SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oncaspar 750 U/ml powder for solution for injection/infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3,750 Units (U)** of pegaspargase*.
After reconstitution, 1 ml of solution contains 750 U pegaspargase (750 U/ml).

* The active substance is a covalent conjugate of *Escherichia coli*-derived L-asparaginase with monomethoxypolyethylene glycol
**One unit is defined as the quantity of enzyme required to liberate 1 µmol ammonia per minute at pH 7.3 and 37°C

The potency of this medicinal product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section 5.1.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.
White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients.

4.2 Posology and method of administration

Oncaspar should be prescribed and administered by physicians and/or 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 for any adverse reactions throughout the administration period (see section 4.4).

Posology

Oncaspar is usually administered as part of combination chemotherapy protocols with other antineoplastic agents (see also section 4.5).

Paediatric patients and adults ≤21 years
The recommended dose in patients with a body surface area (BSA) ≥0.6 m^2 and who are ≤21 years of age is 2,500 U of pegaspargase (equivalent to 3.3 ml Oncaspar)/m^2 body surface area every 14 days.

Children with a body surface area <0.6 m^2 should receive 82.5 U of pegaspargase (equivalent to 0.1 ml Oncaspar)/kg body weight every 14 days.

Adults >21 years
Unless otherwise prescribed, the recommended posology in adults aged >21 years is 2,000 U of pegaspargase (equivalent to 2.67 ml Oncaspar)/m^2 body surface area every 14 days.

Treatment may be monitored based on the trough serum asparaginase activity measured before the next administration of pegaspargase. If asparaginase activity values fail to reach target levels, a switch to a different asparaginase preparation could be considered (see section 4.4).

Special populations
Renal impairment
As pegaspargase is a protein with a high molecular weight, it is not excreted renally, and no dose adjustment is necessary in patients with renal impairment.

Hepatic impairment
No dose adjustment is necessary in patients with hepatic impairment.

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

Method of administration

Oncaspar can be given by intramuscular (IM) injection or intravenous (IV) infusion.

For smaller volumes, 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 a higher volume is given, the dose should be divided and given at several injection sites.

Intravenous infusion of Oncaspar is usually given over a period of 1 to 2 hours in 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution.

The diluted solution can be given together with an already-running infusion of either sodium chloride 9 mg/ml or 5% glucose. Do not infuse other medicinal products through the same intravenous line during administration of Oncaspar.

For instructions on reconstitution and dilution of this medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Severe hepatic impairment (bilirubin >3 times upper limit of normal [ULN]; transaminases >10 times ULN).
History of serious thrombosis with prior L-asparaginase therapy.
History of pancreatitis, including pancreatitis related to previous L-asparaginase therapy (see section 4.4).
History of serious haemorrhagic events with prior L-asparaginase therapy (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Asparaginase antibodies
The presence of anti-asparaginase antibodies may be associated with low asparaginase activity levels due to potential neutralising activity of these antibodies. In such cases, a switch to a different asparaginase preparation should be considered.

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

Hypersensitivity
Hypersensitivity reactions to pegaspargase, including life-threatening anaphylaxis, can occur during therapy, including in patients with known hypersensitivity to *E. coli*-derived asparaginase formulations. Other hypersensitivity reactions can include angioedema, lip swelling, eye swelling, erythema, decreased blood pressure, bronchospasm, dyspnoea, pruritus and rash (see sections 4.3 and 4.8).

As a routine precautionary measure, the patient should be monitored for an hour after administration; resuscitation equipment and other appropriate means for the treatment of anaphylaxis should be available (epinephrine, oxygen, intravenous steroids, etc.). Oncaspar should be discontinued in patients with serious hypersensitivity reactions (see sections 4.3 and 4.8). Depending on the severity of the symptoms, administration of antihistamines, corticosteroids and vasopressors may be indicated as a counter-measure.

Pancreatic effects
Pancreatitis, including haemorrhagic or necrotising pancreatitis with fatal outcomes, has been reported in patients receiving Oncaspar (see section 4.8).

Patients should be informed of the signs and symptoms of pancreatitis which, if left untreated, could become fatal.

If pancreatitis is suspected, Oncaspar should be discontinued; if pancreatitis is confirmed, Oncaspar should not be restarted.

Serum amylase and/or lipase levels should be monitored frequently to identify early signs of pancreatic inflammation. Blood glucose levels should be monitored, as impaired glucose tolerance may occur with concomitant use of Oncaspar with prednisone.

