PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr ONCASPAR®*

Pegaspargase Injection

Solution, 3750 U / 5 mL

(750 U / mL)

Antineoplastic Agent

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ONCASPAR

Pegaspargase Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular Injection; Intravenous Injection	Solution for Injection/Infusion; 3750 U per 5 mL (750 U per mL)	Not Applicable *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

ONCASPAR (pegaspargase) is a pegylated form of L-asparaginase, an enzyme that breaks down L-asparagine. L-asparaginase hydrolyses the non-essential amino acid, L-asparagine, into aspartic acid and ammonia, thus depleting the circulating pool of serum L-asparagine. L-asparaginase has a unique mechanism of action as it selectively starves leukaemic cells in acute lymphoblastic leukaemia (ALL) which are unable to synthesize adequate amounts of L-asparagine and normally rely on serum L-asparagine as their source for protein synthesis. Normal cells have the ability to independently synthesize L-asparagine.

INDICATIONS AND CLINICAL USE

ONCASPAR is indicated as:

- A component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukaemia (ALL).

Geriatric (≥ 65 years of age):

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

Pediatrics (< 18 years of age):

The safety and efficacy of ONCASPAR were evaluated in pediatric patients (see **CLINICAL TRIALS**).

The safety and efficacy of ONCASPAR in children < 1 year of age are very limited.

CONTRAINDICATIONS

ONCASPAR is contraindicated in patients with:

- Anaphylactic or severe hypersensitivity reactions to the active substance or to any of the excipients. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- Known serious allergic reactions to ONCASPAR.
- Severe hepatic impairment (bilirubin > 3 times upper limit of normal [ULN]; transaminases > 10 times ULN).
- Known serious thrombosis during previous L-asparaginase therapy.
- Known pancreatitis including pancreatitis related to previous L-asparaginase therapy (see **WARNINGS AND PRECAUTIONS – Pancreatitis**).
- Known serious hemorrhagic events with previous L-asparaginase therapy.

WARNINGS AND PRECAUTIONS

General

ONCASPAR should be prescribed and administered by physicians and health care personnel experienced in the use of antineoplastic products. It 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 throughout the infusion period.

Anaphylaxis and Serious Allergic Reactions

Hypersensitivity reactions to ONCASPAR, such as life-threatening anaphylaxis and serious allergic reactions, can occur in patients receiving ONCASPAR. The risk of serious allergic reactions is higher in patients with known hypersensitivity to other forms of L-asparaginase (particularly *E. coli* derived asparaginase). Monitor patients for an hour after administration, having resuscitation equipment and other means required for the treatment of anaphylaxis in readiness (epinephrine, oxygen, intravenous steroids, etc.). Discontinue ONCASPAR in patients with serious allergic reactions (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**). Depending on the severity of the symptoms, administration of antihistamines,

corticosteroids and possibly circulation stabilising medical products, inotropes, and/or vasopressors are indicated as counter-measure.

Other hypersensitivity reactions can include: angioedema, lip swelling, eye swelling, blood pressure decreased, bronchospasm, dyspnoea, hypotension, laryngeal edema, local erythema or swelling, pruritus, systemic-rash, and urticaria.

Thrombosis/Coagulopathy

Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving ONCASPAR. Discontinue ONCASPAR in patients with 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 **DRUG INTERACTIONS**).

Increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia can occur in patients receiving ONCASPAR. Monitor coagulation parameters at baseline and periodically 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 simultaneously (see **DRUG INTERACTIONS**).

Patients receiving ONCASPAR are at increased risk of bleeding **(see DRUG INTERACTIONS)**. Regular monitoring of the coagulation profile is necessary. Fibrinogen can be regarded as a parameter of the pro- and anticoagulatory system. When there is a marked drop in fibrinogen or Antithrombin III (ATIII) deficiency, consider appropriate replacement therapy.

Hepatotoxicity and Abnormal Liver Function

Combination therapy with ONCASPAR can result in severe hepatic toxicity. Caution is required when ONCASPAR is given in combination with other hepatotoxic substances especially if there is pre-existing hepatic impairment. In this case, patients should be monitored for liver impairment. ONCASPAR may worsen pre-existing liver impairment. Because of this, there is a possibility that ONCASPAR may increase toxicity of other concomitant medication, which are hepatically metabolized.

Hepatotoxicity and abnormal liver function including elevations of AST, ALT, alkaline phosphatase, bilirubin (direct and indirect) and depression of serum albumin and plasma fibrinogen can occur. Appropriate monitoring should be performed.

There is an increased risk of hepatic effects (such as increase in transaminases, bilirubin increased, hypofibrinogenaemia) among patients >18 years of age.

In the presence of symptoms of hyperammonemia (e.g. nausea, vomiting, lethargy, irritation), ammonia levels should be monitored closely.

Pancreatitis

There have been reported adverse reactions of pancreatitis, in few cases with a fatal outcome. Patients should be informed of the characteristic symptom of pancreatitis that, if left untreated, could become fatal: persistent abdominal pain that could be severe, which may radiate to the back. If pancreatitis occurs permanently discontinue ONCASPAR. Appropriate investigations should be performed. As the precise pathogenesis is unknown, only supportive measures can be recommended as per local clinical practice. Disturbances of exocrine pancreatic function can result in diarrhoea.

Serum amylase and/or lipase measurements should be carried out frequently to identify early signs of inflammation of the pancreas.

Hemorrhagic or necrotising pancreatitis with fatal outcome has been reported. Blood and urine glucose levels should be monitored during treatment with ONCASPAR as they may rise **(see Monitoring and Laboratory Tests)**.

Central Nervous System Toxicity

Combination therapy with ONCASPAR can result in central nervous system toxicity. ONCASPAR may cause central nervous system dysfunctions manifesting as convulsion, and less frequently confusional state and somnolence (mildly impaired consciousness). If ONCASPAR is used in association with neurotoxic products (such as vincristine and methotrexate), the patient should be closely monitored (see **DRUG INTERACTIONS**).

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

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

Renal

Decrease in the number of circulating lymphoblasts and leukocyte counts can be associated with a marked rise in the serum uric acid level. Uric acid nephropathy may develop. Monitor closely patient's uric acid levels (see **Monitoring and Laboratory Tests**).

Infections (Myelosuppression)

ONCASPAR possesses immunosuppressive activity and may cause myelosuppression, either directly or indirectly (by altering myelosuppressive effects of other agents such as methotrexate or 6-mercaptopurine). It is therefore possible that the use of this medicinal product promotes infections. Simultaneous vaccination with live vaccine increases the risk of severe infections (see **DRUG INTERACTIONS**).

Infections are very common and sepsis is commonly reported in patients treated with ONCASPAR (see **ADVERSE REACTIONS**). Monitor closely patient's peripheral blood count (see **Monitoring and Laboratory Tests**).

Glucose Intolerance

Glucose intolerance can occur in patients receiving ONCASPAR. Glucose intolerance can be irreversible. Inhibition of insulin production may lead to clinical hyperglycemia, which requires treatment with insulin, in 2-3% of patients treated with ONCASPAR. Therefore, monitor patients for hyperglycemia as well as signs and symptoms of hyperglycemia (see **Monitoring and Laboratory Tests**).

