ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Oncaspar 750 U/ml solution for injection/infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 750 units (U)** of pegaspargase*.
One vial of 5 ml solution contains 3750 Units.

* The active substance is a covalent conjugate of *Escherichia coli*-derived L-asparaginase with monomethoxypropylene 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 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

Solution for injection/infusion.
Clear, colourless solution.

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 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.

Posology

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

Paediatric patients and adults ≤ 21 years

The recommended dose of Oncaspar in patients with a body surface area ≥0.6 m^2 and who are ≤21 years of age is 2500 U (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 (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 2000 U/m^2 every 14 days.

Treatment may be monitored based on the trough serum asparaginase activity measured before the next administration of Oncaspar. 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 is limited data available for patients older than 65 years.

Method of 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.

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 together with an already-running infusion.

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 the related to previous asparaginase therapy (see section 4.4).
History of serious hemorrhagic events with prior L-asparaginase therapy (see section 4.4).

4.4 Special warnings and precautions for use

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

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

Hypersensitivity reactions to Oncaspar, e.g. life-threatening anaphylaxis, can occur during the therapy. As a routine precautionary measure the patient should be monitored for an hour after administration, having resuscitation equipment and other means required for the treatment of anaphylaxis in readiness (epinephrine, oxygen, intravenous steroids etc.). Oncaspar should be discontinued in patients with serious allergic reactions (see sections 4.3 and 4.8). Depending on the severity of the symptoms,

administration of antihistamines, corticosteroids and possibly circulation-stabilising medical product is indicated as counter-measure.

Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving Oncaspar. Oncaspar should be discontinued in patients with serious thrombotic events.

Increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia can occur in patients receiving Oncaspar. Coagulation parameters should be monitored at baseline and periodically during and after treatment; particularly when other medicinal products with coagulation-inhibiting effects such as acetylsalicylic acid and nonsteroidal anti-inflammatory medicinal products are used simultaneously (see section 4.5).
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 AntithrombinIII (ATIII) deficiency, consider targeted substitution (e.g. fresh frozen plasma).

Oncaspar may possess immunosuppressive activity. It is therefore possible that use of this medicinal product promotes infections in patients.

Combination therapy with Oncaspar can result in severe hepatic toxicity and central nervous system 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.

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

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

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.

There have been reported adverse reactions of pancreatitis. 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 is suspected, Oncaspar should be discontinued; if pancreatitis is confirmed, Oncaspar should not be restarted. Appropriate investigations (e.g. ultrasound) should therefore be performed up to four months after termination of Oncaspar therapy. As the precise pathogenesis is unknown, only supportive measures can be recommended. Disturbances of exocrine pancreatic function can result in diarrhoea.

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

In single cases, haemorrhagic 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.

Effective contraception must be used 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 (see sections 4.5 and 4.6).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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 interfere 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 enzymatic detoxification of other medicinal products, especially in the liver.

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 anticoagulants such as 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 can increase the toxicity of Oncaspar and increases the risk of anaphylactic reactions. Therefore, vincristine should be given in a timely manner before administration of Oncaspar in order to minimise toxicity.

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 combination of Oncaspar with oral contraception is not recommended. Another method than oral contraception shoud be used in women of childbearing potential (see sections 4.4 and 4.6).

Simultaneous vaccination with live vaccines increases 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 section 4.4). Vaccination with live vaccines should therefore be given 3 months at the earliest after termination of the entire antileukaemic treatment.

4.6 Fertility, pregnancy and lactation

<u>Women of childbearing potential/Contraception in males and females</u>
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 sections 4.4 and 4.5).

<u>Pregnancy</u>
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 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 into 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 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 may have a major influence on the ability to drive and use machines, by altering the ability to react.
Patients should be advised not to drive or operate machines if they experience confusion or somnolence or other adverse reactions which can impair their ability to drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile
The adverse reaction described in this section is gathered from a combination of adverse reactions from clinical trial data and the post-marketing experience of Oncaspar in ALL patients. The safety analyses were done considering the clinical study 1 [CCG-1962] and study 2 [AALL07P4] adverse drug reactions (see section 5.1). In addition, the post-marketing reports with Oncaspar that include spontaneous reports as well as serious adverse events from clinical studies.