Coagulopathy
Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving pegaspargase (see section 4.8). Oncaspar should be discontinued in patients with serious thrombotic events.

Increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenaemia can occur in patients receiving pegaspargase. Coagulation parameters should be monitored at baseline and periodically during and after treatment, particularly when other medicinal products with anticoagulant effects (such as acetylsalicylic acid and non steroidal anti inflammatory medicinal products) are used simultaneously (see section 4.5), or when concomitant chemotherapy regimen including methotrexate, daunorubicin, corticosteroids is administered. When there is a marked decrease in fibrinogen or antithrombin III (ATIII) deficiency, consider appropriate replacement therapy.

Hepatic effects
Combination therapy with Oncaspar and other hepatotoxic products can result in severe hepatic toxicity.

Caution is required when Oncaspar is given in combination with hepatotoxic products, especially if there is pre-existing hepatic impairment. Patients should be monitored for changes in liver function parameters.

There may be an increased risk of hepatotoxicity in Philadelphia chromosome positive patients, for whom treatment with tyrosine kinase inhibitors (e.g., imatinib) is combined with L-asparaginase therapy. This should be taken into account when considering the use of Oncaspar in these patient populations.

Due to the risk of hyperbilirubinaemia, it is recommended to monitor bilirubin levels at baseline and prior to each dose.

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 (see section 4.8).

Oncaspar may cause central nervous system signs and symptoms manifesting as somnolence, confusion, convulsions. Patients should be closely monitored for such symptoms, especially if Oncaspar is used in association with neurotoxic products (such as vincristine and methotrexate; see section 4.5).

Myelosuppression
Pegaspargase may cause myelosuppression, either directly or indirectly (by altering the myelosuppressive effects of other agents such as methotrexate or 6-mercaptopurine). Therefore, use of Oncaspar could increase the risk of infections.

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. This can be associated with a marked rise in the serum uric acid level. Uric acid nephropathy may develop. To monitor the therapeutic effect, the peripheral blood count and the patient's bone marrow should be monitored closely.

Hyperammonaemia
Asparaginase facilitates the rapid conversion of asparagine and glutamine to aspartic acid and glutamic acid, with ammonia as the shared by-product of both reactions (see section 5.1). Intravenous administration of asparaginase may therefore cause serum levels of ammonia to rise sharply following administration.

The symptoms of hyperammonaemia are often transient in nature and can include: nausea, vomiting, headache, dizziness and rash. In severe cases, encephalopathy can develop with or without hepatic impairment, especially in older adults, which can be life-threatening or fatal. If symptoms of hyperammonaemia exist, ammonia levels should be monitored closely.

Contraception
Effective non-oral method of contraception must be used during Oncaspar treatment and for at least 6 months after Oncaspar discontinuation. Since an indirect interaction between the oral contraceptives and pegaspargase cannot be ruled out, the use of oral contraception is not considered an acceptable method of contraception (see sections 4.5 and 4.6).

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

In addition, by inhibiting protein synthesis and cell division, pegaspargase 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 with Oncaspar: their prior administration can increase the action of pegaspargase synergistically. If these substances are given subsequently, the effect of pegaspargase can be weakened antagonistically.

Pegaspargase 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.

The use of Oncaspar can lead to fluctuation in coagulation factors. This can promote the tendency to bleeding and/or thrombosis. Caution is therefore needed when anticoagulants such as coumarin, heparin, dipyridamole, acetylsalicylic acid or non-steroidal anti-inflammatory medicinal products are given concomitantly, or when concomitant chemotherapy regimen including methotrexate, daunorubicin, corticosteroids is administered.

When glucocorticoids (e.g., prednisone) and pegaspargase 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 can increase the toxicity of pegaspargase. Administration of Oncaspar before vincristine may increase the neurotoxicity of vincristine. Therefore, vincristine should be given at least 12 hours prior to administration of Oncaspar in order to minimise 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 sections 4.4 and 4.6).

Simultaneous vaccination with live vaccines may increase the risk of severe infections attributable to the immunosuppressive activity of pegaspargase, the presence of the underlying disease and combination chemotherapy (see section 4.4). Vaccination with live vaccines should therefore be given no earlier than 3 months after termination of the entire antileukaemic treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Men and women should use effective contraception during treatment and for at least 6 months after Oncaspar discontinuation. Since an indirect interaction between oral contraceptives and pegaspargase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation. A method other than oral contraception should be used in women of childbearing potential (see sections 4.4 and 4.5).

