegaspargase antibodies, platelet count decreased, hyperammonaemia
Metabolism and nutrition disorders	*Very Common:* Decreased appetite, hyperglycaemia *Common:* Hypertriglyceridaemia, hyperlipidaemia, hypercholesterolaemia *Not known:* Diabetic ketoacidosis, hypoglycaemia
Musculoskeletal and connective tissue disorders	*Common*: Pain in extremities *Not known:* Osteonecrosis (see section 4.4 *Special warnings and precautions for use* and section 4.5 *Interactions with other medicines and other forms of interactions*)
Nervous system disorders	*Common*: Seizure, convulsion, peripheral motor neuropathy, syncope *Rare:* Posterior reversible leukoencephalopathy syndrome

MedDRA Standard System Organ Class	Adverse Reaction
	Not known: Somnolence, tremor*
Psychiatric disorders	*Not known:* Confusional state
Renal and urinary disorders	*Not known:* Renal failure acute*
Respiratory, thoracic and mediastinal disorders	*Common:* Hypoxia
Skin and subcutaneous tissue disorders	*Very common:* Rash *Not known:* Toxic epidermal necrolysis*
Vascular disorders	*Very common:* Embolism** *Common*: Thrombosis*** *Not known:* Cerebrovascular accident, haemorrhage, superior sagittal sinus thrombosis
Endocrine disorders	*Very Common*: Hyperglycaemia

* Adverse reactions observed with other asparaginases in the class

** Cases of pulmonary embolism, venous thrombosis, venous thrombosis limb, and thrombophlebitis superficial were observed in DFCI 11-001

*** CNS thrombosis

****Cases of antithrombin III and neutrophil count decreased were observed in ONCASPAR post-marketing studies.

Description of selected adverse reactions

The following adverse reactions have been observed in association with asparaginase therapy. Although they have not been specifically associated with the use of pegaspargase, they may occur with the use of ONCASPAR.

Blood and lymphatic system disorders

ONCASPAR can cause mild to moderate myelosuppression, and all three blood cell lines can be affected.

About half of all serious haemorrhages and thromboses affect cerebral vessels and can lead to stroke, seizures, headache or loss of consciousness. ONCASPAR may also cause: neutrophil count decreased and platelet count decreased.

Gastrointestinal disorders

About half of patients develop mild to moderate gastrointestinal reactions such as loss of appetite, nausea, vomiting, abdominal cramps, diarrhoea and weight loss.

Acute pancreatitis can occur commonly. There have been isolated reports of formation of pseudocysts (up to four months after the last treatment).

Haemorrhagic or necrotising pancreatitis occurs rarely. One case of pancreatitis with simultaneous acute parotitis has been described with asparaginase treatment. In single cases, haemorrhagic or necrotising pancreatitis with fatal outcome has been reported.

Serum amylase can rise during and also after the conclusion of ONCASPAR therapy.

ONCASPAR may also cause dehydration and hepatic failure.

General disorders and administration side conditions

Pyrexia can occur after the injection, which usually subsides spontaneously. ONCASPAR may also cause fatigue, and pain.

Hepatobiliary disorders

Alteration of liver parameters is very common. A dose independent rise in serum transaminases and serum bilirubin is commonly observed.

Rapid weight gain, fluid retention with ascites, hepatomegaly, associated with rapid increase of serum bilirubin and persistent thrombocytopenia might indicate a risk of developing severe VOD, which if left untreated, can be fatal (see section 4.4 *Special warnings and precautions for use*).

Fatty liver can be observed very frequently. There have been rare reports of hepatic cell necrosis, cholestasis, icterus and hepatic failure with fatal outcome.

Impaired protein synthesis can lead to a decline in the serum proteins. There is a dose independent decrease in serum albumin in the majority of patients during the treatment.

The type of side effects of ONCASPAR largely coincides with that of native non pegylated asparaginase (e.g. native *E. coli* asparaginase).

Immune system disorders

Specific antibodies to pegaspargase have been measured. Neutralising antibodies reducing clinical efficacy were also observed. ONCASPAR may also cause anaphylactic shock.

Hypersensitivity reactions to ONCASPAR, including life-threatening anaphylaxis, angioedema, lip swelling, eye swelling, erythema, blood pressure decreased, bronchospasm, dyspnoea, pruritus and rash, can occur during therapy (see sections 4.3 - *Contraindications* and 4.4 - *Special warnings and precautions for use*).

Metabolism and nutrition disorders

An alteration in serum lipid levels was observed and changes in serum lipid values, in most cases without clinical symptoms, are very common.

A rise in serum urea occurs regularly, is dose independent and nearly always a sign of pre-renal metabolic imbalance.

Nervous system disorders

ONCASPAR may cause central nervous system dysfunctions manifesting as convulsion, and less frequently confusional state and somnolence (mildly impaired consciousness).

In rare cases, a reversible posterior leukoencephalopathy syndrome (RPLS) may occur.

In very rare cases, mild tremor in the fingers has been described.

Renal and urinary disorders

Acute renal failure may develop in rare cases during treatment with asparaginase containing regimens.

Skin and subcutaneous tissue disorders

Allergic reactions can manifest in the skin. One case of toxic epidermal necrolysis (Lyell‘s syndrome) has been described in association with asparaginase.

Vascular disorders

ONCASPAR may cause haemorrhage, and superior sagittal sinus thrombosis.

Endocrine disorders

Alterations in endocrine pancreatic function are observed commonly and are expressed mainly in the form of abnormal glucose metabolism. Both diabetic ketoacidosis and hyperosmolar hyperglycaemia have been described, which generally respond to administration of exogenous insulin.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre telephone: 131126 (Australia) or 0800 764 766 [0800 POISON] (New Zealand)

There have been a few cases of accidental overdose have been reported with ONCASPAR. Following overdose, increased liver enzymes, rash and hyperbilirubinaemia have been observed. There is no specific pharmacological treatment. In case of overdose, patients must be carefully monitored for signs and symptoms of adverse reactions, and appropriately managed with symptomatic and supportive treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacodynamics

Pharmacodynamic effect of ONCASPAR was evaluated in two studies, Study CCG-1962 and Study AALL07P4.

In Study CCG-1962, pharmacodynamics were assessed in 57 newly diagnosed paediatric patients with standard-risk Acute Lymphoblastic Leukaemia (ALL) who received three intramuscular (IM) doses of ONCASPAR (2,500 U/m^2), one each during induction and two delayed intensification treatment phases (see section 5.1 - *Pharmacodynamic properties-Clinical Trials*).

A reduction in serum asparagine concentration was evident by the 4th day after the first Induction dose and reached an apparent nadir by the 10^{th} day after the dose. Low concentrations of approximately 1 µM persisted for approximately 3 weeks. An apparent trend was observed where asparagine concentration fell to < 3 µM when asparaginase activity was > 0.1 U/mL. Cerebrospinal fluid (CSF) asparagine fell from pre-treatment concentrations of 2.3 µM to 1.1 µM on Day 7 and 0.6 µM on Day 28 of induction. Pharmacodynamic activity was assessed through serial measurements of asparagine in sera (n=57) and cerebrospinal fluid (CSF) (n=50). The data for asparagine depletion are presented in CLINICAL TRIALS (see section 5.1 - *Pharmacodynamic properties-Clinical Trials*).

The pharmacodynamic effect of ONCASPAR was also assessed in 47 evaluable subjects with high risk B-precursor ALL (Study AALL07P4) who received IV doses of ONCASPAR.

2,500 U/m^2 during the induction and consolidation phases (see section 5.1 - *Pharmacodynamic properties-Clinical Trials*).

Within 24 hours following the induction and first consolidation dose, ONCASPAR depleted plasma L-asparagine concentrations to below the assay limit of quantification. Depletion was sustained for approximately two weeks. Following the induction dose, CSF asparagine concentrations were reduced by the 4th day and remained largely undetectable by Day 18 after dosing. These results

demonstrate that a 2,500 U/m^2 dose of ONCASPAR provides maintenance of L-asparagine depletion for approximately two weeks following dosing.

Mechanism of action

Pegaspargase is a PEGylated form of the enzyme L-asparaginase which catalyses the conversion of the amino acid L-asparagine into aspartic acid and ammonia. The PEGylation does not change the enzymatic properties of the asparaginase, but it influences the pharmacokinetics and immunogenicity of the enzyme. The mechanism of action of pegaspargase is thought to be based on selective destruction of leukaemic cells due to depletion of plasma L-asparagine.

Leukaemic cells with low expression of asparagine synthetase have a reduced ability to synthesise L-asparagine and therefore depend on an extracellular source of asparagine for protein synthesis and survival. Normal cells, however, due to their ability to synthesise L-asparagine, are less affected by the depletion of plasma L-asparagine.

Clinical trials

The efficacy of ONCASPAR was evaluated based upon three clinical studies using ONCASPAR solution for injection/infusion in the first line treatment of ALL in both standard and high-risk patients: Study CCG-1962, Study AALL07P4, and Study DFCI 11-001.

For the relapse/refractory haematological diseases, ONCASPAR efficacy was based on pooled data from 94 ALL patients with a history of prior clinical allergic reactions to native *E. coli* asparaginase, from six open-label studies.

Clinical studies in first-line (non-hypersensitive population) in ALL

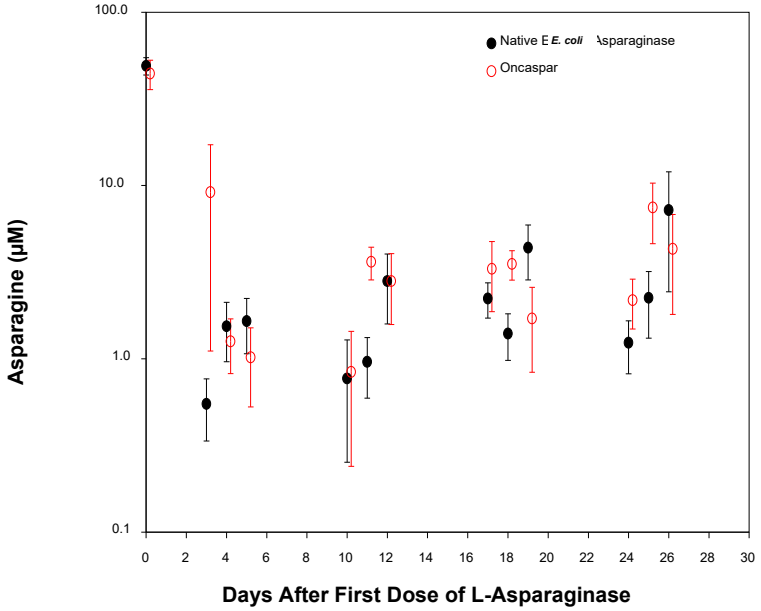
Study CCG-1962

The safety and effectiveness of ONCASPAR was evaluated in an open-label, multicentre, randomised, active-controlled study (Study CCG-1962). In this study, 118 paediatric patients aged 1 to 9 years with previously untreated standard-risk ALL were randomised 1:1 to ONCASPAR or native *E. coli* asparaginase as part of combination therapy. ONCASPAR was administered IM at a dose of 2,500 U/m^2 on Day 3 of the 4-week induction phase and on Day 3 of each of two 8-week delayed intensification phases. Native *E. coli* asparaginase was administered IM at a dose of 6,000 U/m^2 three times weekly for 9 doses during induction and for 6 doses during each delayed intensification phase.

One determination of effectiveness was based on demonstration of similar asparagine depletion (magnitude and duration) in the ONCASPAR and native *E. coli* asparaginase treatment groups. The protocol-specified goal was achievement of asparagine depletion to a serum concentration of ≤1 µM. The proportion of patients with this level of depletion was similar between the two study arms during all 3 phases of treatment at the protocol-specified time points.

In all phases of treatment, serum asparagine concentrations decreased within 4 days of the first dose of asparaginase in the treatment phase and remained low for approximately 3 weeks for both ONCASPAR and native *E. coli* asparaginase groups. Serum asparagine concentrations during the induction phase are shown in Figure 1. The patterns of serum asparagine depletion in the 2 delayed intensification phases are similar to the pattern of serum asparagine depletion in the induction phase.

Figure 1. Mean (± Standard Error) Serum Asparagine Concentrations during Study CCG-1962 Induction Phase



Note: ONCASPAR (2,500 U/m^2 IM) was administered on Day 3 of the 4-week induction phase. Native *E. coli* asparaginase (6,000 U/m^2 IM) was administered 3 times weekly for 9 doses during induction.

CSF asparagine concentrations were determined in 50 patients during the induction phase. CSF asparagine decreased from a mean pre-treatment concentration of 3.93 µM to 1.53 µM on Day 5 and 0.55 µM at 26 days after administration of ONCASPAR. These findings were similar to those observed in the native *E. coli* asparaginase treatment arm.

Event-Free Survival (EFS) for the ONCASPAR and native *E. coli* asparaginase arms are summarised in Table 4 Study CCG-1962 was not designed to evaluate for differences in EFS rates.

Table 4. Event-Free Survival Rate at 3, 5 and 7 years (Study CCG-1962)

	ONCASPAR	**native *E. coli* asparaginase**
3-Year EFS Rate, % (95 % CI)	83 (73, 93)	79 (68, 90)
5-Year EFS Rate, % (95 % CI)	78 (67, 88)	73 (61, 85)
7-Year EFS Rate, % (95 % CI)	75 (63, 87)	66 (52, 80)

Study AALL07P4

This was a pilot study conducted by the Children's Oncology Group (COG) in newly diagnosed patients 1 to < 31 years of age with National Cancer Institute (NCI) high risk B-precursor ALL. This

was an open label, controlled, randomised study comparing an investigational pegylated asparaginase versus ONCASPAR in the first line treatment of ALL.

White blood cell (WBC) criteria were: (a) Age 1.000-9.999 years: WBC ≥ 50,000/micro litre; (b) Age 10.000-30.999 years: Any WBC; (c) Prior steroid therapy: Any WBC. Patients were not allowed prior cytotoxic chemotherapy with the exception of steroids and intrathecal cytarabine.

A total of 166 patients were randomised, 163 of whom were treated with the study drug; of these, 54 patients were treated with ONCASPAR 2500 U/m^2. ONCASPAR was administered IV during induction/extended induction, consolidation, delayed intensification and interim maintenance phases of an augmented Berlin-Frankfurt-Münster (aBFM) treatment regimen.

The primary objective of the study was to determine the pharmacokinetic comparability of the investigational pegylated asparaginase *versus* ONCASPAR when given intravenously during induction and consolidation. Efficacy outcomes collected for both treatment arms included Minimal Residual Disease (MRD) at Day 29 of induction, EFS and OS rates.

In the full analysis set, the percentage of patients in the ONCASPAR treatment arm with evaluable MRD negative status (< 0.1 % leukaemia cells in bone marrow) at Day 29 of induction was 80 % (40/50). At 4 years, the EFS and overall survival (OS) for the ONCASPAR treatment arm were, 81.8 % [95 % CI: 62.9, 91.7] and 90.4 % [95 % CI: 78.5, 95.9], respectively.

Study DFCI 011-001

Study DFCI 011-001, conducted by the Dana-Farber Cancer Institute (DFCI), is an ongoing, active-controlled, randomised, multicenter study of an intravenous investigational pegylated asparaginase *versus* intravenous ONCASPAR, in children and adolescents aged 1 to < 22 years with newly diagnosed ALL treated with a DFCI ALL consortium therapeutic backbone.

A total of 239 patients were randomised, 237 of whom were treated with study drug (146 male/91 female); of these, 119 patients (115 with a diagnosis of ALL) were treated with ONCASPAR 2,500 U/m^2. Treatment was administered during induction (Day 7), and then every 2 weeks for a total of 30 weeks post induction therapy. Randomisation of patients was stratified based on risk group (standard/high/very high risk), including both B- and T-cell ALL.

The primary objective of the study was to assess the safety and feasibility of administering the investigational pegylated asparaginase compared with ONCASPAR, when administered intravenously as a single dose during induction and every 3 weeks for 30 weeks post-induction therapy. Efficacy outcomes collected for both treatment arms included rates.

In the full analysis set, the percentage of patients in the ONCASPAR arm with evaluable Low End-Induction MRD (< 0.001 detectable disease by PCR) at Day 32 was 87.9 % (80/91). The one-year EFS was 98.0 % [95 % CI: 92.3, 99.5]; the one-year OS was 100 [95 % CI: 100, 100] in this study.

ALL Patients with hypersensitivity to native *E. coli* asparaginase

Six open-label studies evaluated ONCASPAR in relapse/refractory haematological diseases. In these studies, a total of 94 patients with ALL and a history of prior clinical allergic reactions to native *E. coli* asparaginase were exposed to ONCASPAR. One patient received ONCASPAR doses of 250 and 500 U/m^2 IV. The remaining patients were treated with 2000 or 2500 U/m^2 administered IM or IV. Patients received ONCASPAR as a single agent or in combination with multi-agent chemotherapy.

Using the highest therapeutic response from 65 patients with ALL (from 5 studies) treated with ONCASPAR, complete remission was observed in 30 patients (46 %), partial remission in 7 patients (11 %) and haematological improvement in 1 patient (2 %). In contrast, in the other study, 29 patients with ALL were treated with ONCASPAR; 11 patients were evaluated for response during induction. Of these, 3 patients achieved complete remission (27 %), 1 patient had partial remission (9 %), 1 patient had haematologic improvement (9 %) and 2 patients had therapeutic efficacy (18 %). Therapeutic efficacy was defined as a clinical improvement which did not meet the criteria for other beneficial outcomes. During the maintenance phase, 19 patients were evaluated, with 17 patients achieving complete remission (89%), and 1 patient with therapeutic efficacy (5 %).

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetic assessments of ONCASPAR were based on an enzymatic assay measuring asparaginase activity after IM (CCG-1962) and IV (AALL07P4, DFCI 11-001) administration.

In Study CCG-1962, mean asparaginase activity peaked on Day 5 after the injection and averaged 1 U/mL. The mean half-life of absorption from the injection site was 1.7 days and the elimination half-life was 5.5 days. The volume of distribution at steady-state and clearance were estimated at 1.86 L/m^2 and 0.169 L/m^2 per day, respectively.

In Study AALL07P4, PK parameters after a single 2,500 U/m2 IV dose during Induction were calculated by noncompartmental PK analysis from sequential plasma asparaginase activity samples and are depicted in Table 5 (see section 5.1 - *Pharmacodynamic properties-Clinical Trials*). The C_{max} and AUC of ONCASPAR trended lower in males, subjects with larger BMI, and older age subjects (> 10 years). During Induction, following a single IV dose of ONCASPAR 2,500 U/m^2, asparaginase activity ≥ 0.1 U/mL was sustained for up to 18 days post-dose in 95.3 % of subjects.

Table 5 - Pharmacokinetic Parameters After a Single IV Dose of ONCASPAR 2,500 U/m^2 During Induction (N=47; Study AALLP074)

PK Parameters	**Arithmetic Mean (SD)**
Cmax (mU/mL)*	1638 (459.1)
Tmax (hr)*	1.25 (1.08, 5.33)†
AUC_{0-t} (mU/day/mL)*	14810 (3555)
$AUC_{0-\infty}$ (mU/day/mL)‡	16570 (4810)
$t_{½}$(day)‡	5.33 (2.33)
CL (L/day)‡	0.2152 (0.1214)
Vss (L)‡	1.95 (1.13)
* N=47 evaluable subjects. † Median (10th, 90th percentiles). ‡ N= 46 evaluable subjects.	

In Study DFCI 11-001, assessments of asparaginase activity were performed following a single IV dose of ONCASPAR 2,500 U/m^2 during induction, and every two weeks during post-induction (see section 5.1 - *Pharmacodynamic properties-Clinical Studies*). During induction, plasma asparaginase activity ≥ 0.1 U/mL was sustained in 93.5 % of subjects 18 days after administration. During the post-induction phase, a nadir (trough) asparaginase activity above 0.4 U/mL was sustained in 100 % of subjects from Week 7 up until Week 25. These results indicate that, when ONCASPAR 2,500 U/m^2 is administered as single and repeated doses every two weeks, clinically relevant asparaginase activity is sustained over the entire dosing interval (i.e. two weeks).

Pharmacokinetics in special patient groups

The controlled studies were not designed to formally evaluate the pharmacokinetics of ONCASPAR in specific populations. A population pharmacokinetic evaluation of ONCASPAR based on data obtained from Studies AALLP074 (IV), DFCI 11-001 (IV), and CCG-1962 (IM) identified that clearance (linear and saturable) increased approximately proportional to BSA and volume of distribution increased slightly more proportional to BSA. No statistically significant differences in PK characteristics between male and female subjects were identified in this analysis.

Renal impairment

The impact of renal impairment on the PK of ONCASPAR has not been evaluated. As pegaspargase is a protein with a high molecular weight, it is not excreted renally and no change in the pharmacokinetics of ONCASPAR in patients with renal impairment is expected.

Hepatic impairment

ONCASPAR is contraindicated in patients with severe hepatic impairment (see section 4.3 - *Contraindications*).

Use in elderly

Data are minimal for the use of ONCASPAR in elderly patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity of pegaspargase was not adequately investigated, but pegaspargase is not expected to be genotoxic.

Carcinogenicity

Long-term investigations of carcinogenicity in animals were not conducted with pegaspargase.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium dihydrogen phosphate monohydrate
Disodium phosphate heptahydrate
Sodium chloride
Sucrose
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 INCOMPATIBILITIES

This medicine must not be mixed with other medicines except those mentioned in section 4.2 - *Dose and method of administration*. For interactions, please refer to section 4.5 - *Interactions with other medicines and other forms of interactions.*

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ONCASPAR must be stored under refrigerated conditions (2° to 8°C).

Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type

ONCASPAR lyophilised formulation is available in 5 mL Type I glass vials with a rubber stopper (chlorobutyl) and an aluminium seal with flip-off cap.

Pack size

1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

ONCASPAR is for single use only. Any unused solution or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number:

130167-69-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8 SPONSOR

Australia
Servier Laboratories (Aust.) Pty. Ltd.
www.servier.com.au
Level 4, Building 9,
588A Swan Street
Burnley, 3121, Victoria

New Zealand
Servier Laboratories (NZ) Ltd
Level 4, Zurich House
21 Queen Street
Auckland Central,
Auckland 1010

9 DATE OF FIRST APPROVAL

08 March 2019

10 DATE OF REVISION

07 May 2024

SUMMARY TABLE OF CHANGES

Section(s) Changed	Summary of new information
4.4, 4.8	Addition of VOD as a new important risk related to hepatoxicity, AE: Antithrombin III and neutrophil count decreased frequency changed from common to very common.