Overall, the most common adverse reactions reported by CTC grade 2 and higher in the >=20% are hypersensitivity including anaphylactic reaction, febrile neutropenia, anaemia, hyperglycaemia platelet count decreased, neutrophil count decreased, blood bilirubin increased.

Tabulated list of adverse reactions
Adverse reactions and their frequencies are reported in table 1.

The frequency of side effects is defined by the following convention: very common (≥1/10), common (≥1/100 to ≤1/10), uncommon (≥1/1,000 to ≤1/100), rare (≥1/10,000 to ≤1/1,000), very rare (≤1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 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	Common: Febrile neutropenia, Anaemia, Thrombosis
Immune system disorders	Very common: Hypersensitivity, Urticaria, Rash, Anaphylactic reactions
Endocrine disorders	Very Common: Hyperglycaemia
Metabolism and nutrition disorders	Common: Hypertriglyceridaemia, Hyperlipidaemia
Nervous system disorders	Common: Convulsion, Peripheral Motor Neuropathy, Syncope
Vascular disorders	Common: Thrombosis
Respiratory, thoracic and mediastinal disorders	Common: Hypoxia
Gastrointestinal disorders	Very common: Pancreatitis, , Diarrhoea, Abdominal pain Common: Vomiting, stomatitis

MedDRA Standard System Organ Class	Adverse Reaction
Musculoskeletal and connective tissue disorders	Common: Pain in extremities
Investigations	Common: Amylase increased, Alanine aminotransferase increase, Blood bilirubin increase, Neutrophil count decreased, Platelet count decreased, Activated partial thromboplastin time prolonged

Description of selected adverse reactions

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

Nervous system disorders
Oncaspar may cause central nervous system dysfunctions manifesting as convulsion, and less frequently confusional state and somnolence (mildly impaired consciousness).
In rare cases, a reversible posterior leukoencephalopathy syndrome (RPLS) may occur.
In very rare cases, mild tremor in the fingers has been described.

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 in 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 exogenous insulin.

Metabolism and nutrition disorders
An alteration in serum lipid levels was observed and changes in serum lipid values, in most cases without clinical symptoms, are very common.
A rise in serum urea occurs regularly, is dose-independent and nearly always a sign of pre-renal metabolic imbalance.

General disorders and administration side conditions
Pyrexia can occur after the injection, which usually subsides spontaneously.

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

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

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

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

The type of side effects of Oncaspar largely coincides with that of native non-pegylated 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 national reporting system listed in Appendix V

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 serum results in inhibition of protein-synthesis, DNA-synthesis and RNA-synthesis, especially in leukaemic blasts which are not able to synthetise 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.

Pharmacodynamic effects
Anti-leukaemic effect of L-asparaginase is related to a sustained L-asparagine depletion. In Study 1, pharmacodynamics was assessed in 57 newly diagnosed paediatric patients with standard-risk ALL who received three intramuscular doses of Oncaspar (2500 Units/m^2), one each during induction and two delayed intensification treatment phases. Pharmacodynamic activity was assessed through serial measurements of asparagine in serum (n=57) and cerebrospinal fluid (CSF) (n=50).

Clinical efficacy and safety

Oncaspar efficacy and safety was evaluated on the basis of two clinical studies using Oncaspar in the first line treatment of ALL: Study 1 in standard risk ALL patients, and Study 2 in high risk ALL patients.

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

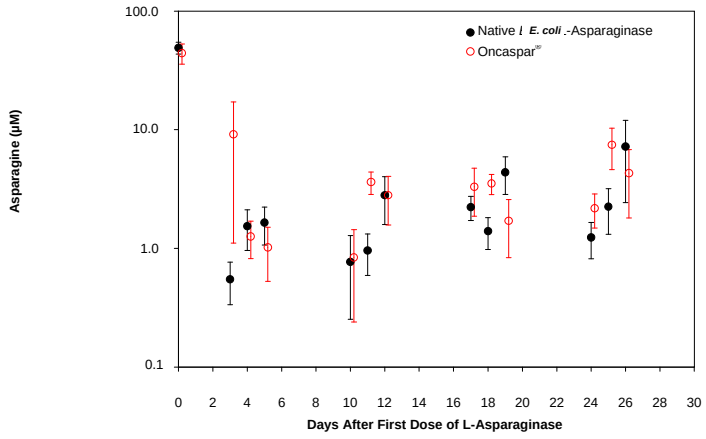
Clinical studies in First-Line (non-hypersensitive population) ALL

The safety and efficacy of Oncaspar was evaluated in an open-label, multicenter, randomized, active-controlled study (Study 1). In this study, 118 paediatric patients aged 1 to 9 years with previously untreated standard-risk ALL were randomized 1:1 to Oncaspar or native *E. coli* L-asparaginase as part of combination therapy. Oncaspar was administered intramuscularly at a dose of 2500 Units/m^2 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 three times weekly for 9 doses during induction and for 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 1 induction phase



Note: Oncaspar (2500 Units/m^2 intramuscular) was administered on Day 3 of the 4-week induction phase. Native *E. coli* L-asparaginase (6000 Units/m^2 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 are summarized in Table 2, Study 1 was not designed to evaluate for differences in EFS rates.

Table 2: Event-free survival rate at 3, 5 and 7 years (Study 1)

	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 1, 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 30 years of age with high risk B-precursor ALL (Study 2). This was a controlled, randomized study comparing Oncaspar to another pegylated asparaginase product in combination with multi-agent chemotherapy in the first line treatment. White blood cell (WBC) criteria were: a) Age 1-10 years: WBC $\geq$ 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 randomized to treatment with 2500 U/m^2 Oncaspar and 111 patients were randomized to another pegylated asparaginase product. Oncaspar was administered intravenously at the dose of 2500 Units/m^2 during Induction, Consolidation, DI, and Interim Maintenance phases in patients with high-risk ALL receiving augmented Berlin-Frankfurt-Munster therapy. At 3-years, the EFS and overall survival (OS) for the Oncaspar treatment arm were 85.1% [95% CI 72-92%] and 92.4% [95% CI 81-97%], respectively. Overall, in the group receiving Oncaspar, all grade of hypersensitivity was 9.8%, anaphylactic reactions was 19.6%, and pancreatitis 5.9%. Grade 3 or higher of febrile neutropenia was 37.9%.

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 intravenously. The remaining patients were treated with 2000 or 2500 U/m^2 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 were 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 achieved complete remission (27%), 1 patient had partial remission (9%), 1 patient had haematologic improvement (9%) and 2 patients had therapeutic efficacy (18%). Therapeutic efficacy was defined as a clinical improvement which did not meet the criteria for other beneficial outcomes. During the maintenance phase, 19 patients were evaluated, with 17 patients achieving complete remission (89%), and 1 patient with therapeutic efficacy (5%).

5.2 Pharmacokinetic properties

Oncaspar pharmacokinetic assessments were based on an enzymatic assay measuring asparaginase activity.
In adults with leukaemia, the initial enzymatic activity after intravenous adminstration of Oncaspar was proportional to the dose. The elimination half-life from the plasma was between 1 and 6 days and appeared to be unaffected by the dose.

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

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

Patients with newly diagnosed ALL received a single intramuscular injection of Oncaspar (2500 U/m² body surface area) or native asparaginase from *E. coli* (25000 U/m² body surface area) or from *Erwinia* (25000 U/m² body surface area). The plasma elimination half-life of Oncaspar was statistically significantly longer (5.7 days) than the plasma elimination half-lives of the native 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 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).

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 is no data available for elderly patients.

5.3 Preclinical safety data

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.

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

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 intravenous. In rabbits doses of 50 or 100 U/kg intravenous 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate monohydrate
Disodium phosphate heptahydrate
Sodium chloride
Water for injections

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

8 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

5 ml solution in a vial (type I glass) with stopper (rubber) and a seal (aluminium) with flip-off cap.
Pack size of 1.

6.6 Special precautions for disposal and other handling

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.

Do not use if the solution is cloudy or a precipitate has formed.
Do not shake.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1070/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Sigma-Tau PharmaSource, Inc.
6925 Guion Road
Indianapolis
Indiana 46268
USA

Name and address of the manufacturer responsible for batch release

Sigma-tau Arzneimittel GmbH
Liebherrstrasse 22
D-80538 Munich
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal. The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further define the efficacy and safety of Oncaspar in patients with newly diagnosed acute lymphoblastic leukaemia, the MAH should submit the results of Study CAALL-F01, a prospective multicentre cohort study evaluating Oncaspar used in the first-line treatment of children and adolescents with ALL along with multi-agent chemotherapy. The clinical study report should be submitted by:	December 2025
Post-authorisation efficacy study (PAES): In order to further define the efficacy and safety of Oncaspar in adult patients with ALL, the MAH should submit the results of a multicenter, open label single arm phase II trial evaluating the efficacy and toxicity of treatment regimens including Oncaspar in adults (aged 18-60) with newly diagnosed Philadelphia chromosome-negative acute lymphoblastic leukemia. The clinical study report should be submitted by:	December 2018

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Oncaspar 750 U/ml solution for injection/infusion
pegaspargase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 750 U of pegaspargase.
One vial of 5 ml solution contains 3750 U.

3. LIST OF EXCIPIENTS

Sodium dihydrogen phosphate monohydrate, disodium phosphate heptahydrate, sodium chloride, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection/infusion
1 vial of 5 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous or intramuscular use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if a precipitate has formed, or if the solution is cloudy.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1070/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Oncaspar 750 U/ml solution for injection/infusion.
Pegaspargase
For intravenous or intramuscular use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot.

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Oncaspar 750 U/ml solution for injection/infusion
pegaspargase

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor.This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Oncaspar is and what it is used for

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 asparagine for themselves, while some cancer cells cannot. Oncaspar lowers asparagine level in blood cancer cells and stops the cancer cells growing.

Oncaspar is used to treat acute lymphoblastic leukaemia (ALL) in children from birth to 18 years and adults. 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.

2. What you need to know before you are given Oncaspar

Do not use Oncaspar:
- if you are allergic to pegaspargase or to any of the other ingredients of this medicine (listed in section 6).
- if you ever had pancreatitis.
- if you ever had severe bleeding following L-asparaginase therapy.
- if you ever had blood clots following L-asparaginase therapy.

Warnings and precautions
Talk to your doctor before you are given Oncaspar:
- 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.
- if you suffer from a bleeding disorder or had serious blood clots.
- if you get a fever. This medicine may make you more susceptible to infections.

- if you 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.
- if you suffer abdominal pain. Inflammation of the pancreas, that in some cases caused the death, can occur with Oncaspar treatment.

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

If you are the parent of a child being treated with Oncaspar, tell the doctor if any of the above conditions apply to your child.

During treatment with Oncaspar
When you receive Oncaspar you will be closely watched for an hour after the start of treatment for any signs of serious allergic reactions. Medical equipment to treat allergic reactions will be available nearby.

Additional monitoring tests
Blood and urine sugar levels, liver and pancreas function and other tests will be carried out regularly to monitor your health during and after treatment because this medicine can affect your blood and other organs.

Other medicines and Oncaspar
Tell your doctor if you are taking, have recently taken or might take any other medicines This is important as Oncaspar may increase the side effects of other medicines through its effect on the liver which plays an important role in removing medicines from the body. In addition, it is especially important to tell your doctor if you are also using any of the following medicines:
- 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, for example 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.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor 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 physician 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 doctor for advice on the best contraceptive method that you can use.

It is not known whether pegaspargase is excreted into the breast milk. As a precautionary measure, breast feeding should be discontinued during treatment with Oncaspar and should not be re-started after treatment with Oncaspar is discontinued.

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

Oncaspar contains sodium
This medicine contains less than 1 mmol sodium per dose, i.e. it is essentially ´sodium free´.

3. How Oncaspar is given

Your treatment with Oncaspar has been prescribed by a doctor experienced in medicines used to treat cancer. Your doctor will decide what dose of the medicine is needed and how often, based on your age and body surface area (BSA) which is calculated from your height and weight.

The medicine is a solution which is given by injection into a muscle or, if more suitable, into a vein.

If you are given too much Oncaspar
As your doctor will administer the medicine, it is very unlikely you will be given more than you need.

In the unlikely event of accidental overdose, you will be monitored carefully by medical staff and treated appropriately.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor **immediately** if you get:
- Severe bleeding or bruising;
- Inflammation or other disorders of the pancreas causing severe stomach pain which may spread to your back (pancreatitis);
- Serious allergic reactions with symptoms such as rash, itching, swelling, hives, shortness of breath, fast heart beat and drop in blood pressure;
- Violent shaking (seizures) and loss of consciousness;
- Headaches, high blood pressure and visual disturbances, which are symptoms of a condition called reversible posterior leukoencephalopathy syndrome;
- Loss of kidney function (e.g. change in urine output, swelling of feet and ankles) ;
- Very high fever;
- Problems with your liver (elevated transaminases, hyperbilirubinemia);
- Fast heart rate, breathing difficulty, and weakness;
- Increase in blood sugar levels (hyperglycemia).

Other side effects
Talk to your doctor if you get any of the following:

Very common side effects (may affect more than 1 in 10 people)
- Loss of appetite, feeling sick, being sick, stomach cramps, diarrhoea or weight loss;
- Pain or swelling at the injection site.

Common side effects (may affect up to 1 in 10 people)
- Agitation, confusion and drowsiness;
- Changes in the electroencephalogram (a trace of the electrical activity of your brain)
- Changes in the function of the pancreas;
- Fever and flu-like symptoms;

- Back, joint or abdominal pain.

Uncommon side effects (may affect up to 1 in 100 people)
- Swollen salivary glands (parotitis);
- Increased levels of uric acid and ammonia in the blood.

Rare side effects (may affect up to 1 in 1,000 people)
- Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome characterized by headache, confusion, seizures and visual loss which resolves after some time.

Very rare side effects (may affect up to 1 in 10,000 people)
- Mild twitching of the fingers;
- Fluid in the abdominal area (increase of size of abdominal area);
- Reduced thyroid function which may cause tiredness, weight gain and feeling cold.

Not known (frequency cannot be estimated from the available data)
- Impaired sensation, fatigue

Reporting of side effects
If you get any side effects you think might be related to your chemotherapy , talk to your doctor.This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Oncaspar

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

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

Do not use this medicine if you notice the solution is cloudy or a precipitate has formed.

6. Contents of the pack and other information

What Oncaspar contains
The active substance is pegaspargase. One ml of solution contains 750 units pegaspargase . One vial of 5 ml solution contains 3750 units of pegaspargase.

The other ingredients are: sodium dihydrogen phosphate monohydrate, disodium phosphate heptahydrate, sodium chloride, and water for injections (see section 2 “Oncaspar contains sodium”).

What Oncaspar looks like and contents of the pack
Oncaspar is a clear, colourless solution for injection contained in a glass vial. Each pack contains 1 vial.

Marketing Authorisation Holder

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A-1221 Vienna
Austria

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This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

In view of the unpredictability of adverse reactions, Oncaspar should be administered only by health care personnel experienced in the use of cancer chemotherapeutic medicinal products.

Particularly in patients with known hypersensitivity to the other forms of L-asparaginase, hypersensitivity reactions to Oncaspar can occur during the therapy, e.g. anaphylaxis. A routine precaution is to observe the patients for an hour with resuscitation equipment and other items required for the treatment of anaphylaxis in readiness (epinephrine, oxygen, intravenous steroids etc.).

Patients should be informed about possible hypersensitivity reactions to Oncaspar, including immediate anaphylaxis. Patients who receive Oncaspar are at increased risk of bleeding and thrombotic disorders. It should be explained to patients that Oncaspar should not be used at the same time as other medicines associated with an increased risk of bleeding (see “Other medicines and Oncaspar”).

This medicinal product can cause irritation on contact. The solution must therefore be handled and administered with particular care. Inhalation of the vapour and contact with the skin and mucosa, particularly that of the eyes, must be avoided. In the event of contact, the area should be irrigated with plenty of water for at least 15 minutes.

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

Further detailed information can be found in the SmPC.