EU Risk Management Plan 7.0

ONCASPAR (pegaspargase)

RMP version to be assessed as part of this application:

RMP Version number : 7.0

Data lock point for this RMP : 14 Jul 2022

Date of final sign off : 14 October 2024

Rationale for submitting an updated RMP:

PRAC recommendation (Procedure no.: EMEA/H/C/PSUSA/00010457/202207) to remove some safety concerns as these are considered to be sufficiently well characterised, the important identified and potential risks are adequately addressed in the product information and no additional pharmacovigilance activities are ongoing to further characterise any of these safety concerns.

Summary of significant changes in this RMP:

Removal of the safety concerns:

- Hypersensitivity removed as an Important Identified Risk,
- Pancreatitis removed as an Important Identified Risk,
- Haemorrhage removed as an Important Identified Risk,
- Thromboembolic events removed as an Important Identified Risk,
- Hepatotoxicity removed as an Important Identified Risk,
- Hyperammonaemia removed as an Important Identified Risk,
- Immunogenicity removed as Important Potential risk,
- Adverse events with a long latency removed as Missing Information.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

RMP version number : 6.0

Approved with procedure : EMEA/H/C/003789/IB/0051

Date of approval (opinion date) : 23 January 2023

Qualified Person for Pharmacovigilance (QPPV) name : **Dr Fairouz SMAIL, MD**

QPPV signature: QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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List of In-Text Tables

ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
ALL	Acute Lymphoblastic Leukaemia
ASNase	Asparaginase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the concentration-time curve
BSA	Body Surface Area
BW	Body Weight
C_{max}	Maximum observed concentration
CMC	Chemistry, Manufacturing and Controls
CNS	Central Nervous System
COMP	Committee For Orphan Medicinal Products
DFCI	Dana Farber Cancer Institute
EEA	European Economic Area
e.g.	For Example
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GLP	Good Laboratory Practice
i.e.	Id est
IM	Intramuscular
i.p.	Intraperitoneal
IV	Intravenous
IVIG	Intravenous Immunoglobulin
INN	International Non-Proprietary Name
IU	International Unit
KH	Kyowa-Hakko
MAH	Marketing Authorisation Holder
NA	Not Applicable
NCI	National Cancer Institute
NOEL	No Observed Effect Level
Oncaspar LIQ	Oncaspar Liquid Presentation
Oncaspar LYO	Oncaspar Lyophilised Presentation
PEG	Polyethylene Glycol
PD	Pharmacodynamic
PK	Pharmacokinetic

PL	Package Leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAS	Safety Analysis Set
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary Of Product Characteristics
SMQ	Standardised Meddra Query
U	Units
ULN	Upper Limit of Normal
US	United States of America

PART I: PRODUCT(S) OVERVIEW

Table 1. Product Overview

Active Substance (International Non-proprietary Name (INN) or generic name)	Pegaspargase
Pharmacotherapeutic group (Anatomical Therapeutic Chemical Classification System (ATC) Code)	L01XX24
Name of Marketing Authorisation Holder (MAH):	Les Laboratoires Servier
Medicinal products to which this Risk Management Plan (RMP) refers	ONCASPAR
Invented name in the European Economic Area (EEA):	ONCASPAR
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Oncaspar is an antineoplastic and immunomodulating agent.
	Summary of mode of action Its use is based on the metabolic defect in the L-asparagine synthesis of certain malignant cells, especially those of lymphatic leukaemia. Malignant cells depend on an exogenous source of L-asparagine to survive. Normal cells are less affected by its rapid withdrawal during treatment with the enzyme L-asparaginase.
	Important information about its composition Oncaspar contains a pegylated form of E. coli L-asparaginase called pegaspargase. The active substance pegaspargase is a covalent conjugate of Escherichia coli-derived L-asparaginase and monomethoxypolyethylene glycol.
Hyperlink to the Product Information	Module 1.3.1
Indication in the EEA	**Current:** 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.
Dosage in the EEA	**Current:** Oncaspar is usually administered as part of combination chemotherapy protocols with other antineoplastic agents. *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.
Pharmaceutical forms and strengths	**Current:** Oncaspar 750 U/ml solution for injection/infusion. One ml of solution contains 750 Units (U)** of pegaspargase*. One vial of 5 ml solution contains 3,750 U. Oncaspar 750 U/ml powder for solution for injection/infusion. Each vial contains 3,750 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
Is/will the product be subject to additional monitoring in the European Union (EU)?	No.

INTRODUCTION

Pegaspargase-containing medicinal products all using the brand name “Oncaspar” have a complex history. Single products differ in the manufacturer of enzyme moiety and the geographical regions in which they were or have been marketed.

Oncaspar in the United States

Oncaspar in its liquid presentation received the first marketing authorisation in the United States of America (US) in 1994 for the second-line treatment of acute lymphoblastic leukaemia (ALL) following the development of hypersensitivity to native L-asparaginase. This “original” Oncaspar referred to as “Oncaspar-Merck” was developed by Enzon Pharmaceuticals Inc. It featured enzyme manufactured by Merck which contains L-asparaginase linked to polyethylene glycol (PEG) via a succinimidyl succinate linker. Marketing authorisation of Oncaspar-Merck was based on quality, non-clinical and clinical data according to the standards of the day. The application filed in support of that marketing authorisation included eight clinical studies discussed in SIII – Clinical Trial Exposure and summarised in Table 31 (studies ASP-001, ASP-001C/003C, ASP-102, ASP-201A, ASP-203, ASP-302, ASP-304 and ASP-400).

In 2006, Oncaspar-Merck was authorized in the US for the first-line treatment of ALL. This new indication was based on two pivotal studies CCG-1962 and CCG-1991, and three supportive studies CCG-1961, DFCI-87-001 and DFCI-91-01 (for details see SIII – Clinical Trial Exposure and Table 31). All these studies have never been submitted to EU regulatory authorities.

In 2010, a supplement was authorized in the US in which the enzyme manufacturer was switched from Merck to Lonza in response to Merck discontinuing manufacture of

asparaginase. The Lonza enzyme Master Cell Bank is a descendant of the Master Cell Bank used by Merck. This change in enzyme manufacturer was supported by a quality-based comparability data showing that Oncaspar-Merck and Oncaspar-Lonza are analytically comparable. No new clinical data were generated in support of the change in active substance manufacturer and no changes in safety aspects of product information were proposed as a part of the regulatory approval process in the US. The resulting medicinal product referred to as "Oncaspar-Lonza" is currently marketed in the US. Oncaspar-Merck is no longer available on the market.

Oncaspar in the EU

Marketing authorisation for Oncaspar in its liquid presentation has been granted in Germany in 1994 and in Poland in 2008. Historically, this medicinal product has been known as "Oncaspar-Medac", named after the past marketing authorisation holder which was Medac GmbH. The manufacturer of the enzyme is KyowaHakko (KH). Oncaspar-Medac was also developed by Enzon Pharmaceuticals Inc. Marketing Authorisation Holder (MAH) of the national Polish license and of the national German license is Les Laboratoires Servier. Oncaspar-Medac is currently being marketed in Poland, and the product under the German license was provided to patients via the named patient access program, or through special access to other EU markets (where Oncaspar-Lonza is not launched); and International Markets. Medac GmbH is the MAH in Russia, Kazakhstan, Ukraine, Belarus, and Argentina where it markets the product in these markets. As of November 2017, Oncaspar-Medac is not currently being manufactured or released, however the different licenses are still active. Most of the countries that have received Oncaspar Medac will either launch Oncaspar Lonza (where a regulatory license is applicable) or continue to provide access to Oncaspar Lonza either via Name Patient Access or Named Patient Programme internationally.