Sexual Function/Reproduction

No studies investigating the effect of pegaspargase on fertility have been performed.

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 **DRUG INTERACTIONS**).

Special Populations

Philadelphia Chromosome-Positive Patients:

Safety and efficacy in Philadelphia chromosome-positive patients have not been established. A possible increased risk of hepatotoxicity when combining imatinib with L-asparaginase therapy should be taken into account prior to deciding to use ONCASPAR in this patient population.

Pregnant Women: There are limited amount of data from the use of L-asparaginase and no data from the use of ONCASPAR, in pregnant women. No reproduction studies in animals with pegaspargase were performed. It is unknown whether ONCASPAR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, L-asparaginase has been shown in animals to possess embryotoxic teratogenic activity. Therefore, and due to its pharmacological properties, ONCASPAR should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the possible risks.

Nursing Women: It is not known whether ONCASPAR is excreted into human breast milk. Based on its pharmacological properties, any risk including serious adverse events to the breast-fed newborns/infants cannot be excluded. Consequently, a decision should be made whether to discontinue breast-feeding, or discontinue ONCASPAR therapy, taking into account the benefit of breast-feeding for the child and the benefit of ONCASPAR therapy for the woman.

Pediatrics (< 18 years of age):

The safety and efficacy of ONCASPAR were evaluated in pediatric patients (see **CLINICAL TRIALS**).

The safety and efficacy of ONCASPAR in children < 1 year of age are very limited.

Geriatric (≥ 65 years of age):

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

Monitoring and Laboratory Tests

Measurement of the L-asparaginase activity level in serum or plasma may be undertaken in order to rule out an accelerated reduction of L-asparaginase activity.

Low L-asparaginase activity levels are often accompanied by the appearance of anti-L-asparaginase antibodies. In such cases, a switch to a different L-asparaginase preparation should be considered. Expert advice should first be sought.

The decrease in the number of circulating lymphoblasts is often quite marked, and normal or too low leukocyte counts are often seen in the first days after the start of therapy. To monitor the therapeutic effect, the peripheral blood count and the patient's bone marrow should be monitored closely.

Anaphylaxis and serious allergic reactions may occur. Patients should be monitored for one hour after administration, having resuscitation equipment and other means required for the treatment of anaphylaxis (epinephrine, oxygen, IV steroids, etc.)

Monitor coagulation parameters at baseline and periodically during and after treatment, particularly when used simultaneously with other coagulant/anticoagulant medicinal products such as methotrexate, daunorubicin, corticosteroids, acetylsalicylic acid and nonsteroidal anti-inflammatory medicinal products.

Monitor liver function tests, including: AST, ALT, ALP, bilirubin (direct and indirect), serum albumin as ONCASPAR can result in hepatotoxicity.

In the presence of symptoms of hyperammonemia (e.g. nausea, vomiting, lethargy, irritation), ammonia levels should be monitored closely.

Serum amylase and/or lipase measurements should be carried out frequently to identify early signs of inflammation of the pancreas.

Blood and urine glucose levels should be monitored during treatment with ONCASPAR as they may rise.

ONCASPAR may result in central nervous system toxicities. As such, patients should be monitored for signs of central nervous system dysfunctions, including but not limited to: convulsions, somnolence, confusion and tremor.

Closely monitor patient's uric acid levels, particularly during Induction therapy as tumor lysis syndrome may result in uric acid nephropathy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety profile of ONCASPAR is based on the analysis of safety data from clinical trials and post-marketing experience of ONCASPAR in ALL patients. The most frequently reported Adverse Drug Reactions (ADRs) from clinical trials are presented in Table 1.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1. Adverse Reactions reported with ONCASPAR therapy

MedDRA Standard System Organ Class	Adverse Reaction
Blood and lymphatic system disorders	Very Common: Febrile neutropenia Common: Anaemia, Thrombosis, Coagulopathy (increased prothrombin time, increased partial thromboplastin time, and hypofibrinogenaemia).
Gastrointestinal disorders	Very Common: Pancreatitis, Diarrhoea, Abdominal pain Common: Vomiting, stomatitis, ascites
Hepatobiliary disorders	Common: Hepatoxicity
Immune system disorders	Very Common: Hypersensitivity, Urticaria, Rash, Anaphylactic reactions Unknown: Anaphylactic shock
Infections and infestations	Very Common: Infections Common: Sepsis

Investigations	Very Common: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Blood fibrinogen decreased, Lipase increased, International normalized ratio increased, Amylase increased, Activated partial thromboplastin time prolonged Common: Neutrophil count decreased, Platelet count decreased
Metabolism and nutrition disorders	Very Common: Hyperglycaemia, Hypertriglyceridaemia, Hypoalbuminaemia Common: Decreased appetite, Hyperlipidaemia, Hypercholesterolaemia, Hypokalaemia
Musculoskeletal and connective tissue disorders	Common: Pain in extremities
Nervous system disorders	Common: Convulsion, Peripheral Motor Neuropathy, Syncope
Respiratory, thoracic and mediastinal disorders	Common: Hypoxia
Vascular disorders	Very Common: Embolism* Common: Thrombosis**

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10)

*The following were observed in DFCI 11-001: Pulmonary embolism (common), venous thrombosis (common), venous thrombosis limb (uncommon), thrombophlebitis superficial (uncommon)
**Including CNS Thrombosis

Less Common Clinical Trial Adverse Drug Reactions

There were no clinically important adverse reactions less than the 1% that were reported in clinical trials with ONCASPAR included in Table 1.

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

The safety was evaluated based upon ~~two~~ 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.

Study CCG-1962, was a multicenter randomized 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 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 (Table 2 below). The total number of patients

with preferred term infection of any grade was 31 (53%) in the ONCASPAR arm and 32 (54%) in the Native E. coli L-asparaginase arm.