Pregnancy
There are limited data on the use of L-asparaginase and no data on the use of Oncaspar in pregnant women. No reproduction studies in animals with pegaspargase were performed but studies in animals with L-asparaginase have shown teratogenicity (see section 5.3). Therefore and due to its pharmacological properties, Oncaspar should not be used during pregnancy unless the clinical conditions of the woman require treatment with pegaspargase.

Breast-feeding
It is not known whether pegaspargase is excreted in breast milk. Based on its pharmacological properties, any risk to the breast-fed newborns/infants cannot be excluded. As a precautionary measure, breast-feeding should be discontinued during treatment with Oncaspar and should not be restarted until after discontinuation of Oncaspar.

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

4.7 Effects on ability to drive and use machines

Oncaspar has 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 be advised not to 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 (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile
The adverse reactions described in this section are derived from studies data and post-marketing experience of Oncaspar in ALL patients. The safety profile is based on randomised, controlled, prospective, open-label multicentre studies using Oncaspar at a dose of 2500 U/m^2 administered intravenously as a comparative treatment (studies DFCI 11-001 and AALL07P4). In addition, Oncaspar studies using the intramuscular route of administration (studies CCG-1962 and CCG-1991) were also considered to determine the safety profile (see section 5.1).

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

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, aspartate aminotransferase increased, blood bilirubin increased, febrile neutropenia, hyperglycaemia, lipase increased, and pancreatitis.

Tabulated list of adverse reactions
Adverse reactions and their frequencies are reported in Table 1. Frequencies are 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 1: Adverse reactions reported with Oncaspar therapy

MedDRA standard system organ class	**Adverse reaction**
Infections and infestations	Common: Infections, sepsis
Blood and lymphatic system disorders	Very common: Febrile neutropenia
	Common: Anaemia, coagulopathy
	Not known: Bone marrow failure
Immune system disorders	Very common: Hypersensitivity, urticaria, anaphylactic reaction
	Not known: Anaphylactic shock
Metabolism and nutrition disorders	Very common: Decreased appetite, hyperglycaemia
	Common: Hyperlipidaemia, hypercholesterolaemia
	Not known: Diabetic ketoacidosis, hypoglycaemia
Psychiatric disorders	Not known: Confusional state

MedDRA standard system organ class	Adverse reaction
Nervous system disorders	Common: Seizure, peripheral motor neuropathy, syncope
	Rare: Posterior reversible leukoencephalopathy syndrome
	Not known: Somnolence, tremor*
Vascular disorders	Very common: Embolism**
	Common: Thrombosis***
	Not known: Cerebrovascular accident, haemorrhage, superior sagittal sinus thrombosis
Respiratory, thoracic and mediastinal disorders	Common: Hypoxia
Gastrointestinal disorders	Very common: Pancreatitis, diarrhoea, abdominal pain, nausea
	Common: Vomiting, stomatitis, ascites
	Rare: Pancreatitis necrotising, pancreatitis haemorrhagic
	Not known: Pancreatic pseudocyst, parotitis*
Hepatobiliary disorders	Common: Hepatotoxicity, fatty liver Rare: Hepatic necrosis, jaundice, cholestasis, hepatic failure
Skin and subcutaneous tissue disorders	Very common: Rash
	Not known: Toxic epidermal necrolysis*
Musculoskeletal and connective tissue disorders	Common: Pain in extremities
Renal and urinary disorders	Not known: Renal failure acute*
General disorders and administration site conditions	Not known: Pyrexia
Investigations	Very common: Weight decreased, hypoalbuminaemia, alanine aminotransferase increased, aspartate aminotransferase increased, hypertriglyceridaemia, blood fibrinogen decreased, lipase increased, amylase increased, activated partial thromboplastin time prolonged, blood bilirubin increased
	Common: Prothrombin time prolonged. international normalised ratio increased, hypokalaemia, blood cholesterol increased, hypofibrinogenaemia, gamma-glutamyl transferase increased
	Not known: Blood urea increased, anti-pegaspargase antibodies, neutrophil count decreased, platelet count decreased, hyperammonaemia

*Adverse reactions observed with other asparaginases in the class

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

***Legend: CNS thrombosis

Description of selected adverse reactions

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

Blood and lymphatic system disorders

Oncaspar can cause mild to moderate myelosuppression, and all three blood cell lines can be affected. About half of all serious haemorrhages and thromboses affect cerebral vessels and can lead to e.g., stroke, seizure, headache or loss of consciousness.