The initial national marketing authorisation of Oncaspar-Medac in Germany and Poland was for the second-line treatment of ALL following the development of hypersensitivity to native L-asparaginase.

The ONCASPAR[1] liquid centralised procedure for both the first- and the second-line treatment of ALL was authorized on 14 January 2016.
The overview of various Oncaspar medicinal products is summarised in the Table 2.

Table 2. Overview of Oncaspar marketing authorisation history in the US and EU

Name of the medicinal product	Holder of EU licence	Enzyme manufacturer	Current marketing authorisation status in the US and EU
Oncaspar-Merck	Not applicable	Merck	Product has never been available in the EU and is no longer available in the US.
Oncaspar	Les Laboratoires Servier	Lonza	Authorized in EU via centralised procedure. Currently authorised in the US for the first-line treatment of ALL.
Pegaspargase	Les Laboratoires	Kyowa-Hakko	Medicinal product authorised through national procedure in Germany for second-

[1]The term ONCASPAR in capital letters will be used throughout the document to specify the medicinal product currently authorized Oncaspar liquid presentation (LIQ) or involved in the extension application Oncaspar lyophilised presentation (LYO). Term "Oncaspar" in small letters will be used in case of the previously authorised pegaspargase-containing medicinal products. The further identification of the type of Oncaspar medicinal product will be provided by the name of manufacturer (i.e., Merck, Lonza) or by other clause (i.e., Medac) added to the Oncaspar denomination, whenever applicable or required by the coherence.

	Servier		line treatment of ALL. Never available in the US.
Pegaspargase	Les Laboratoires Servier	Kyowa-Hakko	Medicinal product authorised through national procedure in Poland for second-line treatment of ALL. Never available in the US.

A new pharmaceutical form, (ONCASPAR lyophilised powder) was authorized on 8 December 2017 in EU. The main purpose for the development of the lyophilised Oncaspar presentation was to create a product that has improved stability (id dest [i.e.] suitable shelf-life for up to 36 months) when compared to the liquid Oncaspar presentation ensuring continuous drug product availability. Additional comprehensive Chemistry, manufacturing and controls (CMC) and non-clinical studies were performed to support this extension to demonstrate that the lyophilisation process has no impact on the drug product. Non-clinical studies included local tolerability (nociception), haemocompatibility and pharmacokinetics. There were no additional clinical studies performed studying the lyophilised presentation.

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

Table 3. Epidemiology for Acute Lymphoblastic Leukaemia (ALL)

Incidence	ALL is the most commonly diagnosed cancer in children and represents 25% of cancer diagnoses among children younger than 15 years of age. [2,3] Nonetheless in absolute terms, ALL is a very rare disease, even in children. Its incidence has a bimodal distribution with a sharp peak among children aged 2 to 3 years (>90 cases per million per year), with rates decreasing to 30 cases per million for ages 8 to 10 years. [4] A second steady increase in the incidence of ALL begins at approximately 50 years of age, with a peak incidence of about 2 cases per 100,000. [5] Overall estimated incidence in the EU is 1.28 cases per 100,000 persons, corresponding to a total of approximately 5,600 new cases per year. [6]
Prevalence	The prevalence is estimated at 7 / 100,000 (EMA/COMP/456792/2008 Rev.3), with range 1-9 / 100,000. [1]
Demographics of the population in the authorised indication	ALL is the most common type of leukaemia in young children but the disease also affects adults, especially those aged 65 and older. ALL is more prevalent in males.
Main existing treatment options	The main types of ALL treatment are chemotherapy, targeted therapy and stem cell transplantation. [7] Surgery or radiation therapy are used under special circumstances. [7] Chemotherapeutics commonly used in the treatment of ALL are vincristine, doxorubicin, cytarabine, L-asparaginase, pegaspargase, etoposide or 6-mercaptopurine. Targeted therapy in patients harbouring Philadelphia chromosome (abnormal chromosome formed by a material between chromosomes 9 and 22) includes use of biologics known as tyrosine kinase inhibitors (e.g., imatinib, dasatinib, nilotinib, bosutinib and ponatinib). The treatment of ALL usually takes place in 3 phases [7] • Induction (or remission induction), • Consolidation (intensification),

	• Maintenance. The main goal of induction phase is a remission. Different chemotherapeutics in combination with other drugs are used during this phase, including vincristine, glucocorticoids (dexamethasone or prednisone), doxorubicin or a similar anthracycline drug. Based on the patient's prognostic factors, cyclophosphamide, L-asparginase, etoposide, methotrexate and cytarabine or biological agent imatinib are used in the induction phase. [7] The wide-spreading of leukaemia cells into the central nervous system may be prevented or treated by intrathecal chemotherapy (methotrexate or cytarabine are used for these purposes) or by radiation therapy. [7] Consolidation phase include the same drug regimens as induction phase. In some patients, allogenic or autologous stem cell transplantation may take place at this time. [7] Maintenance phase include administration of methotrexate and 6-mercaptopurine, in some cases combined with vincristine or prednisone. This phase is believed to may be omitted in case of adult T-cell ALL or Burkitt's lymphoma. [7]
Natural history of the indicated condition in the population, including mortality and morbidity	ALL can lead to the following: anaemia, thrombocytopenia, neutropenia, infection, bone pain and arthralgia, extra-medullary deposition can result in lymphadenopathy, hepatosplenomegaly, frequent involvement of the Central Nervous System (CNS); testicular infiltration; and hyperuricaemia with renal failure. ALL may be fatal. Paediatric ALL: cure rate 85%. [10] Adults: 5-year survival is approx. 40%. [11] Cure/survival data used as surrogate, since mortality rates are not readily available.
Important co-morbidities	Previous epidemiological studies have shown significant correlations in incidence between ALL and Type 1 diabetes mellitus at both the international and regional level, with potential but unproven links with an infectious aetiology. [8,9] As a result of the ALL and chemotherapy treatments, patients may experience, mostly opportunistic, infections of various kinds (bacteraemia, fungaemia).

PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Pegaspargase is a covalently modified form of enzyme L-asparaginase. Pegaspargase has a polyethylene glycol (PEG) molecule attached to the L-asparaginase molecule derived from Escherichia coli, in the process known as PEGylation.

PEGylation in general increases retention of drug in the circulation by protecting the molecule against proteolytic degradation, by decreasing the rate of renal clearance and by reducing the generation of neutralising antibodies. [12]

The medicinal product ONCASPAR (using native enzyme produced by Lonza) liquid presentation does not have an original non-clinical development programme.

All non-clinical studies were carried out with PEG-L-asparaginase manufactured by ENZON using native enzyme produced by Merck, on which national authorisation of ONCASPAR as second line therapy in Germany (1994) and Poland (2008), as well as in the USA (1994) were based. The only exception is for the pharmacokinetic study carried out in Rhesus monkeys, in which PEG-L-asparaginase was manufactured by ENZON using native enzyme produced by Kyowa-Hakko.