Table 2. Study CCG-1962-Per Patient Incidence of Selected Adverse Reactions (Grade 3 and 4)†

System Organ Class (SOC) Preferred Term (PT)	**ONCASPAR (n=58) n (%)**	**Native *E. coli* L-Asparaginase (n=59) n (%)**
Gastrointestinal Disorders		
Pancreatitis	1 (2)	1 (2)
Constipation	2 (3)	0 (0)
Diarrhoea	2 (3)	0 (0)
Immune System Disorders		
Clinical Allergic Reactions to Asparaginase*	1 (2)	0
Infection and Infestations		
Infection	3 (5)	3 (5)
Sepsis	2 (3)	0
Investigations		
Abnormal Liver Tests	3 (5)	5 (8)
Elevated Transaminases[a]	2 (3)	4 (7)
Hyperbilirubinaemia	1 (2)	1 (2)
Metabolic and Nutritional		
Hyperglycaemia	3 (5)	2 (3)
Nervous system disorders		
Nervous system disorders	5 (9)	3 (5)
Neuropathy Peripheral	4 (7)	0 (0)
Skin And Subcutaneous Tissue Disorders		
Skin disorder	3 (5)	1 (2)
Vascular Disorders		
Central Nervous System Thrombosis	2 (3)	2 (3)
Coagulopathy[b]	1 (2)	3 (5)
Hypotension	2 (3)	0 (0)

[a] Aspartate aminotransferase, alanine aminotransferase
[b] Prolonged prothrombin time or partial thromboplastin time; or hypofibrinogenaemia
* The allergic reaction in the table refers to one case of Grade 3 hives. Other allergic reactions reported in the study are an unspecified allergic reaction (Grade 1) and an anaphylactic shock (ungraded).
† Pre-specified adverse reactions are identified as asparaginase-induced adverse reactions and for grade 3 and 4

Study AALL07P4 was a multicenter, randomized, open-label, active comparator controlled trial, in which patients received ONCASPAR intravenously in the control arm. The most common adverse events reported in the ONCASPAR arm were hypersensitivity/anaphylactic reactions, elevated hepatic and pancreatic enzymes, pancreatitis and abnormalities in albumin, metabolic electrolytes and glycaemic levels. Hematological disorders included decreased platelet count, neutropenia, leukocytopenia and anaemia. Coagulopathy included increased INR, aPTT, and fibrinogen decreased. Common nervous system disorder included syncope,

convulsions and peripheral neuropathy. In addition, febrile neutropenia, abdominal pain, infections (including sepsis) and hypoxia were observed. Most of these adverse events were of Grade 3-4. This adverse events profile was generally consistent with described events in other studies with ONCASPAR.

Study DFCI 11-001 is an open-label, randomized, active-controlled multicenter clinical trial that treated 237 children and adolescents with newly-diagnosed ALL, who received an investigational pegylated asparaginase product or ONCASPAR (used as comparator, n=119) as part of an DFCI ALL Consortium backbone therapy. The study population characteristics in ONCASPAR arm were: median age on enrollment was 4 years (range 1-18 years); the majority of patients were male (60%) and white (75%). Most patients were considered standard risk (SR, 59%) and had B-cell lineage ALL (87%). The median number of doses during the study was 16 doses for ONCASPAR (administered every two weeks). The median duration of exposure was 8 months for ONCASPAR. The safety profile in this study was consistent with other studies with ONCASPAR. The most common adverse events included hypoalbuminemia, alanine aminotransferase increased, aspartate aminotransferase increased, hypertriglyceridemia, blood fibrinogen decreased, blood bilirubin increased, lipase increased and hyperglycemia.

The most common severe adverse reactions with ONCASPAR (graded 3 or 4) observed in studies DFCI 11-001 and AALL07P4 with a frequency of >5% included: alanine aminotransferase increased, AST increased, blood bilirubin increased, febrile neutropenia, hyperglycemia, lipase increased, pancreatitis, and hypersensitivity.

Other first-line studies:

Studies DFCI 05-001[2] and CCG-1991[4] both also incorporated ONCASPAR as part of multi-chemotherapy regimens for the treatment of pediatric ALL. Asparaginase-related adverse events remained consistent with other ONCASPAR inclusive studies: allergy, pancreatitis and thrombosis. Deaths due to infections, pancreatitis (n=3) and central nervous haemorrhage (n=2) occurred in patients receiving ONCASPAR in study CCG-1991. In study DFCI 05-001, infections and hypertriglyceridaemia occurred more frequently in the ONCASPAR arm. The following grade 4 adverse events were also reported for subjects on the ONCASPAR only; these events were not reported in other studies (each in one subject): agitation, chyle or lymph leakage, fatigue, iron overload, mood changes or depression, perforation of the small bowel, skin breakdown or decubitus ulcer, wound (non-infectious).[2]

Patients with previously treated ALL and/or hypersensitivity to native *E. coli* asparaginase

Adverse reaction information was obtained from clinical trials that enrolled a total of 174 patients with relapsed ALL who received ONCASPAR as a single agent or in combination with multi-agent chemotherapy. The toxicity profile of ONCASPAR in patients with previously treated relapsed ALL is similar to that reported above with the exception of clinical allergic reactions (see Table 3). The most common adverse reactions of ONCASPAR were clinical allergic reactions (bronchospasm, hypotension, laryngeal edema, local erythema or swelling,

systemic rash, and urticaria), elevated transaminases, hyperbilirubinaemia, and coagulopathies. The most common serious adverse events due to ONCASPAR treatment were thrombosis (4%), hyperglycaemia requiring insulin therapy (3%), and pancreatitis (1%).

Among 62 patients with relapsed ALL and prior hypersensitivity reactions to asparaginase, 35 patients (56%) had a history of clinical allergic reactions to native *Escherichia (E.) coli* L-asparaginase, and 27 patients (44%) had a history of clinical allergic reactions to both native *E. coli* and native *Erwinia* L-asparaginase. Twenty of the 62 patients (32%) experienced clinical allergic reactions to ONCASPAR (see Table 3).

Among 112 patients with relapsed ALL with no prior hypersensitivity reactions to asparaginase, 11 patients (10%) experienced clinical allergic reactions to ONCASPAR (see Table 3).

Table 3
Incidence of Clinical Allergic Reactions, Overall and By Severity Grade

	Toxicity Grade, n (%)				
Patient Status	**1**	**2**	**3**	**4**	**Total**
Previously Hypersensitive Patients (n=62)	7 (11)	8 (13)	4 (6)	1 (2)	20 (32)
Non-Hypersensitive Patients (n=112)	5 (4)	4 (4)	1 (1)	1 (1)	11 (10)

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity, defined as development of binding and/or neutralizing antibodies to the product.

In Study CCG-1962, ONCASPAR-treated patients were assessed for evidence of binding antibodies using an enzyme-linked immunosorbent assay (ELISA) method. The incidence of protocol-specified "high-titer" antibody formation was 2% in Induction (n=48), 10% in Delayed Intensification 1 (n=50), and 11% in Delayed Intensification 2 (n=44). There is insufficient information to determine whether the development of antibodies is associated with an increased risk of clinical allergic reactions, altered pharmacokinetics, or loss of anti-leukemic efficacy.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to ONCASPAR with the incidence of antibodies to other products may be misleading.

The immunogenicity assessment and assay used in the study have limitations therefore, the incidence of antibody development might not have been reliably determined.

Post-Market Adverse Drug Reactions

The type of adverse reactions seen in post-market experience with ONCASPAR is largely similar to that of native non-pegylated L-asparaginase (e.g. native *E. coli* L-asparaginase), and is consistent with those observed in ONCASPAR clinical trials.

In the global post-marketing experience of ONCASPAR, the most frequently reported terms are those likely to be associated with an immune response (urticaria, hypersensitivity, anaphylactic reaction, rash, pruritus, lip swelling, swelling face and erythema), followed by hypertriglyceridaemia, pancreatitis, hepatotoxicity, sepsis, renal failure, infection, and disease progression.

Adverse reactions reported in post-marketing experience by system organ class are presented below.