Nervous system disorders
Oncaspar may cause central nervous system dysfunctions manifesting as convulsions, 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.

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 L-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.

Renal and urinary disorders
Acute renal failure may develop in rare cases during treatment with L-asparaginase-containing regimens.

Skin and subcutaneous tissue disorders
Allergic reactions can manifest on the skin. One case of toxic epidermal necrolysis (Lyell's syndrome) has been described in association with L-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 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 site conditions
Pyrexia can occur after the injection, which usually subsides spontaneously.

Immune system disorders
Specific antibodies to pegaspargase have been detected; uncommonly they were associated with hypersensitivity reactions. Neutralising antibodies reducing clinical efficacy were also recorded.

Hypersensitivity reactions to Oncaspar, including life-threatening anaphylaxis, angioedema, lip swelling, eye swelling, erythema, blood pressure decreased, bronchospasm, dyspnoea, pruritus and rash, can occur during therapy (see sections 4.3 and 4.4).

Hepatobiliary disorders
Alteration of liver parameters is 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 types of adverse reactions with Oncaspar are similar to those observed with native non-pegylated L-asparaginase (e.g., native *E. coli* asparaginase).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 for the overdose. 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

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, other antineoplastic agents, ATC code: L01XX24

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 results in inhibition of protein-synthesis, DNA-synthesis and RNA-synthesis, especially in leukaemic blasts which are not able to synthesise L-asparagine, thus undergoing apoptosis.

Normal cells, in contrast, are capable of synthesising L-asparagine and are less affected by its rapid depletion 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.

Pharmacodynamic effects

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 intramuscular (Study CCG-1962) and intravenous administration (AALL07P4).

In Study CCG-1962, PD effect of Oncaspar was assessed through serial measurements of asparagine in serum (n=57) and CSF (n=50) of newly diagnosed paediatric patients with standard-risk ALL who received three intramuscular doses of Oncaspar (2,500 Units/m^2 BSA), one each during Induction and two during delayed intensification treatment phases. A reduction in serum asparagine concentration was evident by the 4th day after the first Induction dose and reached an apparent nadir by the 10th day after the dose. Serum asparagine concentrations of approximately 1 µM persisted for approximately 3 weeks.

Asparagine concentration fell to <3 μM when asparaginase activity was >0.1 U/mL. CSF asparagine of 2.3 μM pre-treatment fell to 1.1 μM on Day 7 and 0.6 μM on Day 28 of Induction (see Clinical efficacy and safety).

In Study AALL07P4, the PD effect of Oncaspar was assessed in 47 evaluable subjects with high risk B-precursor ALL who received intravenous 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 by the 18th day after dosing.

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

Clinical efficacy and safety

Oncaspar efficacy and safety were evaluated on the basis of three clinical studies using Oncaspar solution for injection/infusion in the first line treatment of ALL: Study CCG-1962 in standard risk ALL patients; Study AALL07P4 in high risk ALL patients; Study DFCI 11-001 enrolled both standard and high-risk ALL patients.

Oncaspar efficacy in ALL in patients with relapse/refractory disease and a history of prior clinical allergic reaction to native *E. coli* L-asparaginase was based on a pool of 94 patients from six open-label studies [ASP-001, ASP-201A, ASP-302, ASP-304, ASP-400 and ASP-001C/003C].

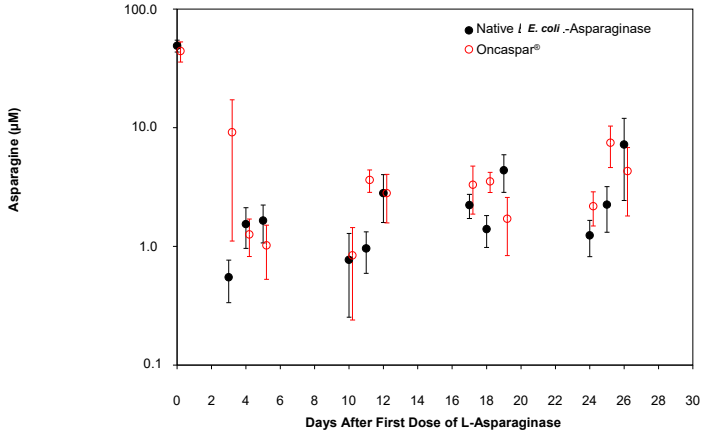
First-Line (ALL patients non-hypersensitive to native E. coli L-asparaginase)