Most of the pharmacodynamic, pharmacokinetic and toxicology studies were conducted during 1980s and early 1990s. Two more recent non-GLP pharmacokinetics and pharmacodynamic studies in rats (#04-2861 performed at Huntingdon Life Science in 2005) and dogs (#04-3082 performed at Huntingdon Life Science in 2006), and two Good Laboratory

Practice (GLP) toxicology/toxicokinetic studies (rats #824-015 performed at MPI Research, Michigan in 2007) and dogs (#824-016 performed at MPI Research, Michigan in 2007) are available.

Additional *in vitro* and *in vivo* non-clinical studies were conducted in mice and dogs to demonstrate comparability. The objectives were to assess the nociceptive response to the addition of 5% sucrose in the formulation, determine the haemocompatibility of the liquid and lyophilised presentation in dog and human blood, and to compare the pharmacokinetics, of the ONCASPAR presentations in dogs with additional assessments of the pharmacodynamic and anti-drug antibody profiles.
The key non-clinical findings with the relevance to human use (if applicable) are summarised in Table 4 for ONCASPAR LIQ and Table 5 for ONCASPAR LYO below.

Table 4. Overview of Non-Clinical Studies (ONCASPAR LIQ)

Key safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Key issues identified from acute or repeat-dose toxicity studies Only very high doses of pegaspargase given to mice intraperitoneally as a single dose (25,000 – 100,000 IU/kg body weight) caused the death of 14% of all treated mice. Mild hepatotoxicity was observed with the same dosages. Side effects included loss of body weight, piloerection and reduced activity. A decrease in weight of spleen (starting from the dose of 10,000 IU/kg) occurred. Pegaspargase was well tolerated both in rats and dogs when administered intravenously in single dose up to 500 IU/kg. The appearance and behaviour of animals in subacute and subchronic studies were not affected by the treatment. Only very large doses in the acute studies resulted in inactivity, hunched posture, piloerection, low grade hepatic toxicity, and death of a few of the animals. The LD50 however, could not be established. Histological evaluations revealed some low-grade hepatic toxicities in mice treated with very high doses of the test article. A four-week study in rats with a dosage of 400 IU/kg/day intraperitoneally (i.p.) resulted in a fall in food intake and body weight compared to the control group. A three-month study of pegaspargase at doses up to 500 IU/kg i.p. or intramuscularly (IM) in mice resulted in slight hepatocellular changes only at the highest i.p. dose. A temporary suppression in body weight gains and a temporary reduction in total leukocyte counts were observed in dogs which were treated intravenously or intramuscularly IM with 1200 IU/kg weekly for 2 weeks. Increased Serum Glutamic Pyruvic Transaminase (SGPT) activity also occurred in one out of four dogs.	The toxicity effects observed occurred at high doses and were consistent with those known to be associated with native L-asparaginase. The described effects were considered to be unlikely of relevance to humans. Depressed splenic weights could indicate possible immunosuppressive properties of pegaspargase and that the main toxicity target organ is the spleen. As a consequence, in clinical practice, the patients might be at increased risk for infection. The hepatotoxicity represents safety concern of pegaspargase.
Reproductive/developmental toxicity No preclinical studies of reproductive toxicity were conducted with pegaspargase. However, 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 IU/kg IV. In rabbits doses of 50 or 100 IU/kg IV 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.	There is no experience with use of pegaspargase during pregnancy and lactation in humans. The described embryotoxic effects of L-asparaginase were considered to be of relevance to humans. L-asparaginase is considered as an agent with potential teratogenic effects. Based on the similarities of pegaspargase with L-asparaginase,

L-asparaginase had teratogenic effects on cultured rat embryos. Embryos exhibited growth and development retardation together with malformations of the brain, eyes, face, and trunk. Neural ectoderm alterations were observed upon histological examination together with strong vascular dilatations at the cephalic level. [13] Several investigations have been conducted on the teratogenic effect of L-asparaginase in vivo. Female rats were treated from day 6 to 15 of gestation, given 300, 1,000, 3,000 and 10,000 IU/kg, by intravenous route, 300 was the no observed effect level (NOEL). Embryotoxic and teratogenic were clearly dose related. Malformations consisted in microphthalmia, malformation in vertebral column, sternal cleft and exenteria. [14] A species difference in the embryotoxic and teratogenic effect of L-asparaginase was described by Adamson et al. [15] Viable foetuses with congenital malformations were observed after treatment of pregnant New Zealand rabbits with 50 or 100 IU/kg intravenous on days 8 and 9 of gestation. It was also proven that L-asparaginase crosses the placenta. [15]	potential teratogenicity is considered relevant to pegaspargase therapy as well.;
Genotoxicity Pegaspargase was not mutagenic in the Ames test performed using Salmonella typhimurium strains.	Pegaspargase is not predicted to be mutagenic in humans as a result of the negative Ames test.

Table 5. Overview of Non-Clinical Studies (ONCASPAR LYO)

Key safety findings (from non-clinical studies)	Relevance to human usage
Pharmacokinetics/Pharmacodynamics	
An IV single-dose and 4 week repeat-dose PK/PD study in dogs was conducted to compare the pharmacokinetic (PK), pharmacodynamic (PD), and anti-drug antibody development of liquid and lyophilised Oncaspar. Doses were administered IV at a dose level of 500 IU/kg, via slow bolus injection, to Beagle dogs, once (Day 1) or on Days 1, 15, 22, 29 and 36. The two Oncaspar presentations were shown to be equivalent with respect to C_{max} and AUC_{0-552}. PK modelling and simulation suggests the lyophilised presentation to result in highly similar exposures (C_{max} and AUC) as the liquid Oncaspar observed in ALL patients. Additionally, there were no overt group differences in the pharmacodynamics and immunogenicity related readouts in this study.	Oncaspar LYO is expected to have similar PK/PD profiles as the liquid presentation when used in humans. There are no signs for changes in the immunogenicity profile of Oncaspar LYO when compared to Oncaspar LIQ.
Other toxicity-related information or data	
Sucrose toxicity A study in mice testing the nociceptive effects of 5% sucrose addition to Oncaspar (as an excipient in the lyophilised presentation), showed that Oncaspar liquid with or without 5% sucrose did not produce significant nociceptive responses or paw swelling in mice. In a toxicological risk assessment, the threshold for renal injury from exposure to sucrose contained in Intravenous Immunoglobulin (IVIG) products was determined at 1 g/kg BW [26] and corresponding to a >160 fold safety margin for the treatment with reconstituted Oncaspar lyophilised presentation.	No safety risk from sucrose exposure is anticipated for patients receiving lyophilised Oncaspar intravenously or intramuscularly at the indicated doses.
Haemotoxicity In vitro, there were no observed haemocompatibility effects from the liquid formulation and the lyophilised formulation of Oncaspar on human whole blood at the final concentration of 750 IU/mL.	No haemocompatability risk is anticipated for patients receiving lyophilised Oncaspar.

PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

Brief overview of development

The clinical data presented are based on the clinical development programme conducted for the original marketing authorisation of Oncaspar liquid presentation as second-line treatment of ALL in Germany and Poland. In addition, the clinical data used as a support of the first-line use of Oncaspar in the US are also included.
There were no additional clinical studies performed for the lyophilised presentation of ONCASPAR.

The original clinical development programme took place in late 1980's in adult and paediatric patients. In the early phase, patients with known hypersensitivity to native L-asparaginase were excluded from study population. Subsequently, hypersensitive patients were treated on a compassionate use basis under a compassionate use programme (study ASP-001C/003C). The development was subsequently focused on ALL patients with known hypersensitivity to native L-asparaginase. Clinical data are presented in both patient populations –hypersensitive and non-hypersensitive.
The clinical studies supporting the current marketing authorisation of Oncaspar liquid presentation may be divided into four groups:

- Three Phase I and six Phase II/III clinical trials which supported the marketing authorisation of Oncaspar-Merck included study subjects with various haematological malignancies. The overview of conducted clinical trials is presented in Table 6.

Table 6. Overview of the original clinical development programme for Oncaspar-Merck supporting the second-line indication – ALL patient population

Study reference/Study design	Objectives	Patient population
Phase I study		
ASP-001 Open-label, ascending multiple dose study	1. Pharmacokinetics 2. Safety and tolerance 3. Clinical efficacy	Adult patients in relapse with malignant haematological disorder
ASP-102 Open-label, uncontrolled study	[a] Methotrexate toxicity "rescue therapy" by pegaspargase 4. Recommended Phase II dose 5. Safety and tolerance	Adult patients with solid tumours and lymphomas
ASP-203 Open-label, uncontrolled study	[b] Safety and tolerance 6. Clinical efficacy	Relapsed adult patients with non-Hodgkin's lymphoma
Phase II/III studies		
ASP-001C/ASP-003C Open-label, uncontrolled study	[c] Clinical efficacy 7. Safety and tolerance	a. Relapsed ALL b. Compassionate use c. Multi-regimens for induction/maintenance d. Hypersensitive e. Non-hypersensitive
ASP-201A Open-label, uncontrolled study	[d] Clinical efficacy 8. Safety and tolerance	Relapsed ALL paediatric patients a. Hypersensitive

		b. Non-hypersensitive
ASP-301 [16] A comparative study	The pharmacokinetics of different asparaginase preparations was studied in a subset of the DFCI-87-001 patients. The data from this sub-study are recorded as study ASP-301. [e] Pharmacokinetics 9. L-asparagine depletion 10. Cell kill in vivo 11. Safety and tolerance	Newly-diagnosed ALL (comparative trial of pegaspargase versus native E. coli asparaginase and native Erwinia chrysanthemi asparaginase)
ASP-302 Open-label, uncontrolled study	[f] Pharmacokinetics 12. Safety and tolerance	Relapsed ALL paediatric patients a. Hypersensitive b. Non-hypersensitive
ASP-304 Randomised, open-label comparative study in non-hypersensitive subjects Open-label, directly assigned to Oncaspar in hypersensitive subjects	[g] Clinical efficacy 13. Safety and tolerance 14. Antibody titres 15. Pharmacokinetics	Relapsed ALL paediatric patients a. Hypersensitive b. Non-hypersensitive (Comparative trial of pegaspargase versus native E. coli L-asparaginase)
ASP-400 Open-label, uncontrolled study	[h] Clinical efficacy 16. Safety and tolerance	Relapsed ALL patients

- The first-line ALL application in the US was based on two pivotal Phase II/ III and three supportive Phase III clinical trials performed with Oncaspar-Merck as summarised in Table 7.

Table 7. Overview of the clinical development programme conducted with Oncaspar-Merck supporting the first-line indication

Study reference/Study design	Objectives	Patient population
CCG-1962 [17] A randomised, prospective, open-label, comparative study	To determine whether the incidence of high-titre anti-asparaginase antibodies is decreased by at least 50% by use of pegaspargase in place of native enzyme during Delayed Intensification #1 (primary endpoint) To evaluate safety, efficacy, and pharmacokinetics of a single intramuscular dose of pegaspargase instead of multiple intramuscular doses of native E. coli L-asparaginase in each of 3 phases of therapy	Standard-risk, newly diagnosed ALL paediatric patients
CCG-1991 A multicentre, randomised study	Study CCG-1991 is also included within this group, even though Oncaspar was a background therapy rather than an investigational product.	Paediatric ALL patients
DFCI-87-001[18] A multicentre, randomised, prospective study	To investigate the pharmacokinetics, pharmacodynamics and immunogenicity of native E. coli L-asparaginase (Elspar), native Erwinia L-asparaginase (Erwinase) and Oncaspar	Newly diagnosed paediatric ALL patients

DFCI-91-01[19] A multicentre, randomised, prospective study	To improve the outcome of children with newly diagnosed ALL while minimising toxicity	Newly diagnosed paediatric ALL patients
CCG-1961[3,19,20,21] A randomised, prospective study	To investigate the anti-asparaginase antibody and L-asparaginase enzymatic activity in the sera of high-risk ALL patients	Patients with high-risk ALL

- Additional proprietary study AALL07P4 included in the clinical development evaluated pegaspargase with a succinyl carbamate linker between PEG molecule and L-asparaginase (calaspargase pegol) instead of succinyl succinate linker present in the pegaspargase molecule used in all Oncaspar products (i.e., Oncaspar-Merck, Oncaspar-Medac, Oncaspar-Lonza). Oncaspar-Merck was used as a comparator in an active control arm.

Study AALL07P4 is an open-label, multicentre, randomised, active-controlled study in mostly paediatric patients (patients up to age 31 were eligible, few adults up to age 26 years were enrolled) with newly diagnosed high-risk B-precursor ALL.

- Since the marketing authorisation approval in Germany in 1994, post-authorisation non-proprietary clinical studies with Oncaspar (Kyowa-Hakko as enzyme source) have been conducted. These mostly academic, investigator-initiated studies include AIEOP-BFM-ALL 2009, CO-ALL-08-09, GMALL 07/2003, HOVON 100 ALL / EORTC 06083, IntReALL SR 2010, ALL-MB 2008, UK ALL 14 and UK ALL 2011. Studies, CO-ALL-08-09, HOVON 100 ALL / EORTC 06083, IntReALL SR 2010, AIEOP-BFM ALL-2009, UK ALL 2011 and UK ALL 2014 used Oncaspar as a backbone therapy while studies ALL-MB 2008, GMALL 07/2003, used Oncaspar as investigational medicinal product.

There are very limited safety data arising from these ALL clinical studies available to the Applicant. Such information as is available is consistent with the expected safety profile of ONCASPAR and other L-asparaginase preparations.

Detailed information about all clinical studies included in the ONCASPAR clinical development programme is provided in Table 31.