Blood and lymphatic system disorders

There have been reports of 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, for example, to stroke, seizures, headache or loss of consciousness.

Cardiac disorders

Tachycardia may occur.

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.

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 occurs 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 L-asparaginase treatment. Haemorrhagic or necrotising pancreatitis with fatal outcome has been reported.

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

General disorders and administration site conditions

Pyrexia can occur after the injection, which usually subsides spontaneously.

Hepatobiliary disorders

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

There have been reported cases of hepatic steatosis (fatty liver), cholestasis, icterus, hepatic cell necrosis and hepatic failure with fatal outcome.

Impaired protein synthesis can lead to a decline in the serum protein. A dose-dependent decrease in serum albumin was observed in most patients during treatment.

Immune system disorders

Hypersensitivity reactions (i.e. urticaria, rash, pruritus, lip swelling, swelling face and erythema) and anaphylactic reactions, including anaphylactic shock, have been reported.

Specific antibodies to pegaspargase have been measured. Neutralizing antibody reducing clinical efficacy were also observed.

Investigations

Blood cholesterol increased and gamma-glutamyl transferase increased have been reported.

Metabolism and nutrition disorders

Alterations in serum lipid levels have been observed and changes in serum lipid values, in most cases without clinical symptoms, are very common.

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

Cases of hypercalcemia, hypoglycemia, and hyponatremia have been reported.

Dehydration may occur.

Nervous system disorders

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

There have been reports of reversible posterior leukoencephalopathy syndrome (RPLS).

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

Renal and urinary disorders

Acute renal failure cases have been reported, that may develop in rare cases during treatment with L-asparaginase-containing regimens.

Skin and subcutaneous tissue disorders

Allergic reactions can manifest in the skin. Toxic epidermal necrolysis has been associated with L-asparaginase treatment.

Vascular disorders:

Superior sagittal sinus thrombosis has been reported.

DRUG INTERACTIONS

Drug-Drug Interactions

No formal drug interaction studies have been conducted with ONCASPAR and other drugs.

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

In addition, 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 interact differently: Prior administration of these substances can increase the action of ONCASPAR synergistically. If these substances are given subsequently, the effect of ONCASPAR can be weakened antagonistically.

ONCASPAR can 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 chemotherapy products 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 WARNINGS AND PRECAUTIONS).

The use of ONCASPAR can lead to fluctuating coagulation factors. This can promote the tendency to bleeding and/or thrombosis. Caution is therefore needed when pro-coagulant/anticoagulants such as methotrexate, daunorubicin, corticosteroids, coumarin, heparin, dipyridamole, acetylsalicylic acid or nonsteroidal anti-inflammatory drugs are given concomitantly.

When glucocorticoids (e.g. prednisone) and ONCASPAR are given at the same time, alterations in coagulation parameters (e.g. fall in fibrinogen and Antithrombin III deficiency, ATIII) can be more pronounced.

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

An indirect interaction cannot be ruled out between pegaspargase and oral contraceptives due to pegaspargase hepatotoxicity that may impair the hepatic clearance of oral contraceptives. Therefore, the concomitant use of ONCASPAR with oral contraceptives is not recommended. Another method than oral contraception should be used in women of childbearing potential (see **WARNINGS AND PRECAUTIONS**).

Simultaneous vaccination with live vaccines may increase the risk of severe infections attributable to the immunosuppressive activity of ONCASPAR and overall situation taking into account the underlying disease and the usually combined chemotherapy (see **WARNINGS AND PRECAUTIONS**). Vaccination with live vaccines should therefore be given 3 months at the earliest after termination of the entire anti-leukaemic treatment.

Combination therapy with ONCASPAR can result in central nervous system toxicity. ONCASPAR may cause central nervous system dysfunctions manifesting as convulsion, and less frequently confusional state and somnolence (mildly impaired consciousness). If ONCASPAR is used in association with neurotoxic products (such as vincristine and methotrexate), the patient should be closely monitored.

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

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

Drug-Lifestyle Interactions

ONCASPAR may have a major influence on the ability to drive and use machines. The following adverse reactions have been reported in patients treated with ONCASPAR along with other chemotherapy medicinal products: somnolence, confusion, dizziness, syncope, seizure. Patients should not drive or operate machines while receiving ONCASPAR if they experience these or other adverse reactions which can impair their ability to drive or operate machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ONCASPAR is employed as part of combination chemotherapy protocols with other antineoplastic agents.

Recommended Dose and Dosage Adjustment

The recommended dose of ONCASPAR is 2500 U (equivalent to 3.3 mL ONCASPAR)/m² body surface area every 14 days in paediatric patients with body surface area >0.6 m^2 and under 21 years of age.

There are data suggesting that the dose of ONCASPAR could be adjusted to 82.5 U (equivalent to 0.1 mL ONCASPAR)/kg body weight every 14 days in children with a body surface area <0.6 m², or to 2000 U (equivalent to 2.67 mL ONCASPAR)/m^2 body surface area every 14 days in adult patients >21 years of age in order to decrease toxicities (e.g. hyperbilirubinemia).

Treatment may be monitored based on the trough serum L-asparaginase activity measured before the next administration of ONCASPAR. If L-asparaginase activity values fail to reach target levels, a switch to a different L-asparaginase preparation could be considered (see **WARNINGS AND PRECAUTIONS**).

Special populations

No formal studies were conducted in patients with renal or hepatic impairment.

Administration

ONCASPAR can be given by intramuscular injection or intravenous infusion.

For smaller volumes of ONCASPAR, the preferred route of administration is intramuscular. When ONCASPAR is given by intramuscular injection the volume injected at one site should not exceed 2 mL in children and adolescents and 3 mL in adults. If higher volume is given, the dose should be divided and given at several injection sites. ONCASPAR does not contain a preservative. Use only one dose per vial; discard unused product.

Intravenous infusion of ONCASPAR is usually given over a period of 1 to 2 hours in 100 mL of sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose solution, through an infusion that is already running.

OVERDOSAGE

There have been cases of overdose 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

Pharmacodynamics

Anti-leukaemic effect of L-asparaginase is related to a sustained L-asparagine depletion in blood and cerebrospinal fluid (CSF). The pharmacodynamic (PD) effect of ONCASPAR was assessed after IM (Study CCG-1962) and IV administration (AALL07P4).

In Study CCG-1962, pharmacodynamics was assessed through serial measurements of L-asparagine in serum (n=57) and cerebrospinal fluid (CSF) (n=50) in 57 newly diagnosed paediatric patients with standard-risk ALL who received IM doses of ONCASPAR(2,500 U/m²), during induction and intensification treatment phases. 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. CSF asparagine concentrations decreased from a mean pretreatment 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 (see **CLINICAL TRIALS**)..

In Study AALL07P4, the PD effect of ONCASPAR was assessed in 47 evaluable subjects with high risk B-precursor ALL who received IV doses of ONCASPAR 2,500 U/m^2 BSA during the Induction and Consolidation phases. Plasma L-asparagine concentrations were depleted to below the assay limit of quantification within 24 hours following the Induction and first Consolidation dose of ONCASPAR and depletion was sustained for approximately two weeks. CSF asparagine concentrations were reduced by the 4th day following the Induction dose, and remained largely undetectable until the 25th day after dosing.