The safety and efficacy of Oncaspar was evaluated in an open-label, multicentre, randomised, active-controlled study (StudyCCG-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* L-asparaginase as part of combination therapy. Oncaspar was administered intramuscularly at a dose of 2,500 Units/m^2 BSA on Day 3 of the 4-week Induction phase and on Day 3 of each of two 8-week Delayed Intensification (DI) phases. Native *E. coli* L-asparaginase was administered intramuscularly at a dose of 6,000 Units/m^2 BSA three times weekly for a total of 9 doses during Induction and for a total of 6 doses during each Delayed Intensification phase.

The primary determination of efficacy was based on demonstration of similar asparagine depletion (magnitude and duration) in the Oncaspar and native *E. coli* L-asparaginase arms. 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 2 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* L-asparaginase arms. 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 during Study CCG-1962 Induction phase



Note: Oncaspar (2,500 Units/m^2 BSA intramuscular) was administered on Day 3 of the 4-week Induction phase. Native *E. coli* L-asparaginase (6,000 Units/m^2 BSA intramuscular) 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* L-asparaginase treatment arm.

Event-free survival (EFS) for the Oncaspar and native *E. coli* L-asparaginase arms is summarised in Table 2, Study CCG-1962 was not designed to evaluate differences in EFS rates.

Table 2: Event-free survival rate at 3, 5 and 7 years (Study CCG-1962)

	Oncaspar	native *E. coli* L-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)

In Study CCG-1962, the most common adverse reactions were infections, including two life-threatening infections (1 patient in each arm). In general, incidence and type of adverse reactions Grade 3 and 4 were similar between the two treatment groups. Two patients in the Oncaspar arm had allergic reactions during Delayed Intensification (DI) DI #1 (Grade 1 allergic reaction and Grade 3 hives).

A pilot study was conducted for newly diagnosed patients from 1 to <31 years of age with high risk B-precursor ALL (Study AALL07P4). This was an open-label, controlled, randomised study comparing an investigational pegylated asparaginase product to Oncaspar as a component of multi-agent chemotherapy in the first line treatment of ALL. White blood cell (WBC) criteria were: a) Age 1-10 years: WBC ≥50,000/µL; b) Age 10-30 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; 54 patients were randomised to treatment with 2,500 U/m^2 BSA Oncaspar and 111 patients were randomised to the investigational pegylated asparaginase product. Oncaspar was administered intravenously at a dose of 2,500 Units/m^2 BSA during Induction, Consolidation, Delayed Intensification, and Interim Maintenance phases in patients with high-risk ALL receiving augmented Berlin-Frankfurt-Münster therapy.

The percentage of patients in the Oncaspar treatment arm with evaluable minimal residual disease (MRD) negative status (<0.1% leukaemia cells in bone marrow) at Day 29 of Induction was 80% (40/50). At 4-years, the EFS and overall survival (OS) for the Oncaspar treatment arm were 81.8% [95% CI 62.9-91.7%] and 90.4% [95% CI 78.5-95.9%], respectively. Overall, in the group receiving Oncaspar, the rate of all grade hypersensitivity was 5.8%, anaphylactic reactions was 19.2%, and pancreatitis 7.7%. Grade 3 or higher febrile neutropenia was 15.4%.

Study DFCI 11-001, conducted by the Dana-Farber Cancer Institute (DFCI), is an ongoing, active-controlled, randomised multicentre study of an intravenous investigational pegylated asparaginase product versus Oncaspar, in children and adolescents aged 1 to <22 years with newly diagnosed ALL treated with a DFCI ALL consortium therapeutic backbone. A total of 239 patients were randomised, 237 of whom were treated with study drug (146 male and 91 female), of these, 119 patients (115 with a diagnosis of ALL) were treated with Oncaspar 2500 U/m^2. Treatment was administered during Induction (Day 7), and then every 2 weeks for a total of 30 weeks post-Induction therapy. Randomisation of patients was stratified based on risk group (standard/high/very high risk), including both B- and T-cell ALL. The percentage of patients in the Oncaspar arm with evaluable Low End-Induction MRD (<0.001 detectable disease) at Day 32 was 87.9% (80/91). The One-year EFS was 98.0 [95%CI 92.3, 99.5]; the One-year OS was 100 [95% CI 100, 100] in this study.