SIII.1. Duration of Exposure

Table 8. Patient exposure to investigational medicinal products by indication (totals)

Total population[a]		
Indication	**Persons**	**Person time**
ALL	5,231	Not Applicable (NA)
Non-ALL	73	NA
Total	**5,304**	**NA**

[a] Includes study subjects of studies ASP-001, ASP-201A, ASP-301, ASP-302, ASP-304, ASP-400, ASP-102, ASP-203, CCG-1961, CCG-1962, DFCI-87-001, DFCI-91-01, CCG-1991 and AALL07P

Table 9. Patient exposure to Oncaspar by hypersensitivity to L asparaginase status by study (by ALL indication)

Study	**Persons**	
	Hypersensitive	**Non-hypersensitive**
ALL		
ASP-001	1	7
ASP-001C/003C	29	5
ASP-102	0	0
ASP-201A	7	30
ASP-203	0	0
ASP-302	4	17
ASP-304	40	19
ASP-400	13	29
CCG-1961	142	138
CCG-1962	0	57
DFCI-87-001	0	84
DFCI-91-01	0	377
Sub-total	**236**	**763**
Total	**999**	
Non-ALL		
ASP-001	0	29
ASP-001C/003C	1	6
ASP-102	NA	NA
ASP-201A	2	3
ASP-203	NA	NA
ASP-302	0	0
ASP-304	0	0
ASP-400	0	2
CCG-1961	0	0
CCG-1962	0	0
DFCI-87-001	0	0
DFCI-91-01	0	0
Sub-total	**3**	**40**
Total	**43**	

SIII.2. Age Group and Gender

Table 10. Patient exposure by age groups (totals)

Total population[a]		
	Persons	**Person time**
Adults	85	NA
Paediatric patients	5,178	NA
Unspecified	41	NA
Total	**5,304**	**NA**

[a] Includes study subjects of studies ASP-001, ASP-201A, ASP-301, ASP-302, ASP-304, ASP-400, ASP-102, ASP-203, CCG-1961, CCG-1962, DFCI-87-001, DFCI-91-01, CCG-1991 and AALL07P

Table 11. Exposure by age group and gender (totals)

Total population[a]					
Age group	**Persons**	**Persons**		**Person time**	
		Male	**Female**	**Male**	**Female**
Adults (> 18 years)	85	36	49	NA	NA
Adolescents (12-17 years)	49	33	16	NA	NA
Children (2-11 years)	152	66	38	NA	NA
Infants/Toddlers (< 2 years)	18	3	4	NA	NA
2-18 years	44	NA	NA	NA	NA
0-11months	15	NA	NA	NA	NA
12-23 months	56	NA	NA	NA	NA
24 months-9 years	504	NA	NA	NA	NA
9-18 years	171	NA	NA	NA	NA
1-9 years	229	NA	NA	NA	NA
10-15 years	324	NA	NA	NA	NA
>16 years	76	NA	NA	NA	NA
Unspecified age group	-	2,491	2,006	NA	NA
Sub-total	**-**	**2,629**	**2,113**	**NA**	**NA**
Unspecified gender and age group	3,581	562		NA	
Total	**5,304**	**5,304**		**NA**	

[a] Includes study subjects of studies ASP-001, ASP-201A, ASP-302, ASP-304, ASP-400, ASP-102, ASP-203, CCG-1961, CCG-1962, DFCI-87-001, DFCI-91-01, CCG-1991 and AALL07P

Table 12. Age/sex stratification of patients >18 years

Study	Total	Sex (M/F)	Stratified						
			19-20	21-30	31-40	41-50	51-60	61-70	>70
ASP001	35	16M/19F	1	7	3	6	8	8	2
ASP302	2	1M/1F	1	-	1	-	-	-	-
ASP102	10	2M/8F	-	-	-	-	7	3	-
ASP001-003	5	4M/1F	-	1	-	-	2	2	-
ASP201A	10	6M/4F	2	5	2	1	-	-	-
ASP203	21	9M/12F	-	-	1	2	9	4	5
ALL07P4	3	3F	2	1	-	-	-	-	-
Total	**86**	**38M/48F**	**6**	**13**	**6**	**8**	**25**	**17**	**7**

SIII.3. Dose

Table 13. Exposure by dose administered (totals)

Total population[a]		
Dose (International Unit (IU)/m^2)	**Persons**	**Person time**
250	1	NA
500	1	NA
1,000	21	NA
2,000	116	NA
2,500	5,103	NA
4,000	8	NA
8,000	13	NA
Unspecified[b]	41	NA
Total	**5,304**	**NA**

[a] Includes study subjects of studies ASP-001, ASP-201A, ASP-301, ASP-302, ASP-304, ASP-400, ASP-102, ASP-203, CCG-1961, CCG-1962, DFCI-87-001, DFCI-91-01, CCG-1991 and AALL07P

[b] Dose administered in study ASP-001C/003C ranged from 2,000 to 2,500 IU/m2

Table 14.Exposure by number of doses, treatment duration and follow-up time

Study	Test product(s); dosage regimen: route of administration	Number of subjects	Duration of treatment
ASP-001	Oncaspar 500-8,000 IU/m^2 Intravenous (IV)	37	2-4 courses of 2 weeks
ASP-001C/ASP-003C	Oncaspar 2,000 (2,500 IU/m^2 dose allowed only to one investigator) IM	41	2-weekly during induction (total doses: 64/range 1-7) 1-weekly during maintenance as long as patients profited (total doses: 121/range 1-16)

ASP-102	Methotrexate 40-80 mg/m^2 Oncaspar 1,000-2,000 IU/m^2 IM	11	Repeated every 2 weeks until progressive disease or toxicity appeared (1-17 courses)
ASP-201A	Oncaspar 2,000 IU/m^2 IM Oncaspar 10,000 IU/m^2 (3 patients only) IV	42	IM: 2-weekly doses up to 33 doses per patient IV: 1 or 2 times over a 2 hour period for the highest dose (3 patients only)
ASP-203	Oncaspar 2,000 IU/m^2 IM	21	Every 2 weeks for 2 to 6 treatment courses
ASP-302	Oncaspar 2,500 IU/m^2 IM	21	Every 2 weeks during re-induction and remission therapy (52 weeks)
ASP-304	Oncaspar 2,500 IU/m^2 Elspar®; 10,000 IU/m^2 IM	76	Oncaspar: 2 doses (days 1 and 15) Elspar®: 3 times a week for 26 days (12 doses)
ASP-400	Oncaspar 2,000 IU/m^2 IV	44	Phase I (induction treatment lasting 15 days): 1 dose on day 12; Phase II (consolidation treatment starting at week 3 and lasting 7 days): 1 dose on day 5; Phase III (consolidation treatment C2 starting at week 6 and lasting 7 days): 1 dose on day 5
CCG-1961	Oncaspar; 2,500 IU/m^2 Native *E coli* ASNase 6,000 IU/m^2 Erwinia-ASNase 6,000 IU/ m^2 (patients allergic to *E.coli* or PEG preparations) IM	2077 (Panosyan) 2078 (Seibel)	Overall 30 weeks Oncaspar: Consolidation:2 doses (day14,42) IM 1&2: 2 or 4 doses (day 1,21) Delayed intensification (DI) 1&2: 2 or 4 doses (day 3,42) ASNase: Induction: 3 doses (day 3,5,7) Ind. Continuation: 9 doses (day 9,11,13,15,17,19) DI 1&2: 6 or 12 doses (day 3,5,7,10,12,14)
CCG-1962	Oncaspar 2,500 IU/m^2 Native *E coli* asparaginase 6,000 IU/m^2 IM	118	Overall 24 weeks: Induction: PEG-ASNase 1 dose (day 3)/ Native ASNase 9 doses (day 3,5,8,10,12,15,17,19,22) DI 1&2: PEG-ASNase 1 dose x 2 (day 3)/ Native ASNase 6 doses x 2 (day 3,5,8,10,12,15)