Based on results from these two studies, a 2,500 U/m^2 BSA dose of ONCASPAR administered IM (CCG-1962) and IV (AALL07P4) provides maintenance of L-asparagine depletion for approximately two weeks following dosing.

Pharmacokinetics

ONCASPAR pharmacokinetic properties were based on an enzymatic assay measuring L-asparaginase activity after IM (CCG-1962) and IV (AALL07P4, DFCI 11-001) administration of 2,500 U/m² in patients with ALL.

Table 3 - Plasma Asparaginase Activity Pharmacokinetic Parameters After a Single Dose of ONCASPAR 2,500 IU/m² in Patients with ALL in Study AALL07P4

	C_{max} (U/mL)*	T_{max} (h) †	$t_{½}$ (h)‡	AUC_{0-t} (day.U/mL)*	$AUC_{0-\infty}$ (day.U/mL)‡	CL (L/day)‡	Vd (L)‡
Single dose Arithmetic mean (%CV)	1.64 (28.0)	1.25 (1.08-5.33)	5.33 (43.8)	14.8 (24.0)	16.6 (29.0)	0.215 (56.4)	1.95 (58.0)

***** N=47 evaluable subjects.
† Median (10^{th}, 90^{th} percentiles).
‡ N= 46 evaluable subjects.

Absorption

The mean maximum asparaginase activity (C_{max}) was reached at approximately 1 U/mL (n=45-52) on Day 5 after a single IM injection. The mean half-life of absorption from the IM site was 1.7 days.

The mean C_{max} and the area under the curve (AUC_{0-inf}) was 1.64 U/mL and 16.6 day.U/mL, respectively, after a single IV infusion (n=47) during the induction phase.

Distribution

The mean volume of distribution at steady state was estimated to be 1.86 L/m^2 after a single IM injection and approximately 2 L after a single IV infusion based on non-compartmental analysis.

Elimination

The mean elimination half-life was approximately 5.8 days following a single IM injection and 5.3 days following a single IV infusion. The clearance was 0.17 L/m^2/day and 0.2 L/day, respectively, for a single IM and IV dose.

In Study AALL07P4, PK parameters after a single 2,500 U/m^2 IV dose during Induction were calculated by noncompartmental PK analysis from sequential plasma samples and are depicted in Table 3. The C_{max} and AUC of ONCASPAR trended lower in males, subjects with larger BMI, and 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.

In Study DFCI 11-001, assessments of asparaginase activity were performed following a single IV dose of ONCASPAR 2,500 U/m^2 BSA during Induction, and every two weeks during post-Induction. 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 evaluable subjects (N) from Week 7 up until Week 25 (i.e. N=86 on Week 7, N=84 on Week 13, and N=78 on Weeks 19 and 25). These results indicate that, when ONCASPAR 2,500 U/m^2 BSA is administered every two weeks, clinically relevant asparaginase activity is sustained over the entire dosing interval (i.e., two weeks).

In study CCG-1962, patients with newly diagnosed ALL received a single intramuscular injection of ONCASPAR (2500 U/m² body surface area) or native L-asparaginase from *E. coli* (25000 U/m² body surface area) or from *Erwinia* (25000 U/m² body surface area). The mean plasma elimination half-life of ONCASPAR was longer than the mean plasma elimination half-lives of the native L-asparaginases from *E. coli* or *Erwinia* (5.7, 1.3, and 0.65 days), respectively. The immediate cell death of leukaemic cells *in vivo*, measured by rhodamine fluorescence, was the same for all three L-asparaginase preparations.

ALL patients with several relapses were treated either with ONCASPAR or with native L-asparaginase from *E. coli* as part of an induction therapy. ONCASPAR was given in a dose of 2500 U/m² body surface intramuscularly 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 (AUC 3.52 U/mL/day).

Special Populations and Conditions

Renal insufficiency

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 of pharmacokinetic of ONCASPAR in patients with renal impairment is foreseen.

Hepatic insufficiency

The impact of hepatic impairment on the PK of ONCASPAR has not been evaluated. Since the proteolytic enzymes responsible for ONCASPAR metabolism are ubiquitously distributed in tissues the exact role of the liver is unknown: however any decrease in liver function is not expected to present clinical relevant problems in the use of ONCASPAR.

Geriatrics

There is no data available for elderly patients.

STORAGE AND STABILITY

Keep refrigerated prior to use at 2°C to 8°C. Do not freeze or shake. Store vials in the original package to protect from light.

Discard any unused portion.

Do not use beyond the expiration date printed on the carton or vial.

SPECIAL HANDLING INSTRUCTIONS

This medicinal product can cause irritation on contact. The solution must therefore be handled and administered with particular caution. Inhalation of the vapour and contact with the skin and mucous membranes, especially the eyes, must be avoided. In case of contact, irrigate with plenty of water for at least 15 minutes.

The solution can be diluted with 5% glucose solution or sodium chloride 9 mg/mL (0.9%) solution for injection before intravenous injection.

Inspect parenteral drug products for particulate matter and discoloration prior to administration. The solution should be clear and colorless in appearance. Do not administer if particulate matter or discoloration is found and notify Servier.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

ONCASPAR is a clear, colourless solution for injection/infusion.

ONCASPAR is supplied in Type I glass vials containing 3,750 Units of L-asparaginase per 5 mL solution.

Each carton contains one single-use vial and one package insert.

List of Excipients

- Dibasic Sodium Phosphate
- Monobasic Sodium Phosphate
- Sodium Chloride
- Water for injection

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Pegaspargase

Molecular formula and molecular mass: Pegaspargase is an L-asparaginase (L-asparagine amidohydrolase) that is covalently conjugated to monomethoxypolyethylene glycol (mPEG). L-asparaginase is a tetrameric enzyme that 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.

Structural formula: The L-asparaginase intermediate used for production of ONCASPAR is a high-affinity type II L-asparaginase expressed in *E. coli*. The complete amino acid sequence of one L-asparaginase monomer is provided in Figure 1 below.