ALL patients hypersensitive to native E. coli L-asparaginase
Six open-label studies evaluated Oncaspar in relapse/refractory haematological diseases. In these studies a total of 94 patients with ALL diagnosis with a history of prior clinical allergic reaction to native *E. coli* L-asparaginase were exposed to Oncaspar. One patient received Oncaspar doses of 250 and 500 Units/m^2 BSA intravenously. The remaining patients were treated with 2,000 or 2,500 U/m^2 BSA administered intramuscularly or intravenously. Patients received Oncaspar as a single agent or in combination with multi-agent chemotherapy. Overall, from five studies analysed based on 65 ALL patients exposed to Oncaspar using the highest therapeutic response during the entire study, complete remission was observed in 30 patients (46%), partial remission in 7 patients (11%) and haematological improvement in 1 patient (2%). In the other study, with 29 hypersensitive ALL patients exposed to Oncaspar, 11 patients were evaluated for response during Induction. Of these, 3 patients (27%) achieved complete remission, 1 patient (9%) had partial remission, 1 patient (9%) had haematologic improvement and 2 patients (18%) had therapeutic efficacy. 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 (89%) achieving complete remission, and 1 patient (5%) with therapeutic efficacy.

5.2 Pharmacokinetic properties

Oncaspar pharmacokinetic properties were based on asparaginase activity measured by an enzymatic assay after intramuscular (CCG-1962) and intravenous (AALL07P4, DFCI 11-001) administration.

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

In Study AALL07P4, PK parameters after a single 2,500 U/m^2 intravenous dose during Induction were calculated by noncompartmental PK analysis from sequential plasma samples and are depicted in Table 3 (see section 5.1). The C_{max} and AUC of Oncaspar trended lower in males, subjects with larger BMI, and subjects >10 years. During Induction, following a single intravenous dose of Oncaspar 2,500 U/m^2, asparaginase activity ≥0.1 U/mL was sustained for up to 18 days post-dose in 95.3% of subjects.

Table 3: **Pharmacokinetic Parameters After a Single intravenous Dose of Oncaspar 2,500 U/m² BSA During Induction (N=47; Study AALL07P4)**

PK Parameters	Arithmetic Mean (SD)
C_{max} (mU/mL)*	1638 (459.1)
T_{max} (hr)*	1.25 (1.08, 5.33)†
AUC_{0-t} (mU·day/mL)*	14810 (3555)
$AUC_{0-\infty}$ (mU·day/mL)‡	16570 (4810)
$t_{1/2}$ (day)‡	5.33 (2.33)
CL (L/day)‡	0.2152 (0.1214)
Vss (L)‡	1.95 (1.13)

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

In Study DFCI 11-001, assessments of asparaginase activity were performed following a single intravenous dose of Oncaspar 2,500 U/m² BSA during Induction, and every two weeks during post-Induction (see section 5.1). During Induction, plasma asparaginase activity ≥0.1 U/mL was sustained in 93.5% of subjects 18 days after administration. During the post-Induction phase, a nadir (trough) asparaginase activity above 0.4 U/mL was sustained in 100% of subjects from Week 7 up until Week 25. These results indicate that, when Oncaspar 2,500 U/m² BSA is administered as single and repeated doses every two weeks, clinically relevant asparaginase activity is sustained over the entire dosing interval (i.e., two weeks).

Patients with newly diagnosed ALL received a single intramuscular injection of Oncaspar (2,500 U/m² BSA) or native asparaginase from *E. coli* (25,000 U/m² BSA) or from *Erwinia* (25,000 U/m² BSA). The plasma elimination half-life of Oncaspar was statistically significantly longer (5.7 days) than the plasma elimination half-lives of the native asparaginases from *E. coli* (1.3 days) and *Erwinia* (0.65 days). 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 asparaginase from *E. coli* as part of an Induction therapy. Oncaspar was given intramuscularly in a dose of 2,500 U/m² BSA 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).

Specific populations

The controlled studies were not designed to formally evaluate the pharmacokinetics of Oncaspar in specific populations. A population pharmacokinetic evaluation of Oncaspar based on data obtained from Studies AALL07P4 (IV), DFCI 11-001 (IV), and CCG-1962 (IM) identified that clearance (linear and saturable) increased approximately proportionally to BSA and volume of distribution increased slightly more proportionally to BSA. No statistically significant differences in PK characteristics between male and female subjects were identified in this analysis.