CCG-1991	Oncaspar 2,500 IU/m^2 IM	2957	Overall 9 months Induction: 1 dose (between day 3 and 5) Consolidation: 2 doses only in augmented regimen (day 14,42) IM1: 2 doses only in augmented regimen (day 1,21) DI1: 1 dose (day 3); 2 doses in augmented regimen (day 3,42) IM2: 2 doses only in augmented regimen ((day 1,21) DI2: 1 dose (day 3); 2 doses in augmented regimen (day 3,42)
DFCI-87-001	Oncaspar 2,500 IU/m^2 Elspar® 25,000 IU/m^2 Erwinase® 25,000 IU/m^2 IM	344	Single dose (day 0 of a 5-day investigational window)
DFCI-91-01	Oncaspar 2,500 IU/m^2 *E coli* L-asparaginase; 25,000 IU/m^2 IM	377	Oncaspar: every 2 weeks x 15 doses in Intensification phase (30 weeks) *E coli* L-asparaginase: weekly x 30 doses
AALL07P4	Oncaspar 2,500 IU/m^2 Calaspargase pegol 2,100 and 2,500 IU/m^2 IV	166	Overall 31 weeks Induction (35 days): 1 dose (day 4) Extended Induction (2 weeks): 1 dose (day 4) Consolidation (8 weeks): 2 doses (day 15,43) IM 1&2 (8 weeks): 2x2 doses (day 2,22) DI 1&2 (8 weeks): 2x2 doses (day 4,43)

SIII.4. Route of Administration

Table 15. Exposure by route of administration (totals)

Total population[a]		
Route of administration	**Persons**	**Person time**
Intramuscular	5,127	NA
Intravenous	135	NA
Intravenous/ intramuscular	42	
Total	**5,304**	**NA**

[a] Includes study subjects of studies ASP-001, ASP-201A, ASP-301, ASP-302, ASP-304, ASP-400, ASP-102, ASP-203, CCG-1961, CCG-1962, DFCI-87-001, DFCI-91-01, CCG-1991 and AALL07P

SIII.5. Clinical Trial Exposure from DFCI 11-001 and AALL07P4

As part of the EU Type II Variation, data from 2 independent, randomised clinical studies, DFCI-11-01 and AALL07P4, where Oncaspar® served as an active control is included. One of these studies is AALL07P4, already listed above, with no final analyses available, in contrast to previously provided interim data. No integration of data from these two studies were performed due to important differences, including target subject populations, difference in schedule of administration, backbone multi-agent chemotherapy regimens, and duration of follow-up.

- Study DFCI-11-001 is a phase 2, open-label, randomised multicentre study to determine the safety and feasibility of administering a new PEG-L-asparaginase product, compared with Oncaspar®, in children and adolescents (aged 365 days to <22 years) with newly diagnosed standard to very high risk acute lymphoblastic leukaemia (ALL) (B-cell and T-cell) and lymphoblastic lymphoma treated with Dana Farber Cancer Institute (DFCI) ALL Consortium therapeutic backbone.
- Study AALL07P4 is a limited institution prospective, open-label, randomised, pilot study in newly diagnosed patients with National Cancer Institute (NCI) high risk B-precursor ALL aged >1 year to <31 years.

Table 16. Duration of Exposure During Clinical Studies [Safety Analysis Set (SAS)]

Duration of exposure [a] (months)	DFCI 11-001[b] Oncaspar® 2500 IU/m²	AALL07P4[c] Oncaspar® 2500 IU/m²
N	119	52
Mean (SD)	6.77 (3.017)	4.76 (3.255)
Median	8.05	6.52
Min, Max	0.0, 11.4	0.0, 11.8

Source: CSR DFCI 11-001 Table 10; CSR AALL07P4 Table 7

[a] Duration of exposure (months) = (last date of study drug - first date of study drug+1)/ 30.4375.

[b] In Study DFCI 11-001 the maximum planned duration of treatment with the Study Drugs (investigational product or Oncaspar®) extended from Induction through Consolidation II

[c] In study AALL07P4, the maximum planned duration of treatment with the Study Drugs (investigational product or Oncaspar®) extended from Induction through Delayed Intensification II.

Table 17.Cumulative ONCASPAR Dose Used in Clinical Studies (SAS)

	DFCI 11-001[a] Oncaspar® 2500 IU/m²	AALL07P4[b] Oncaspar® 2500 IU/m²
Cumulative Dose (IU/m²)		
N	119	52
Mean (SD)	27604.0 (18184.57)	14469.71 (12940.729)
Median	26225.0	10730.00

Min, Max	1680, 87000	566.6, 47450.0
Total Number of Doses		
N	119	52
Mean (SD)	12.3 (5.94)	4.6 (2.93)
Median	16.0	4.5
Min, Max	1, 17	1, 12

17. Source: CSR DFCI 11-001 Table 11; CSR AALL07P4 Table 8
18. In Study DFCI 11-001, the total target number of doses administered for investigational product is 11 and for Oncaspar® is 16. One subject had 106.25% target dose due to being administered a total of 17 doses.
19. For subjects on investigational product 2100 IU/m2 later switched to Oncaspar®, their exposure to Oncaspar® is not summarised in the investigational product 2100 IU/m2 group. If a subject took a wrong treatment, the wrong treatment isn't counted.

Table 18. Demographic Profile of Subjects in Clinical Trials (Full Analysis Set)

Treatment arms	**DFCI 11-001 Oncaspar® 2500 IU/m²**	**AALL07P4 Oncaspar® 2500 IU/m²**
N subjects	119	54
Gender Male [n (%)] Female [n (%)]	 71 (59.7) 48 (40.3)	 31 (57.4) 23 (42.6)
Age (years) Median (min, max)	 4.0 (1,18)	 11.0 (1,23)
Age Groups (years) [n (%)] < 10 years ≥ 10 years 10 to < 16 years ≥ 16 years	 89 (74.8) 30 (25.2) 23 (19.3) 7 (5.9)	 18 (33.3) 36 (66.7) 28 (51.9) 8 (14.8)
Race, n (%)		
Asian	4 (3.4)	1 (1.9)
Black or African American	2 (1.7)	6 (11.1)
Native Hawaiian or Other Pacific Islander	-	0
White	89 (74.8)	43 (79.6)
Unknown	-	4 (7.4)
Other	18 (15.1)	