Figure 1: Amino Acid Sequence of Asparaginase

1	11	21	31	41
LPNITILATG	GTIAGGGDSA	T***K***SNYTAG***K***V	GVENLVNAVP	QL***K***DIANV***K***G
51	61	71	81	91
EQVVNIGSQD	MNDDVWLTLA	***KK***INTDCD***K***T	DGFVITHGTD	TMEETAYFLD
101	111	121	131	141
LTV***K***CD***K***PVV	MVGAMRPSTS	MSADGPFNLY	NAVVTAAD***K***A	SANRGVLVVM
151	161	171	181	191
NDTVLDGRDV	T***K***TNTTDVAT	F***K***SVNYGPLG	YIHNG***K***IDYQ	RTPAR***K***HTSD
201	211	221	231	241
TPFDVS***K***LNE	LP***K***VGIVYNY	ANASDLPA***K***A	LVDAGYDGIV	SAGVGNGNLY
251	261	271	281	291
KTVFDTLATA	A***K***NGTAVVRS	SRVPTGATTQ	DAEVDDA***K***YG	FVASGTLNPQ
301	311	321		
KARVLLQLAL	TQT***K***DPQQIQ	QIFNQY		

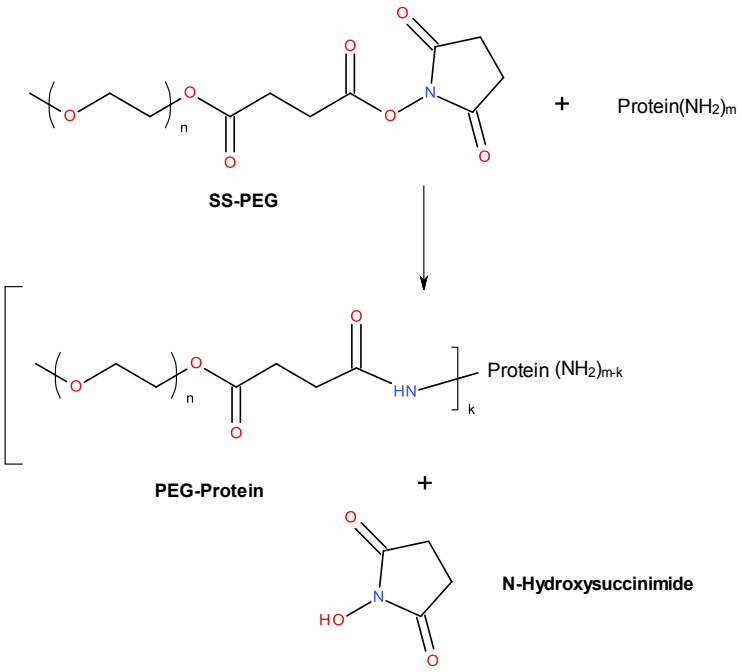
Key to amino acid designations: A = Alanine; C = Cysteine; D = Aspartic Acid; E = Glutamic Acid; F = Phenylalanine; G = Glycine; H = Histidine; I = Isoleucine; K = Lysine; L = Leucine; M = Methionine; N = Asparagine; P = Proline; Q = Glutamine; R = Arginine; S = Serine; T = Threonine; V = Valine; W = Tryptophan; Y = Tyrosine. Residues containing reactive nucleophilic primary amino groups are bolded, italicized, and underlined.

Each L-asparaginase monomer contains two cysteine residues at positions 77 and 105, which are engaged in an intra-molecular disulfide bond.

L-asparaginase is a homotetrameric enzyme, comprised of four identical subunits coupled by weak, non-covalent, largely hydrophobic interactions.

The chemical reaction between monomethoxypolyethylene glycol succinimidyl succinate (SS-PEG) and exposed primary amines on the protein is shown in Figure 2.

Figure 2: Reaction between SS-PEG and a Protein



n=average number of 114
k=number of amino groups modified
m=number of amine groups on the protein

CLINICAL TRIALS

Table 4. Summary of design and patient demographics for clinical trials* when ONCASPAR was used in newly diagnosed patients with acute lymphoblastic leukaemia (ALL)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender (n = M/F)
DFCI 11-001	Ongoing, active-controlled, randomized, multicenter study of an intravenous investigational pegylated asparaginase *versus* intravenous ONCASPAR	ONCASPAR 2,500 U/m^2 Treatment was administered intravenously during Induction (Day 7), and then every 2 weeks for a total of 30 weeks post-Induction therapy	N=119 ONCASPAR treated	children and adolescents aged 1 to <22 years	71/48 ONCASPAR treated
AALL07 P4	Pilot, open label, controlled, randomized study comparing an investigational pegylated asparaginase *versus* ONCASPAR in the first line treatment of ALL	ONCASPAR 2,500 U/m^2 Intravenously during Induction/Extended Induction, Consolidation, Delayed Intensification and Interim Maintenance phases of an augmented Berlin-Frankfurt-Münster (aBFM) treatment regimen	N=54 ONCASPAR treated	1 to <31	31/23 ONCASPAR treated
CCG-1962[1]	Phase II, open-label, randomized study to compare PEG--L-asparaginase and native *E.coli* L-asparaginase in the standard treatment arm of CCG-1952 study for standard-risk ALL	ONCASPAR 2,500 U/m^2 IM single injections during Induction and during each of 2 Delayed Inductions Native *E.coli* L-asparaginase (Elaspar) 6,000 U/m^2 IM, 9 injections over 20 days during Induction and 6 injections over 12 days during each of two delayed Inductions	N=118	1-9 years	64/54

* The patient numbers for the DFCI 11-001 and AALL07P4 studies is FAS as ITT is not available.

Table 5. Summary of design and patient demographics for clinical trials when ONCASPAR was used in patients with relapsed/refractory hematological malignancies, including acute lymphoblastic leukaemia (ALL)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender (n = M/F)
ASP-201A	Phase II/III, open-label, multicenter, international, non comparative study	ONCASPAR 2.000 U/m^2 IM every 2 weeks (three doses in induction, continued after the induction if patient benefit with the treatment). ONCASPAR10.000 U/m^2 IV one or two times over 2 hour infusion with Vincristine, Prednison and Doxorubicin (only 3 patients)	N=42	1-43 years	30/12
ASP-302	Phase II/III, open-label, uncontrolled study conducted in 3 phases: early, re-induction and remission therapy (maintenance)	ONCASPAR 2.500 U/m^2 IM every 2 weeks during re-induction and remission therapy (a total of 29 planned administrations)	N=21	1-35 year	13/8
ASP-304	Phase III, open-label, randomized, comparative study of PEG- L-asparaginase vs native *E.coli* L-asparaginase in combination with standard agents as second induction therapy Known hypersensitive patients were assigned directly to PEG- L-asparaginase	ONCASPAR: 2.500 U/m^2 IM (two doses: day 1 and day 15) vs Elspar: 10.000 U/m^2 IM (twelve doses, three times a week for 26 days)	N=76	1-18 year	47/29
ASP-001C/ASP -003C	Open Label, non-comparative, multicenter, compassionate use study of PEG-L-asparginase in ALL and AUL refractory patients, or with known hypersensitivity to other forms of L-asparaginase.	A dose of ONCASPAR 2.000 U/m^2 IM as a single agent or in combination therapy to induce remission during induction. Patients in complete remission received additional dose of 2.000 U/m^2 IM during maintenance phase as a single agent or in combination therapy	N=41	1-66 years	27/14

Summary of clinical trials when ONCASPAR was used in newly diagnosed patients with ALL

Study CCG-1962[1]

Study demographics and trial design

The CCG-1962 was a multicentre randomized Phase II study, designed to determine the safety, efficacy, and pharmacokinetics of PEG-Asparaginase (ONCASPAR) compared with standard native *E. coli* Asparaginase in children aged 1 through 9 years with newly diagnosed standard-risk ALL (SR ALL). In this study, children were randomized 1:1 to ONCASPAR or native *E. coli* L-asparaginase as part of a combination therapy. ONCASPAR was administered intramuscularly 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 intramuscularly 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.

