AUSTRALIAN PRODUCT INFORMATION
ONCASPAR® (PEGASPARGASE)

1 NAME OF THE MEDICINE

Pegaspargase.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One mL of solution contains 750 units (U) of pegaspargase; one unit is defined as the quantity of enzyme required to liberate 1 µmol ammonia per minute at pH 7.3 and 37 ^{o}C. One vial of 5 mL solution contains 3,750 U.

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

Injection, solution.

Appearance

Clear, colourless solution for injection in a Type I glass vial closed with a grey rubber stopper and an aluminium seal with flip-off cap.

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 and administered by physicians and health care personnel experienced in the use of antineoplastic products. The product should only be given in a hospital setting where appropriate resuscitation equipment is available. Patients should be closely monitored and carefully observed for any adverse reactions, particularly patients starting with therapy.

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

Dosage

Pediatric and adult patients (≤ 21 years of age)

The recommended dose for pediatric patients with a body surface area <0.6 m² is 82.5 U (U equivalent of 0.1 mL)/kg body weight every 14 days.

The recommended dose for patients ≤ 21 years of age and pediatric patients with a body surface area ≥0.6 m^2 is 2500 U (U equivalent of 3.3 mL)/m^2 body surface area every 14 days.

Adult patients (> 21 years of age)

Unless otherwise prescribed, the recommended dose for adult patients > 21 years of age is 2000 U (U equivalent of 2.67 mL)/m^2 body surface area every 14 days.

The recommended dose for patients ≥ 65 years of age 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 IM or IV administration only.

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

When ONCASPAR is given IV, the dose is usually given over a period of 1-2 hours through an infusion of 100 mL sodium chloride 9 mg/mL (0.9 %) or 5 % dextrose together with an already-running infusion.

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 IU/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 use if the solution is cloudy or a precipitate has formed.

Do not use if the vial has been stored at room temperature (not to exceed 25°C) for more than 48 hours. Please discard after storage at room temperature. Do not return to refrigeration.

Do not shake. If the vial has been shaken vigorously, it must not be administered.

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

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

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.
- Suspicion of severe hypersensitivity or anaphylactic-type reactions requires immediate discontinuation of the injection. Adequate medical treatment and provisions should be available for immediate use in the event of an anaphylactic reaction.
- Because of the risk of allergic reactions ONCASPAR administration should be performed under medical observation.

Pancreatic effects

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 *section 4.5 - Interactions with other medicines and other forms of interactions*).

- Increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenaemia 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 pro-coagulant/anticoagulant effects such as, methotrexate, daunorubicin, corticosteroids, acetylsalicylic acid and nonsteroidal 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 drop in fibrinogen or Antithrombin III (ATIII) deficiency, consider targeted substitution.

Hepatic effects

- 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 transaminase, 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.
- Due to the risk of hyperbilirubinemia, it is recommended to monitor bilirubin levels at baseline and prior to each dose.
- If ONCASPAR is used in association with hepatotoxic substances, the patient should be closely monitored for liver impairment, especially if there is pre-existing hepatic impairment.

Central Nervous System effects

- 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 convulsion, 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 ADVERSE 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

- Asparginase 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 hyperammonemia 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

Protein effects

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

By inhibiting protein synthesis and cell division, ONCASPAR can disturb the mechanism of action of other substances which require cell division for their effect, e.g., methotrexate. Methotrexate and cytarabine can interfere differently; prior administration of these substances can increase the action of ONCASPAR synergistically. However, if these substances are given subsequently, the effect of ONCASPAR can be weakened antagonistically.

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 *section 4.4 - Special warnings and precautions for use*).

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 prednisolone and ONCASPAR are given concomitantly.

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 increases the risk of severe infections attributable to the patient's underlying disease and the usually combined chemotherapy. Vaccination with live vaccines should be given, at the earliest, 3 months after the termination of the entire antileukaemic treatment.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of pegaspargase on fertility have not been established.

Men and women 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. ONCASPAR may have a major influence on the ability to drive and use machines. It may result in altering the patient's ability to react. 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)

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.

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 1 below:

Table 1: 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 2 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 2: Adverse reactions reported with ONCASPAR therapy

MedDRA Standard System Organ Class	**Adverse Reaction**
Infections and infestations	Common: Infections, sepsis
Blood and lymphatic system disorders	Common: Febrile neutropenia, anaemia, thrombosis
Immune system disorders	Very common: Hypersensitivity, urticaria, rash, anaphylactic reactions
Endocrine disorders	Very Common: Hyperglycaemia
Metabolism and nutrition disorders	Common: Hypertriglyceridaemia, hyperlipidaemia
Nervous system disorders	Common: Convulsion, peripheral motor neuropathy, syncope
Vascular disorders	Common: Thrombosis
Respiratory, thoracic and mediastinal disorders	Common: Hypoxia
Gastrointestinal disorders	Very common: Pancreatitis, diarrhoea, abdominal pain Common: Vomiting, stomatitis
Musculoskeletal and connective tissue disorders	Common: Pain in extremities
Investigations	Common: Amylase increased, alanine aminotransferase increase, blood bilirubin increase, neutrophil count decreased, platelet count decreased, activated partial thromboplastin time prolonged

Post-Marketing Adverse Reactions

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 e.g. stroke, seizures, headache or loss of consciousness.

ONCASPAR can cause: anemia, coagulopathy, neutrophil count decreased, and platelet count decreased.

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.

ONCASPAR may also cause peripheral neuropathy.

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.

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.

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.

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.

General disorders and administration side conditions

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

Immune system disorders

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

Hepatobiliary disorders

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

Fatty liver can be observed very frequently. There have been rare reports of cholestasis, icterus, hepatic cell necrosis 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).

Investigations

ONCASPAR may cause: blood cholesterol increased, Gamma-glutamyl transferase increased, hypercalcemia, and hyponatremia.

Vascular disorders

ONCASPAR may cause haemorrhage, and superior sagittal sinus thrombosis.

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre telephone: 131126 (Australia).

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

Antileukaemic effect of asparaginase is related to sustained asparagine depletion. 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. 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*).

Mechanism of action

The mechanism of action of asparaginase is the enzymatic cleavage of the amino acid asparagine into aspartic acid and ammonia. Depletion of asparagine in blood serum results in inhibition of protein synthesis, especially in leukaemic blasts which are not able to synthesise asparagine, thus undergoing cell death.

Normal cells, in contrast, are capable of synthesizing asparagine and are less affected by its rapid withdrawal during treatment with the enzyme asparaginase. The PEGylation does not change the enzymatic properties of asparaginase, but it influences the pharmacokinetics and immunogenicity of the enzyme.

Clinical trials

The safety and efficacy was evaluated based upon two clinical studies using ONCASPAR in the first line treatment of ALL: Study CCG-1962 in standard risk ALL patients and Study AALL07P4 in high risk ALL patients.

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.

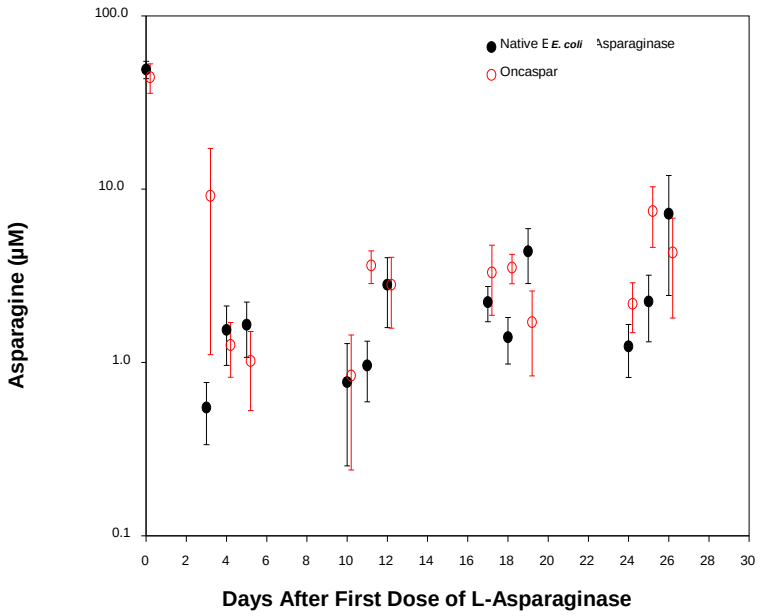
Clinical studies in First-Line (non-hypersensitive population) in ALL

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 3.1 µM to 1.7 µM on Day 4 ± 1 and 1.5 µM at 25 ± 1 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 3. Study CCG-1962 was not designed to evaluate for differences in EFS rates.

Table 3. 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)

A study was conducted for newly diagnosed patients from 1 to 30 years of age with National Cancer Institute high risk B-precursor ALL (Study AALL07P4). This was a controlled, randomised study comparing another pegylated asparaginase product, 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 enrolled in this study; 55 patients were randomised to treatment with 2500 U/m^2 ONCASPAR and 111 patients were randomised to another pegylated asparaginase product. ONCASPAR was administered IV at the dose of 2,500 U/m^2 during Induction, Consolidation, Delayed Intensification and Interim Maintenance phases in patients with high-risk ALL receiving augmented Berlin-Frankfurt-Münster therapy. At 3-years, the EFS and overall survival (OS) for the ONCASPAR treatment arm were, 85.1 % [95 % CI 72-92 %] and 92.4 % [95 % CI 81-97 %], respectively.

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. In adults with leukaemia, the initial enzymatic activity after intravenous (IV) administration of ONCASPAR was proportional to the dose. The elimination half-life from the plasma was between 1 and 6 days and appeared to be unaffected by the dose.

It was also independent of age, sex, body surface area, renal and hepatic function, diagnosis and severity of the illness. However, terminal half-life was shorter in patients hypersensitive to previous asparaginase treatment than in non-hypersensitive patients, and may be decreased due to the formation of high levels of anti-drug antibodies.

Distribution

The distribution volume was in the range of the estimated plasma volume. After a one-hour IV infusion, asparaginase activity was detected for at least 15 days after the first treatment with ONCASPAR.

Elimination

Patients with newly diagnosed ALL received a single IM injection of ONCASPAR (2500 U/m² body surface area) or native asparaginase from *E. coli* (25,000 U/m² body surface area) or crisantaspase (25,000 U/m² body surface area). The plasma elimination half-life of ONCASPAR was statistically significantly longer (5.7 days) than the plasma elimination half-lives of the native *E. coli* asparaginase preparations (1.3 days) and

crisantaspase (0.65 days). The immediate cell death of leukaemic cells in vivo, measured by rhodamine fluorescence, was the same for all three asparaginase preparations.

Patients with ALL with several relapses were treated either with ONCASPAR or with native *E. coli* asparaginase as part of an induction therapy. ONCASPAR was given in a dose of 2500 U/m² body surface IM on days 1 and 15 of induction. The mean plasma half-life of ONCASPAR was 8 days in non- hypersensitive patients (AUC 10.35 U/mL/day), and 2.7 days in hypersensitive patients with ALL (AUC 3.52 U/mL/day).

Pharmacokinetics in special patient groups

Renal impairment

As pegaspargase is a protein with a high molecular weight, it is not excreted renally and no change of pharmacokinetic of ONCASPAR in patients with renal impairment is foreseen.

Hepatic impairment

Since the proteolytic enzymes responsible for pegaspargase metabolism are ubiquitously distributed in tissues the exact role of the liver is unknown.

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 phosphate – dibasic
Sodium phosphate – monobasic monohydrate
Sodium chloride and
Water for injections.

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

8 months from date of manufacture.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ONCASPAR must be stored under refrigerated conditions (2 to 8 ^{o}C).

Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type

ONCASPAR is available in 5 mL Type I glass vials with a rubber stopper and an aluminum seal with a flip-off cap.

Pack size

1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

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9 DATE OF FIRST APPROVAL

31 October 2017

10 DATE OF REVISION

24 December 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Australian PI updated to new SPC format
4.3, 4.7, 4.8, & 4.9	Minor editorial changes
4.8	New list of ADRs under Post-marketing Adverse Reactions
8	Updated sponsor details
8	New sponsor details (PI version 5)