Source: CSR DFCI 11-001 Table 4, CSR AALL07P4 Table 3

PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 19. Exclusion Criteria

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
Hypersensitivity to the active substance	Pegaspargase has much lower potential to cause hypersensitivity reactions than native L-asparaginase and patients hypersensitive to L-asparaginase may be treated with pegaspargase. The hypersensitivity reactions to pegaspargase administration are easily explained as a normal reaction of the human body to a foreign protein. Various allergic reactions are most common at the beginning or during re-induction of the therapy. The potential occurrence increases with the number of administered doses of pegaspargase. As allergic reactions are "common" Adverse Drug Reactions (ADRs) reported from the clinical and post-marketing experience with pegaspargase, it may have an impact on the target population of patients requiring ALL treatment who therefore cannot be treated by ONCASPAR.	No	Hypersensitivity is a known risk with ONCASPAR.
Pancreatitis or history of pancreatitis	ONCASPAR and native L-asparaginase are known to cause pancreatitis. Subjects with pancreatitis or history of pancreatitis must not use ONCASPAR.	No	Pancreatitis is a known risk with ONCASPAR.
History of coagulopathy	The use of ONCASPAR can lead to fluctuating coagulation factors. This can promote the tendency to bleeding and/or thrombosis. Therefore, as a precautionary measure, patients with a history of coagulopathy were excluded from clinical studies with ONCASPAR.	No	Coagulopathy is a known risk with ONCASPAR.
Pregnancy and lactation	Pre-clinical data showed teratogenic effects of native L-asparaginase, suggesting the presence of similar effects for pegaspargase as well. It is not known whether pegaspargase is excreted into breast milk and the potential risk to breast-fed newborns/infants cannot be excluded	No	Teratogenicity has been seen in pre-clinical data with native L-asparaginase and it is unknown whether pegaspargase is excreted into breast milk. As a precautionary measure, ONCASPAR should not be used by pregnant or lactating women unless the clinical conditions of the woman require treatment with ONCASPAR.

SIV.2. Limitations of to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, those due to cumulative effects, those caused by prolonged exposure, or those which are associated with the IV route of administration.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 20. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Elderly patients	There were no confirmed cases of patients with severe hepatic impairment entering any of the clinical trials. There were 6 patients included in CCG-1962 who had hepatomegaly at baseline (4 in the Oncaspar group; 2 in the native enzyme group). However, hepatomegaly does not necessarily result in severe liver impairment; the liver function of these patients is therefore unknown. Most patients with severe hepatic impairment will be elderly and have co-morbidities. This is also a population in which ALL management is often conservative (i.e. no attempt at cure is made) and so asparaginase is frequently not used. Oncaspar is contraindicated in patients with known severe hepatic impairment (bilirubin >3 times upper limit of normal [ULN]; transaminases > 10 times ULN). The data on pegaspargase treatment of patients with renal impairment and potential effects of increased urea concentrations on the kidneys are considered limited. However, as pegaspargase is a protein with a high molecular weight, it is not excreted renally, and no change of pharmacokinetic of pegaspargase in patients with renal impairment is foreseen. There is no data available on pegaspargase pharmacokinetic properties and dosage adjustments in the elderly patients.

PART II: MODULE SV – POST-AUTHORISATION EXPERIENCE

SV.1. Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Sales data is utilised to calculate the patient exposure. The data is collected in monthly intervals, and sales data available up to 14 July 2018 were utilised. Since the sales data do not provide the distribution by age, calculation of ONCASPAR usage by age is not possible.

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

The recommended dose of ONCASPAR per patient (with a body surface area ≥0.6 m^2 and who are ≤21years of age) per application is established as 2,500 U (equivalent to 3.3 ml ONCASPAR)/m^2 body surface area every 14 days.

The recommended posology in adults aged >21 years is 2,000 U/m^2 body surface area every 14 days.

The average dosage per patient per application is established as 3,750 U (content of a single vial of ONCASPAR) and the average duration of treatment is four applications per patient. Therefore, the number of patients exposed to ONCASPAR is calculated as an average dose of 15,000 U per patient.

SV.1.2 Exposure

[redacted]

PART II: MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

The pharmacologic profile of pegaspargase does not suggest any potential of misuse for illegal purposes. The potential risk of misuse is likely to be negligible.

SVI.2. Potential for Transmission of Infectious Agents

Not applicable.

SVI.3. Potential for Medication Errors

ONCASPAR is available in a single strength and may be applied both intramuscularly and intravenously. Single available strength is minimising the risk of confusion.

The introduction of a lyophilised presentation of ONCASPAR does not pose a risk for potential medication errors. Instructions on preparation prior to administration are provided in the Summary of Product Characteristics (SmPC). Once ONCASPAR LYO is reconstituted, the strength and concentration are the same as the liquid presentation. Dosing and administration (IV or IM) will be the same for both ONCASPAR LIQ and LYO.
Intravenous administration of ONCASPAR requires slow, 1-2 hours long infusion in 100 ml through an infusion of 100 mL sodium chloride 9 mg/mL (0.9%) or 5% glucose, together with an already running infusion given over shorter period of time than recommended may lead in susceptible individuals to the onset of allergic reaction with potential harmful impact on patients. As preparation and administration of ONCASPAR will be carried out by qualified professionals in specialised hospital units, the potential for medication errors and consecutive risk for the patients is lowered.

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

The following safety concerns have been removed:

- hyperlipidaemia, hyperglycaemia, infections, neurotoxicity, interactions with anticoagulants, corticosteroids, methotrexate and cytarabine, vincristine, live vaccines, and medicines with increased toxicity due to pegasparagase induced impaired liver metabolism, Reversible posterior leukoencephalopathy, effects on fertility, safety of patients with severe liver impairment and safety in patients with renal impairment due to a regulatory request (Procedure no.: EMEA/H/C/PSUSA/00010457/201807).

- Hypersensitivity (including severe hypersensitivity and anaphylactic shock), Pancreatitis, Haemorrhage, Thromboembolic events, Hepatotoxicity and Hyperammonaemia, Immunogenicity and Adverse events with a long latency due to a regulatory request (Procedure no.: EMEA/H/C/PSUSA/00010457/202207).

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Table 21. Important Identified Risk: Embryotoxicity and Teratogenicity

Potential mechanisms	The exact mechanism is not elucidated. A double teratogenic mechanism for L-asparaginase was postulated: a direct action mainly in younger embryos (before invagination of the embryo into the yolk sac) and a yolk sac-mediated one. [13]
Evidence source(s) and strength of evidence	Embryotoxicity and teratogenicity have been reported in scientific and medical literature.
Characterisation of the risk	Leucopenia has been reported in two cases of newborns following in utero exposure to L-asparaginase in combination with others therapies. [22,13] There have been no further published cases of leucopenia following in utero exposure to L-asparaginase in the 36 years since Okun et al (1979). The two published case reports pre-date Oncaspar by more than a decade. The history of commercial Oncaspar use covers more than 20 years, during which time it is estimated that almost 70,000 patients have been exposed. No case of leucopenia following in utero exposure has been reported to the sponsor during this period. In vitro studies with L-asparaginase in mice showed development retardation together with malformations of the brain, eyes, face and trunk. [13] In in vivo studies with L-asparaginase in rats, microphthalmia, malformations in vertebral column, sternal cleft and exenteria were observed. Embryotoxic and teratogenic effects were dose related. [24]
Risk factors and risk groups	Pre-clinical results suggest that exposure during 1st trimester poses the highest risk for the foetus.
Preventability	Oncaspar must not be used during pregnancy and effective contraception must be used during treatment. In the event of a spontaneous case of pregnancy being reported in a patient undergoing treatment with Oncaspar, routine pharmacovigilance practice would ensure that all pregnancies are followed up and any problems with mother or foetus would be identified.
Impact on the risk-benefit balance of the product	Risk minimisation measures in place are expected to minimise the occurrence and severity of embryotoxicity and teratogenicity. Patients should only be given ONCASPAR during pregnancy if clinical conditions of the woman require it. As there is potential risk to breast-fed infants, breast-feeding should not be performed until after ONCASPAR is terminated.
Public health impact	Based on limited reports in humans, the use of L-asparaginase does not seem to pose a major risk to the foetus when used in the 2nd and 3rd trimesters, or when exposure occurs prior to conception in either females or males. Because of the embryotoxicity and teratogenicity observed in animals and the lack of human data regarding 1st trimester exposure, L-asparaginase should be used cautiously, if at all, during this period. [25]

SVII.3.2. Presentation of the Missing Information

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table 22. Summary of Safety Concerns

Important identified risks	Embryotoxicity and teratogenicity
Important potential risk	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

III.2. Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities.

III.3. Summary Table of Additional Pharmacovigilance Activities

Not applicable as there are no additional pharmacovigilance activities.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

The following study (investigator-sponsored trial) is condition of the marketing authorisation:

Table 23. Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
Efficacy studies which are conditions of the marketing authorisation				
CAALL-F01: a French protocol for the treatment of acute lymphoblastic leukemia (ALL) in children and adolescents On-going	- For children and adolescents with standard or medium risk ALL, the study has two primary objectives: 1) to assess the superiority in terms of PK at D33 of the fractionated scheme; 2) to assess the equivalence in the tolerance of the 2 schemes (from D12 of induction to D49) - In the High/Very High Risk group two primary	To investigate the optimal use of L-Asparaginase (ASNase) with back bone chemotherapy in the treatment of children and adolescents with newly diagnosed ALL	[i] Protocol submission to Competent Authority [j] Study start up – First subject in [k] Interim report after 3 years of inclusion (+ data cleaning period) [l] End of enrolment (end of treatment report) - Last patient will have terminated his/her treatment	[i] 31-Dec- 2015 [j] 30-Jun-2016 [k] 31-Dec-2019 [l] 30-Jun-2025 [m] 22-Sep-2027

	objectives have been defined: 1) to assess the PK at D33; 2) to assess the toxicity of the intensified scheme from D12 of induction to D49		(+data cleaning period) [m]Final study report (Last patient without event will have 5 years follow-up (+ data cleaning period)	

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 24. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Embryotoxicity and teratogenicity	**Routine risk communication:** SmPC Section 4.6 – Fertility, pregnancy and lactation SmPC Section 5.3 – Preclinical safety data Package Leaflet (PL) Section 2 - What you need to know before you are given Oncaspar **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 – ONCASPAR should not be used during pregnancy unless clinically required. Breast-feeding should be discontinued during treatment of ONCASPAR. PL Section 2 – If patients are pregnant or breast-feeding, think they may be pregnant, or are planning to have a baby, they should ask their doctor for advice. Contraception (other than oral contraceptives) should be used during ONCASPAR treatment and for 6 months after discontinuation. Breast-feeding should be discontinued during treatment with ONCASPAR. **Other routine risk minimisation measures beyond the Product Information:** None.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.2.1. Removal of Additional Risk Minimisation Activities

Not applicable.

V.3. Summary of Pharmacovigilance Activities and Risk Minimisation Measures

Table 25. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Embryotoxicity and teratogenicity	**Routine risk minimisation measures:** SmPC Section 4.6 – ONCASPAR should not be used during pregnancy unless clinically required. Breast-feeding should be discontinued during treatment of ONCASPAR. SmPC Section 5.3 PL Section 2 – If patients are pregnant or breast-feeding, think they may be pregnant, or are planning to have a baby, they should ask their doctor for advice. Contraception (other than oral contraceptives) should be used during ONCASPAR treatment and for 6 months after discontinuation. Breast-feeding should be discontinued during treatment with ONCASPAR. **Additional risk minimisation measures:** No additional risk minimisation activities.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** No additional pharmacovigilance activities.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ONCASPAR (pegaspargase)

This is a summary of the risk management plan (RMP) for ONCASPAR. The RMP details the important risk of ONCASPAR, how this risk can be minimised, and how more information will be obtained about ONCASPAR's risk.

ONCASPAR's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ONCASPAR should be used.

This summary of the RMP for ONCASPAR should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ONCASPAR's RMP.

I. The medicine and what it is used for

ONCASPAR is authorised for acute lymphoblastic leukaemia (see SmPC for the full indication). It contains Pegaspargase as the active substance and it is given by an injection of infusion.

Further information about the evaluation of ONCASPAR’s benefits can be found in ONCASPAR’s EPAR, including in its plain-language summary, available on the EMA website (European Medicines Agency).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of ONCASPAR, together with measures to minimise such risks and the proposed studies for learning more about ONCASPAR's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals,
- Important advice on the medicine's packaging,
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly,
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed through signal detection, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of ONCASPAR are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ONCASPAR. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 26. List of Important Risks and Missing Information

Important identified risks	Embryotoxicity and teratogenicity
Important potential risk	None
Missing information	None

II.B Summary of important risks

Table 27. Important Identified Risk – Embryotoxicity and Teratogenicity

Evidence for linking the risk to the medicine	Embryotoxicity and teratogenicity have been reported in scientific and medical literature.
Risk factors and risk groups	Pre-clinical results suggest that exposure during 1st trimester poses the highest risk for the foetus.
Risk minimisation measures	**Routine risk minimisation measures:**

	SmPC Section 4.6 – ONCASPAR should not be used during pregnancy unless clinically required. Breast-feeding should be discontinued during treatment of ONCASPAR. SmPC Section 5.3 PL Section 2 – If patients are pregnant or breast-feeding, think they may be pregnant, or are planning to have a baby, they should ask their doctor for advice. Contraception (other than oral contraceptives) should be used during ONCASPAR treatment and for 6 months after discontinuation. Breast-feeding should be discontinued during treatment with ONCASPAR. **Additional risk minimisation measures:** No additional risk minimisation activities.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation

The following study (investigator-sponsored trial) is condition of the marketing authorisation:

Table 28. Studies Which are Conditions of the Marketing Authorisation

Study name	Purpose of the study
CAALL-F01: a French protocol for the treatment of acute lymphoblastic leukemia (ALL) in children and adolescents	- For children and adolescents with standard or medium risk ALL, the study has two primary objectives: 1) to assess the superiority in terms of PK at D33 of the fractionated scheme; 2) to assess the equivalence in the tolerance of the 2 schemes (from D12 of induction to D49). - In the High/Very High Risk group two primary objectives have been defined: 1) to assess the PK at D33; 2) to assess the toxicity of the intensified scheme from D12 of induction to D49.

II.C.2 Other studies in the post-authorisation development plan

There are no other studies required for ONCASPAR.

PART VII: ANNEXES

Table 29. Annexes

ANNEX	
Annex 1	Eudravigilance Interface
Annex 2	Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme
Annex 3	Protocols for proposed, on-going and completed studies in the pharmacovigilance plan
Annex 4	Specific adverse drug reaction follow-up forms
Annex 5	Protocols for proposed and on-going studies in RMP part IV
Annex 6	Details of proposed additional risk minimisation activities (if applicable)
Annex 7	Other supporting data (including referenced material)
Annex 8	Summary of changes to the risk management plan over time

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.