The study enrolled 118 standard risk patients who had white blood cell counts of ≤50,000/μL and ≤20% surface Ig-positive positive leukaemic blasts.

Patient characteristics between the ONCASPAR and Native E. coli L-asparaginase groups generally well matched for age, sex, race, presenting WBC count, CNS disease status and baseline organomegaly. No patients had B-cell (L3) leukaemia. Three children had Down Syndrome and two of these were treated with ONCASPAR.

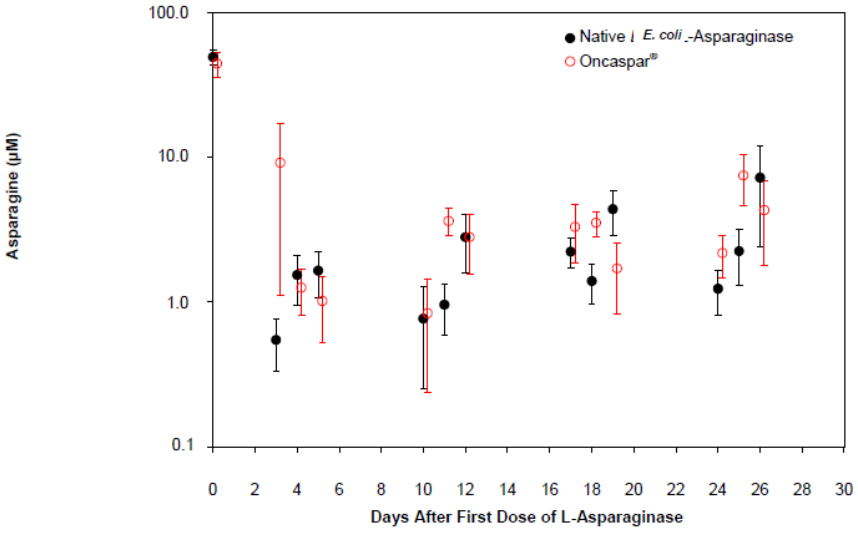
Study Results

L-asparagine Depletion

The efficacy was determined by measuring 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 serumconcentration of ≤1 micro molar. 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 3. 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 3. Mean (± standard error) serum asparagine during Study 1 induction phase



CSF asparagine concentrations were determined in 50 patients during the induction phase. CSF asparagine decreased from a mean pretreatment 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 L-asparaginase treatment arm.

Event-free Survival

While the 3-year EFS were 83% in the ONCASPAR arm and 79% in the native *E.coli* L-asparaginase arm, the study was not designed to detect differences in EFS rates.

Summary of Clinical Trials when ONCASPAR was used in Patients with Relapsed ALL

In a comparative study conducted by the Pediatric Oncology Group (POG #8866), Study ASP-304, multiple relapsed ALL patients were randomized to either ONCASPAR or E.coli L-asparaginase for induction therapy. ONCASPAR was administered at a dose of 2,500 U/m^2 intramuscularly on days 1 and 15 of induction. In comparison, E.coli L-asparaginase was given at a dose of 10,000 U/m^2 intramuscularly every other day for a total of 12 doses during induction therapy. Patients with known hypersensitivity to other forms of L-asparaginase were directly assigned to the ONCASPAR treatment group; the majority of the patients were able to tolerate ONCASPAR without manifestation of any allergic reactions. Three ONCASPAR patients had their overall therapy discontinued due to adverse experiences (toxicity). Two hypersensitive patients experienced systemic hypersensitivity reactions (CTC grades 3 or 4), one during induction therapy and the other during extension therapy. One non-hypersensitive patient experienced CTC grade 4 hyperbilirubinemia. One non-hypersensitive patient treated with E.coli L-asparaginase experienced an episode of hypersensitivity which required discontinuation. This patient was subsequently treated with ONCASPAR and achieved complete remission during reinduction therapy without evidence of hypersensitivity.

Open trials (Studies 001C/003C, ASP-201A and ASP-302) which evaluated the effectiveness of ONCASPAR at a dose of 2,000-2,500 U/m^2 intramuscularly during induction, consolidation or maintenance therapy demonstrated that ONCASPAR (pegaspargase) had similar clinical activity (remission rates) in the treatment of hypersensitive patients as reported in scientific literature between 1995 to 2000. The majority of the patients with known hypersensitivity to the native forms of L-asparaginase were safely treated with ONCASPAR (pegaspargase) without manifestations of any NCI grade 3 or 4 hypersensitivity reactions.

TOXICOLOGY

Acute Toxicity

Only very high doses of pegaspargase given to mice intraperitoneally as a single dose (25000 – 100000 U/kg body weight) caused the death of 14% of all treated mice. Mild hepatotoxicity was observed with the same dosages. Side effects were loss of body weight, piloerection and reduced activity. Reduced splenic weight might be a sign of potential immunosuppressant characteristics of the treatment.

Pegaspargase was well tolerated both in rats and dogs when administered intravenously in single dose up to 500 U/kg.

Repeated Dose Toxicity

A 4-week study in rats with a dosage of pegaspargase of 400 U/kg/day intraperitoneal resulted in a fall in food intake and body weight compared to the control group.

A 3-month study in mice with pegaspargase at doses up to 500 U/kg intraperitoneal or intramuscular resulted in slight hepatocellular changes only at the highest intraperitoneal dose.

A temporarily diminished increase in body weight and a slight temporary reduction in the total leukocyte count was observed in dogs which were treated with pegapargase 1200 U/kg weekly for 2 weeks. Increased serum glutamic pyruvic transaminase activity also occurred in one of four dogs.

Reproductive Toxicity

No studies of reproductive toxicity were conducted with pegaspargase.

Embryotoxicity studies with L-asparaginase have given evidence of teratogenic potential in rats treated from day 6 to 15 of gestation with a No Observed Effect Level (NOEL) for teratogenic effects at 300 U/kg i.v. In rabbits doses of 50 or 100 U/kg i.v. on days 8 and 9 of gestation induced viable fetuses with congenital malformations: 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.

Carcinogenicity, Mutagenicity, Fertility

Long-term investigations of carcinogenicity or studies of the effect on fertility in animals were not conducted with pegaspargase.

Pegaspargase was not mutagenic in the Ames test using *Salmonella typhimurium strains*.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

ONCASPAR®* (ŏn-kă-spăr)
Pegaspargase Injection

Read this carefully before you start taking **ONCASPAR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ONCASPAR**.

What is ONCASPAR used for?

ONCASPAR is used to treat acute lymphoblastic leukaemia (ALL). ALL is a white blood cell cancer type in which certain immature white cells (named lymphoblasts) start growing out of control thus preventing the production of functional blood cells. ONCASPAR is used together with other medicines.

How does ONCASPAR work?