The impact of renal and hepatic 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.

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.

There are no data available for elderly patients.

5.3 Preclinical safety data

Pharmacokinetic/pharmacodynamic nonclinical comparability between the two pharmaceutical forms of Oncaspar, solution for injection/infusion, and powder for solution, was demonstrated in dogs after single and repeated doses (500 U/kg), by the intravenous route. The below mentioned studies were performed on the solution for injection/infusion formulation.

Acute toxicity
Only very high doses of pegaspargase given to mice intraperitoneally as a single dose (25,000 – 100,000 U/kg body weight) caused the death of 14% of all treated mice. Mild hepatotoxicity was observed with the same doses. Adverse reactions were loss of body weight, piloerection and reduced activity. Reduced splenic weight might be a sign of potential immunosuppressant effect of the treatment.

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

Repeated dose toxicity
A 4-week study in rats treated with a dose of pegaspargase of 400 U/kg/day intraperitoneally 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 intraperitoneally or intramuscularly resulted in slight hepatocellular changes only at the highest intraperitoneal dose.

A temporary suppression in body weight gain and a temporary reduction in total leukocyte counts were observed in dogs which were treated with pegaspargase 1200 U/kg weekly for 2 weeks. Increased serum glutamic pyruvic transaminase activity also occurred in one out of four dogs.

Immunogenicity
No immunogenic response was detected in a 12-week study in mice in which pegaspargase was administered weekly at the dose of 10.5 U/mouse intramuscularly or intraperitoneally.

Reproductive toxicity
No studies of reproductive toxicity were conducted with pegaspargase.

Embryotoxicity studies with L-asparaginase have showed 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 intravenously. In rabbits doses of 50 or 100 U/kg intravenous on days 8 and 9 of gestation induced viable foetuses 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate heptahydrate
Sodium dihydrogen phosphate monohydrate
Sodium chloride

Sucrose
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial:
3 years.

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for 24 hours below 25°C. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Diluted solution
Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C).
Do not freeze.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I flint glass vial with chlorobutyl elastomer stopper, capped with a 20 mm aluminium flip-off seal, containing 3,750 U pegaspargase.

Pack size of 1.

6.6 Special precautions for disposal and other handling

This medicinal product can cause irritation on contact. The powder 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; if the medicinal product comes in contact with eyes, skin or mucous membranes, rinse immediately with plenty of water for at least 15 minutes.

Oncaspar is to be administered intravenously or intramuscularly after reconstitution of the product. The powder must be reconstituted with 5.2 ml water for injections prior to administration (see section 4.2).

Instructions for handling
1. Staff should be trained in how to handle and transfer the medicinal product (pregnant staff should be excluded from working with this medicinal product).

2. Aseptic technique must be used.
3. Procedures for proper handling of antineoplastic agents should be observed.
4. The use of disposable gloves and protective garments is recommended when handling Oncaspar.
5. All items for administration or cleaning, including gloves, should be placed in high-risk waste disposal bags for high-temperature incineration.

Reconstitution
1. 5.2 ml water for injections are injected into the vial using a syringe and 21 gauge needle.
2. The vial should be gently swirled until the powder is reconstituted.
3. After reconstitution, the solution should be clear, colourless and free from visible foreign particles. Do not use if the reconstituted solution is cloudy or if a precipitate has formed. Do not shake.
4. The solution should be used within 24 hours after reconstitution, when stored below 25°C.

Administration
1. Parenteral medicinal products should be inspected for particulate matter prior to administration, only a clear, colourless solution free from visible foreign particles should be used.
2. The medicinal product should be administered intravenously or intramuscularly. The solution should be administered slowly.
   For intramuscular injection, the volume should not exceed 2 ml in children and adolescents and 3 ml in adults.
   For intravenous administration, the reconstituted solution should be diluted in 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution.
   The diluted solution can be given over 1 to 2 hours together with an already-running infusion of either sodium chloride 9 mg/ml or 5% glucose. Do not infuse other medicinal products through the same intravenous line during administration of Oncaspar (see section 4.2).
   After dilution, the solution should be used immediately. If immediate use is not possible, the diluted solution can be stored at 2°C-8°C for up to 48 hours (see section 6.3).

Disposal
Oncaspar is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1070/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 January 2016
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

11/2020

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.