ONCASPAR contains pegaspargase, which is an enzyme that breaks down L-asparagine, an important building block of proteins without which cells cannot survive. Normal cells can make L-asparagine for themselves, while some cancer cells cannot. ONCASPAR lowers L-asparagine level in blood cancer cells and stops the cancer cells growing.

What are the ingredients in ONCASPAR?

Medicinal ingredient:

- Pegaspargase

Non-medicinal ingredients:

- Dibasic Sodium Phosphate
- Monobasic Sodium Phosphate
- Sodium Chloride
- Water for injection

ONCASPAR comes in the following dosage form:

Solution for Injection/Infusion

Do not use ONCASPAR if you:

- are allergic to pegaspargase or to any of the other ingredients of this medicine.
- have severe reduced liver function.
- ever had blood clots with prior L-asparaginase therapy.
- ever had pancreatitis.
- ever had severe bleeding with prior L-asparaginase therapy.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given ONCASPAR. Talk about any health conditions or problems you may have, including if you:

- have had serious allergic reactions to other forms of L-asparaginase, for example, itching, flushing or swelling of the airways, because major allergic reactions to ONCASPAR can occur.
- suffer from a bleeding disorder or had serious blood clots.
- get a fever. This medicine may make you more susceptible to infections.
- have had poor liver function or are taking other medicines which may harm the liver. When ONCASPAR is used in combination with other cancer treatments, liver and central nervous system damage can occur.
- suffer abdominal pain that may radiate to the back. Inflammation of the pancreas, that in some cases caused death, can occur with ONCASPAR treatment.

Other warnings you should know about:

Higher than normal blood and urine sugar levels can occur in patients with ONCASPAR.

This medicine can lead to fluctuation in clotting factors and may increase the risk of bleeding and/or clotting.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your healthcare professional for advice before taking this medicine.

You should not take ONCASPAR if you are pregnant because its effects during pregnancy have not been studied. Your healthcare professional will decide whether your disease requires treatment. You must use reliable contraception during treatment, and for at least 6 months after ONCASPAR treatment was discontinued. Ask your healthcare professional for advice on the best contraceptive method that you can use.

It is not known whether pegaspargase is excreted into the breast milk.The decision to stop breast-feeding or stop ONCASPAR treatment should be discussed with your healthcare professional.

Do not drive or use machines when taking this medicine because it may make you feel drowsy, tired or confused.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ONCASPAR:

- immunisation with live vaccines within three months of completing your leukaemia treatment. This will increase the risk of severe infections.
- vincristine, another cancer medicine. If taken at the same time as ONCASPAR there is an increased risk of side effects or allergic reactions.
- medicines which reduce the blood's ability to clot such as anticoagulants (e.g. warfarin and heparin), dipyridamol, acetylsalicylic acid or nonsteroidal anti-inflammatory drugs. If taken at the same time as ONCASPAR there is a higher risk of bleeding disorders.
- medicines which require cell division for their effect (e.g. methotrexate, a medicine used for cancer as well as arthritis).
- prednisone, a steroid medicine. If taken at the same time as ONCASPAR the effects on the clotting ability of your blood are increased.
- cytarabine, a medicine which can be used in cancer treatment and, could interfere with the effects of ONCASPAR.

ONCASPAR can also cause changes in liver function which can affect the way other medicines work.

How to take ONCASPAR:

ONCASPAR is given by intramuscular injection or intravenous infusion. This product should be administered by your healthcare professional only.

Usual dose:

Your healthcare professional will determine the dose of ONCASPAR you will receive. The dose you receive will be based on your age, and body surface area or body weight.

Overdose:

If you think you have been administered too much ONCASPAR, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss your scheduled treatment, contact your healthcare professional as soon as possible to schedule your next treatment.

What are possible side effects from using ONCASPAR?

The following side effects were observed with different frequencies in patients receiving ONCASPAR: very common side effects (i.e., more than one patient out of every 10 patients) included serious allergic reactions with the following events (rash, itching, red swellings of the skin, hives, and difficult breathing, fast heartbeat, and drop in blood pressure), abdominal pain, diarrhea, rash and generalized weakness.

The following commonly (more than 1 patient out of every 100 patients) observed side effects were: vomiting, pain in the limbs and joints, infections that can be severe with high fever and confusion or loss of consciousness. Also inflammation of the pancreas which can result in pain in the upper abdomen, nausea, vomiting and high blood sugar. Inflammation of the mouth and lips or damage to nerves (may decrease sensation, balance, and cause muscle weakness or loss of consciousness or uncontrolled shaking of the body (convulsions) were also observed. Other events included low grade fever associated with low white blood cells, decrease in the amount of red blood cells (feeling tried, weakness, with difficult breathing, formation of a blood clot, bruising or severe bleeding. Rare side effects (not more than 1 out of every 1000 patients) include reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome characterized by headache, confusion, high blood pressure, seizures and visual loss which resolves after some time. Very rare side effects (not more than 1 out of every 10,000 patients) include mild twitching of the fingers and fluid in the abdominal area (increase in size of abdominal area).

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Serious allergic reactions: rash, itching, swelling, hives, shortness of breath, fast heartbeat, and drop in blood pressure		√	√
Abdominal pain	√		

Blood bilirubin increase		√	
Diarrhea	√		
High blood sugar levels		√	
Inflammation of the pancreas: pain the upper abdomen, nausea, vomiting (pancreatitis)			√
Rash	√		
Generalized weakness	√		
Formation of a blood clot		√	
Severe infection with very high fever		√	
COMMON			
Vomiting	√		
Pain in the limbs and joints		√	
Damage to nerves: may impair sensation, balance, movement, gland or organ function, and cause muscle weakness or loss of consciousness		√	
Inflammation of the mouth and lips		√	
Fever with low white blood cells		√	
Decrease in the amount of red blood cells: feeling tried, weakness, shortness of breath with oxygen supply to the body or a region of the body		√	
Infections and sepsis: ~~high fever,~~ increased heart rate, increased breathing rate, confusion		√	
Bruising or severe bleeding		√	
High blood levels of lipid(s)	√		
Convulsion: uncontrolled shaking of body		√	
Investigations: amylase increased, alanine aminotransferase increase, neutrophil count decreased, platelet count decreased, activated partial thromboplastin time prolonged		√	
Build-up of fluid in the stomach (ascites)		√	
RARE			
Loss of kidney function (reversible)		√	
Visual disturbance		√	
UNKNOWN			
Severe allergic reaction that may cause loss of consciousness and could be life-threatening (anaphylactic shock)		√	√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
    - Fax to 1-866-678-6789 (toll-free), or
    - Mail to: Canada Vigilance Program
      Health Canada, Postal Locator 1908C
      Ottawa, ON
      K1A 0K9

Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep refrigerated prior to use at 2°C to 8°C. Do not freeze or shake. Store vials in the original package to protect from light.

This product is to be stored and administered by a healthcare professional only.

Keep out of reach and sight of children.

If you want more information about ONCASPAR:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.servier.ca, or by calling 1-800-363-6093.

This leaflet was prepared by :

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Last Revised: