Summary Report of Benefit-Risk Assessment

ONCASPAR POWDER FOR SOLUTION FOR INJECTION / INFUSION 750 U/ML

NEW DRUG APPLICATION

Active Ingredient(s)	Pegaspargase
Product Registrant	Servier (S) Pte Ltd
Product Registration Number	SIN16408P
Application Route	Abridged evaluation
Date of Approval	27 December 2021

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A INTRODUCTION

Oncaspar is indicated as a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia (ALL).

The active substance, pegaspargase, is a pegylated formulation of L-asparaginase that is derived from *Escherichia coli* (*E. coli*). L-asparaginase is an enzyme that depletes serum L-asparagine, resulting in the inhibition of protein synthesis and apoptosis of leukaemic cells.

Oncaspar is available as a powder for solution for injection / infusion containing 750 U/mL of pegaspargase. Other ingredients in the vial are disodium phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride, sucrose, sodium hydroxide and hydrochloric acid.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, pegaspargase, is manufactured at Exelead, Inc., Indianapolis, USA. The drug product, Oncaspar Powder for Solution for Injection/Infusion 750 U/mL, is manufactured at Lyophilization Services of New England, Inc., Bedford, USA.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates, reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on four consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented for Exelead, Inc. was adequate to support the approved storage condition and shelf life. The packaging is a 20L bioprocess bag. The drug substance is approved for storage at 2 to 8^{o}C with a shelf life of 60 days.

Drug product:
The manufacturing process utilises aseptic processing.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and

non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored between 2ºC and 8ºC. Chemical and physical in-use stability has been demonstrated for 24 hours when stored below 25°C for the reconstituted solution and 48 hours when stored between 2°C to 8°C for the diluted solution. The container closure system is a Type I clear glass vial with chlorobutyl elastomer stopper.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of pegaspargase as a component of antineoplastic combination therapy for the treatment of patients with newly diagnosed ALL and relapsed or refractory ALL was based on data from four pivotal studies, CCG-1962, AALL07P4, DFCI 11-001, and ASP-304, and four supportive studies, ASP-400, ASP-001C/003C, ASP-201A, and ASP-302.

Newly diagnosed ALL

The **CCG-1962 study** was a Phase 2, randomised, open-label study in children aged 1 to 9 years who were newly diagnosed with standard risk ALL. Patients were randomised in a 1:1 ratio to receive standard multi-agent antineoplastic regimen in combination with either intramuscular (IM) injection of pegaspargase 2,500 U/m^2 on day 3 of the induction and delayed intensification phases, or IM injection of native *E. coli* L-asparaginase 6,000 U/m^2 three times weekly during the induction and delayed intensification phases. A total of 118 patients were randomised into the study, comprising 59 patients in the pegaspargase arm and 59 patients in the native *E. coli* L-asparaginase arm. The patient demographics and baseline characteristics were well-balanced between the treatment arms. The median age was 4.7 years (range 1.1 to 9.9 years), 54.0% of patients were male, and 65.0% of patients were White.

At day 14 of the induction phase, a higher proportion of patients in pegaspargase arm achieved M1 bone marrow status (<5% lymphoblasts) as compared to the native *E. coli* L-asparaginase arm (90% vs 75%). The proportion of patients who had M3 bone marrow status (>25% lymphoblasts) was lower in pegaspargase arm compared to the native *E. coli* L-asparaginase arm (0% vs 7%). The event-free survival (EFS) rates were comparable between pegaspargase arm and native *E. coli* L-asparaginase arm (3-year EFS: 83% vs 79%; 5-year EFS: 78% vs 73%; 7-year EFS: 75% vs 66%).

Sustained serum asparaginase activity (SAA) level >0.1 IU/mL for maximal suppression of plasma L-asparagine was observed at higher proportion of patients in pegaspargase arm compared to the native *E. coli* L-asparaginase arm during the first delayed intensification phase (95% vs 19%) and the second delayed intensification phase (91% vs 22%). The extent of depletion of L-asparagine in the plasma and cerebrospinal fluid (CSF) were similar between the treatment arms by day 28 of the induction phase.

The **DFCI 11-001 study** was a Phase 2, randomised, open-label study in patients aged 1 to 22 years who were newly diagnosed with ALL and lymphoblastic lymphoma. Patients were randomised in a 1:1 ratio to receive standard multi-agent antineoplastic regimen in combination with either intravenous (IV) infusion of pegaspargase 2,500 U/m^2 on day 7 of the induction

phase followed by every 2-weekly administration, or IV infusion of calaspargase pegol 2,500 U/m^2 on day 7 of the induction phase followed by every 3-weekly administration. A total of 237 patients were randomised into the study, comprising 119 patients in the pegaspargase arm and 118 patients in the calaspargase pegol arm. The patient demographics and baseline characteristics were well-balanced between the treatment arms. The median age was 5.0 years (range 1.0 to 20.0 years), 61.6% patients were male, and 70.5% patients were White.

The proportion of patients who achieved low minimal residual disease (MRD) level of <0.001% detectable leukemia cells at the end of the induction phase was comparable between pegaspargase arm and the calaspargase pegol arm (87.9% vs 87.5%). A lower complete remission (CR) rate was observed in pegaspargase arm compared to the calaspargase pegol arm (86.7% vs 95.6%). Nonetheless, the 1-year EFS rate (96.5% vs 92.4%) and 5-year overall survival (OS) rate (100% vs 96.5%) were comparable between pegaspargase arm and calaspargase pegol arm.

The SAA after a single pegaspargase infusion during the induction phase peaked at 5 to 10 minutes post-dose (1.6 IU/mL) and decreased gradually to 1.0 IU/mL on day 11, 0.6 IU/mL on day 18 and 0.4 IU/mL on day 25, which supported the recommended 2-weekly dosing frequency of pegaspargase to provide a sustained SAA level above 0.1 IU/mL for maximal depletion of plasma L-asparagine for up to day 25.

The **AALL07P4 study** was a pilot, randomised, open-label study in patients aged 1 to 30 years who were newly diagnosed with high-risk B-cell ALL. Patients were randomised in a 2:1:1 ratio to receive standard multi-agent antineoplastic regimen in combination with IV infusion of pegaspargase 2,500 U/m^2 or calaspargase pegol 2,500 U/m^2 or calaspargase pegol 2,100 U/m^2 during the induction, consolidation and interim maintenance phases. A total of 166 patients were randomised into the study, comprising 55 patients in the pegaspargase arm and 111 patients in the calaspargase pegol arms. The patient demographics and baseline characteristics were well-balanced between the treatment arms. The median age was 11.0 years (range 1.0 to 26.0 years), 50.9% of patients were male, and 82.2% of patients were White.

At the end of the induction phase on day 29, 80.0% of patients in the pegaspargase arm and 84.6% of patients in the calaspargase pegol 2,500 U/m^2 arm achieved low MRD level of <0.1% detectable leukemia cells. The CR rate (92.7% vs 95.2%), 4-year EFS rate (81.8% vs 89.9%) and 4-year OS rate (90.4% vs 90.0%) were comparable between pegaspargase arm and calaspargase pegol arm. The L-asparagine levels in the plasma and CSF were depleted to below limit of assay quantitation (BLQ) in the treatment arms and remained BLQ for up to day 25 during the induction and consolidation phases.

Summary of Efficacy Outcomes (Newly diagnosed ALL)

Study	N	Treatment arms and dose [a]	Disease-free survival [b] [range]	Overall Survival [c] [range]
CCG-1962	59	IM Pegaspargase 2,500 U/m^2	7-year: 75.0% [63.0% - 87.0%]	NR
		IM *E.coli* L-asparaginase 6,000 U/m^2	7-year: 66.0% [52.0% - 80.0%]	
DFCI 11-001	119	IV Pegaspargase 2,500 U/m^2	1-year: 98.0% [92.3% - 99.5%]	1-year: 100.0%
		IV Calaspargase pegol 2500 U/m^2	1-year: 92.4% [85.3% - 96.1%]	1-year: 96.5% [90.8% - 98.7%]

AALL07P4	55	IV Pegaspargase 2,500 U/m^2	4-year: 81.8% [62.9% - 91.7%]	4-year: 90.4% [78.5% - 95.9%]
		IV Calaspargase pegol 2,500 U/m^2	4-year: 89.9% [70.1% - 96.9%]	4-year: 90.0% [75.5% - 96.1%]

IM: intramuscular; IV: intravenous; N: number of patients; NR: Not reported
[a] In combination with multi-agent antineoplastic regimens for ALL
[b] Displayed the longest available disease-free survival data
[c] Displayed the longest available overall survival data

Relapsed or Refractory ALL

The **ASP-304 study** was a Phase 3, randomised, open-label study in patients aged 1 to ≤21 years with relapsed ALL. During the reinduction phase, patients without a history of hypersensitivity to native *E. coli* L-asparaginase (non-hypersensitive cohort) were randomised in a 1:1 ratio to receive standard multi-agent antineoplastic regimens in combination with either IM injections of native *E. coli* L-asparaginase 10,000 U/m^2 three times a week for four weeks, or IM injections of pegaspargase 2,500 U/m^2 on day 1 and day 15. Patients with known hypersensitivity to native *E. coli* L-asparaginase (hypersensitive cohort) were assigned to receive IM injections of pegaspargase 2,500 U/m^2 on day 1 and day 15.

A total of 28 non-hypersensitive patients were randomised into the study, comprising 17 patients in the native *E. coli* L-asparaginase arm and 11 patients in the pegaspargase arm. The patient demographics and baseline characteristics were well-balanced between the treatment arms. The hypersensitive cohort consisted of 40 patients assigned to pegaspargase. The patient demographics and baseline characteristics were well-balanced between the treatment arms. The median age was 8.0 years (range: 2.0 to 18.0 years), 61.8% of patients were male, the median disease duration was 33.0 months (range: 11 – 138 months), and the mean number of disease relapses was 2.2.

Patients in the non-hypersensitive cohort treated with pegaspargase achieved an ORR of 56% as compared to an ORR of 47% for patients treated with the native *E. coli* L-asparaginase arm, of which, the CR rates were 39% vs 47% respectively. The hypersensitive cohort assigned to receive pegaspargase treatment achieved an ORR of 54% and CR rate of 41% which was consistent with that of the non-hypersensitive cohort.

The **ASP-400 study** was a pilot, open-label, uncontrolled study in patients aged 2 to ≤21 years with relapsed or refractory ALL (n=44) and non-Hodgkin lymphoma (NHL) (n=2). Patients received standard multi-agent antineoplastic regimen in combination with IV infusion of pegaspargase 2,000 U/m^2 on day 12 of the reinduction phase, day 5 of the first consolidation phase and day 5 of the second consolidation phase. The patient demographics and baseline characteristics were well-balanced between the treatment arms. The mean age was 9.0 years (range: 2.0 to 18.0 years), 59.1% of patients were male, and the median disease duration was 29.0 months. Of the 44 evaluable patients, 13 (29.5%) patients were hypersensitive to native *E. coli* L-asparaginase, and 31 (70.5%) patients were not hypersensitive to native *E. coli* L-asparaginase.

Patients in the non-hypersensitive cohort achieved an ORR of 81%, of which, 68% were CR. In the hypersensitive cohort, ORR was achieved in 54% of patients, of which, 46% were CR. The response rate in the hypersensitive cohort was generally consistent with that in study ASP-304.

The **ASP-001C/003C study** was a Phase 1/2, open-label, uncontrolled study in patients aged 1 to 66 years with relapsed ALL (n=34), acute undifferentiated leukaemia (AUL) (n=4) or other malignant haematologic disorders (n=3). During the reinduction phase, patients received IM injection of pegaspargase 2,000 U/m^2 as monotherapy or in combination with standard multi-agent antineoplastic regimens. Patients who were in complete remission at the end of the reinduction phase continued to receive weekly maintenance treatment with pegaspargase.

A total of 41 patients were enrolled into the study, comprising 11 non-hypersensitive patients and 30 hypersensitive patients. The hypersensitive cohort had a mean age of 9.1 years (range: 1.0 to 66.0 years) and the mean disease duration was 49.3 months. The non-hypersensitive cohort had a mean age of 26.5 years (range: 3.0 to 66.0 years) and the mean disease duration was 42.8 months.

During the reinduction phase in the hypersensitive cohort, higher ORR was achieved with pegaspargase combination therapy as compared to pegaspargase monotherapy (25% vs 43%), while the CR rate was similar between the combination therapy and monotherapy (25% vs 29%). Likewise, in the non-hypersensitive cohort, patients treated with pegaspargase combination therapy achieved a higher ORR (25% vs 20%) and CR rate (25% vs 0%) compared to patients treated with pegaspargase monotherapy. During the maintenance phase, the ORR in hypersensitive and non-hypersensitive cohorts were 89% and 100% respectively.

The **ASP-201A study** was a Phase 1/2, open-label, uncontrolled study in patients aged 1 to 43 years with relapsed ALL (n=37), relapsed T-cell non-Hodgkin's lymphoma (n=2), relapsed acute non-lymphoblastic leukaemia (n=2) and relapsed acute myeloid leukaemia (n=1). During the reinduction phase, patients received standard multi-agent antineoplastic regimens in combination with IM injection or IV infusion of pegaspargase 2,000 U/m^2 every 2-weekly for 3 doses.

A total of 42 patients were enrolled into the study, comprising 33 non-hypersensitive patients and 9 hypersensitive patients. The patient demographics were well-balanced between the treatment arms. The mean age was 14.0 years (range: 1.0 to 43.0 years), and 71.4% of patients were male.

The hypersensitive cohort achieved an ORR of 63% and CR rate of 50% that were generally consistent with the response rates in studies ASP-304 and ASP-400. A similar ORR of 63% and CR rate of 53% were achieved in the non-hypersensitive cohort.

The **ASP-302 study** was a Phase 1/2, open-label, uncontrolled study in patients aged 1 to 35 years with relapsed ALL. During the reinduction phase, patients received IM injections of pegaspargase 2,000 U/m^2 every two weeks in combination with multi-agent antineoplastic regimen.

A total of 21 patients were enrolled into the study, comprising 17 non-hypersensitive patients and 4 hypersensitive patients. The mean age was 11.0 years (range: 1.0 to 35.0 years), 61.9% of patients were male, the mean disease duration was 53.8 months, and the mean number of disease relapses was 1.6.

The hypersensitive cohort achieved an ORR of 100% and CR rate of 100%, while the non-hypersensitive cohort achieved an ORR of 69% and CR rate of 56%.

Summary of Efficacy Outcomes (Relapsed or Refractory ALL)

Study	Treatment and dose [a]	Patient Cohort	N	Overall Response Rate
ASP-304	IM Pegaspargase 2,500 U/m^2	Non-hypersensitive [b] cohort	18	56%
		Hypersensitive [c] cohort	39	54%
ASP-400	IV Pegaspargase 2,000 U/m^2	Non-hypersensitive [b] cohort	31	81%
		Hypersensitive [c] cohort	13	54%
ASP-001C/003C [d]	IM Pegaspargase 2,500 U/m^2	Non-hypersensitive [b] cohort	11	100%
		Hypersensitive [c] cohort	19	89%
ASP-201A	IM or IV Pegaspargase 2,500 U/m^2	Non-hypersensitive [b] cohort	18	63%
		Hypersensitive [c] cohort	8	63%
ASP-302	IM Pegaspargase 2,500 U/m^2	Non-hypersensitive [b] cohort	16	69%
		Hypersensitive [c] cohort	4	100%

IM: intramuscular; IV: intravenous; N: number of evaluable patients; NR: Not reported
[a] In combination with multi-agent antineoplastic regimens for ALL
[b] Non-hypersensitive to native E.coli L-asparaginase.
[c] Hypersensitive to native E.coli L-asparaginase.
[d] Results during maintenance phase was displayed.

Overall, the pivotal and supportive studies demonstrated comparable efficacy of pegaspargase to that for other L-asparaginase products when used in combination with multi-agent antineoplastic regimen in ALL patients. As expected, numerically better efficacy was seen in the newly diagnosed ALL patient population compared to the relapsed or refractory ALL patient population. The studies also showed that use of pegaspargase in patients hypersensitive to L-asparaginase products resulted in generally comparable overall response rates as that seen in non-hypersensitive subjects. Taken into totality, the efficacy of pegaspargase used in combination with multi-agent antineoplastic regimen for the treatment of ALL was supported.

D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of pegaspargase in combination with multi-agent antineoplastic regimen for the treatment of ALL were mainly derived from the pivotal studies CCG-1962, AALL07P4, DFCI 11-001, and ASP-304, comprising a total of 589 patients (284 patients in the pegaspargase arm and 305 patients in the control arm). In view of the varied multi-agent antineoplastic regimens, patient populations and heterogeneous design of the studies, the safety profile of pegaspargase were presented by individual studies.

Overall of Safety Profile (Study CCG-1962)

Number (%) of patients with any:	Pegaspargase (N = 59)	Native *E.coli* L-asparaginase (N = 59)
Grade 3 or 4 TEAEs [a]	7 (11.9%)	15 (25.4%)
Serious TEAEs	3 (5.1%)	2 (3.4%)

TEAE: Treatment-emergent adverse event
[a] During induction period

The **CCG-1962 study** only captured grade 3 or 4 treatment-emergent adverse events (TEAEs) and the incidence was lower in pegaspargase arm compared to the native *E. coli* L-asparaginase arm. Grade 3 or 4 TEAEs that were reported more frequently in the pegaspargase arm compared to the native *E. coli* L-asparaginase arm included abdominal pain (4% vs 2%), constipation (4% vs 0%), diarrhoea (4% vs 0%), hyperkalaemia (4% vs 2%),

peripheral neuropathy (6% vs 2%), respiratory failure (4% vs 2%), skin disorder (8% vs 2%) and hypotension (4% vs 2%). The adverse event of special interest reported for pegaspargase and native *E. coli* L-asparaginase were coagulopathy (2% vs 5%), hyperglycaemia (4% vs 6%), neurologic dysfunction (6% vs 3%), and pancreatitis (2% vs 0%).

Overall of Safety Profile (Study AALL07P4)

Number (%) of patients with any:	Pegaspargase (N = 52)	Calaspargase pegol [a] (N = 59)
TEAEs	110 (99.1%)	51 (98.1%)
Study drug-related TEAEs	102 (91.9%)	44 (84.6%)
Grade 3 or 4 TEAEs	107 (96.4%)	47 (90.4%)
Study drug-related Grade 3 or 4 TEAEs	92 (82.9%)	40 (76.9%)

TEAE: Treatment-emergent adverse event

[a] Displayed the combined event rates for calaspargase pegol 2,500 IU/m^2 and 2,100 IU/m^2 doses

In **AALL07P4 study**, study drug-related TEAEs (84.6% vs 91.9%) and study drug-related Grade 3 or 4 TEAEs (76.9% vs 82.9%) were reported at lower incidences in pegaspargase arm compared to the calaspargase pegol arm. Grade 3 or 4 TEAEs related to study drug that were reported more frequently in the pegaspargase arm compared to the calaspargase pegol arm included neutrophil count decreased (32.7% vs 23.4%), white blood cell count decreased (19.2% vs 11.7%), platelet count decreased (13.5% vs 12.6%), and anaemia (11.5% vs 7.2%).

The L-asparaginase-specific TEAEs were reported at lower incidence in pegaspargase arm compared to the calaspargase pegol arms, these included pancreatitis (7.7% vs 18.6%), amylase increased (3.8% vs 9.3%), lipase increased (9.6% vs 23.3%), hypersensitivity reaction (5.8% vs 2.3%), anaphylactic reaction (19.2% vs 25.6%), prolonged activated partial thromboplastin time (17.3% vs 30.2%), embolism (1.9% vs 2.3%), and decreased blood fibrinogen (5.8% vs 14.0%).

TEAEs leading to the permanent discontinuation of the study drug were similar across the treatment arms (25.9% in the pegaspargase arm vs 27.5% in the calaspargase pegol arm) and were mainly driven by grade 3 systemic allergic reactions (11.1% vs 15.6%).

Overall of Safety Profile (Study DFCI 11-001)

Number (%) of patients with any:	Pegaspargase (N = 119)	Calaspargase pegol (N = 118)
TEAEs	119 (100.0%)	116 (98.3%)
Study drug-related TEAEs	118 (99.2%)	115 (97.5%)
Grade 3 or 4 TEAEs	114 (95.8%)	110 (93.2%)
Study drug-related Grade 3 or 4 TEAEs	104 (87.4%)	93 (78.8%)
Serious TEAEs	26 (21.8%)	29 (24.6%)
Study drug-related Serious TEAEs	20 (16.8%)	22 (18.6%)
TEAEs leading to discontinuation of study drug	23 (19.3%)	33 (28.0%)
Study drug-related TEAEs leading to discontinuation of study drug	22 (18.5%)	32 (27.1%)

TEAE: Treatment-emergent adverse event

In **DFCI 11-001 study**, the percentage of patients with study drug-related TEAEs was similar across between the treatment arms (99.2% in the pegaspargase arm vs 97.5% in the calaspargase pegol arm). TEAEs related to study drug that were reported more frequently in the pegaspargase arm compared to the calaspargase pegol arm included hypertriglyceridemia (36.1% vs 28.0%), blood fibrinogen decreased (25.2% vs 20.3%), lipase increased (23.5% vs 16.9%), hypoglycaemia (16.8% vs 14.4%), bilirubin conjugated increased (14.3% vs 13.6%),

pancreatitis (16.8% vs 11.9%), febrile neutropenia (15.1% vs 8.5%), embolism (11.8% vs 4.2%), and hypokalaemia (5.0% vs 2.5%).

Study drug-related Grade 3 or 4 TEAEs were reported at a higher incidence in pegaspargase arm (87.4%) compared to the calaspargase pegol arm (78.8%). The Grade 3 or 4 TEAEs related to study drug that were reported more frequently in the pegaspargase arm compared to the calaspargase pegol arm included blood fibrinogen decreased (12.6% vs 8.5%), hyperglycaemia (9.2% vs 6.8%), hypoalbuminemia (9.2% vs 5.1%), lipase increased (6.7% vs 3.4%), hypertriglyceridemia (27.7% vs 16.1%), alanine aminotransferase (ALT) increased (20.2% vs 16.1%), lipase increased (13.4% vs 11.0%), aspartate aminotransferase (AST) increased (10.9% vs 7.6%) and febrile neutropenia (12.6% vs 5.9%).

TEAEs leading to the permanent discontinuation of the study drug were reported at a lower incidence in pegaspargase arm (19.3%) compared to the calaspargase pegol arm (28.0%). The proportion of patients with at least one adverse event of special interest related to study drug was lower in pegaspargase arm (60.5%) compared to the calaspargase pegol arm (66.1%).

Overall of Safety Profile (Study ASP304)

Number (%) of patients with any:	Non-hypersensitive [a] cohort		Hypersensitive [b] cohort
	Pegaspargase (N = 19)	**Native *E.coli* L-asparaginase (N = 17)**	**Pegaspargase (N = 40)**
TEAEs Grade 3 or 4 TEAEs	15 (79%) 6 (32%)	17 (100%) 10 (59%)	34 (85%) 11 (28%)
Coagulation toxicity Grade 3 or 4 coagulation toxicity	3 (16%) 2 (11%)	11 (65%) 7 (41%)	NR NR
Hypersensitivity reactions Grade 3 or 4 hypersensitivity reactions	0 0	0 1 (5.%)	0 1 (2.5%)
Study drug-related TEAEs	22 (96%)		35 (83%)
Study drug-related Grade 3 or 4 TEAEs	7 (29%)		13 (31%)
Study drug-related hypersensitivity reactions (any severity)	2 (5.6%)		5 (12.5%)
Study drug-related Grade 3 or 4 hypersensitivity reactions	1 (2.8%)		2 (5.0%

NR: Not reported; TEAE: Treatment-emergent adverse event
[a] Hypersensitive to native *E.coli* L-asparaginase
[b] Non-hypersensitive to native *E.coli* L-asparaginase

In **ASP304 study**, the percentage of non-hypersensitive patients with TEAEs was lower in pegaspargase arm compared to the native *E. coli* L-asparaginase arm (79% vs 100%). In the non-hypersensitive cohort, the commonly reported TEAEs related to study drug in pegaspargase arm compared to native *E. coli* L-asparaginase arm included hepatotoxicity (74% vs 82%), coagulopathy (16% vs 65%), and hypersensitivity reaction (13% vs 13%).

TEAEs related to pegaspargase were reported at a higher incidence in non-hypersensitive cohort compared to the hypersensitive cohort (96% vs 83%). The commonly reported TEAEs related to pegaspargase in non-hypersensitive cohort compared to the hypersensitive cohort included hepatoxicity (88% vs 66%), coagulopathy (17% vs 39%), hypersensitivity reaction (13% vs 17%) and pancreatitis (4% vs 2%). The percentage of patients who experienced Grade 3 or 4 TEAEs related to pegaspargase was similar across the non-hypersensitive and hypersensitive cohorts (29% vs 31%).

In general, the notable safety concerns with pegaspargase included hypersensitivity reactions, anaphylaxis, pancreatitis, thrombosis, coagulopathy, myelosuppression, hepatotoxicity, myelosuppression, encephalopathy, hyperglycaemia and hyperammonaemia. These safety concerns were not unexpected for pegaspargase due to its mechanism of action and were similar to that for other L-asparaginase products. The tolerability profile of pegaspargase treatment in patients hypersensitive to *E. coli* L-asparaginase was similar to the overall population. Appropriate warnings and precautions for these adverse events have been included in the package insert. Overall, pegaspargase presented an acceptable safety profile for patients with ALL given the poor prognosis of long-term mortality and morbidity outcomes of the disease.

E ASSESSMENT OF BENEFIT-RISK PROFILE

L-asparaginase is a key component of multi-agent chemotherapy regimen for the treatment of ALL. The clinical studies in newly diagnosed ALL patients demonstrated that pegaspargase in combination with multi-agent antineoplastic regimen achieved a clinically relevant 5-year EFS rate ranging from 67.5% to 90% and 5-year OS rate ranging from 94% to 96%. In patients with relapsed or refractory ALL who were hypersensitive to native *E. coli* L-asparaginase and would otherwise have no suitable alternative L-asparaginase treatment, pegaspargase in combination with multi-agent antineoplastic regimens resulted in a clinically relevant ORR ranging from 36% to 100% that was consistent with the response rate in patients without hypersensitivity to native *E. coli* L-asparaginase (ORR ranging from 36% to 81%).

Administration of pegaspargase demonstrated sustained SAA ≥0.1 IU/mL for maximal suppression of plasma and CSF L-asparagine throughout the induction and delayed intensification phases. The extent of L-asparagine depletion in the plasma and CSF was comparable between pegaspargase and native *E. coli* L-asparaginase.

The safety profile of pegaspargase was similar to that for native *E. coli* L-asparaginase. Pegaspargase was also well tolerated in patients who were hypersensitive to native *E.coli* L-asparaginase product. The notable safety concerns with pegaspargase were hypersensitivity reactions, anaphylaxis, pancreatitis, thrombosis, coagulopathy, myelosuppression, hepatotoxicity, myelosuppression, encephalopathy, hyperglycaemia and hyperammonaemia. These adverse events have been adequately addressed in the local package insert via the provision of relevant warnings and precautions.

Overall, the benefit-risk profile of pegaspargase as a component of antineoplastic combination therapy for the treatment of ALL was considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits of pegaspargase as a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia outweighed the risks and approval of the product registration was granted on 27 December 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL).

4.2 Posology and method of administration

Oncaspar should be prescribed and administered by physicians and/or health care personnel experienced in the use of antineoplastic products. It should only be given in a hospital setting where appropriate resuscitation equipment is available. Patients should be closely monitored and carefully observed for any adverse reactions throughout the administration period (see section 4.4).

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

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

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

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

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

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

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

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

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

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

For smaller volumes, the preferred route of administration is intramuscular. When Oncaspar is given by intramuscular injection the volume injected at one site should not exceed 2 ml in children and adolescents and 3 ml in adults. If higher volume is given, the dose should be divided and given at several injection sites.

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

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Central nervous system effects
Combination therapy with Oncaspar can result in central nervous system toxicity. Cases of encephalopathy (including reversible posterior leukoencephalopathy syndrome) have been reported (see section 4.8).

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

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

The decrease in the number of circulating lymphoblasts is often quite marked, and normal or too low leukocyte counts are often seen in the first days after the start of therapy. This can be associated with a marked rise in the serum uric acid level. Uric acid nephropathy may develop. To monitor the therapeutic effect, the peripheral blood count and the patient's bone marrow should be monitored closely.

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

In addition, by inhibiting protein synthesis and cell division, pegaspargase can disturb the mechanism of action of other substances which require cell division for their effect, e.g., methotrexate. Methotrexate and cytarabine can interact differently with Oncaspar: their prior administration can increase the action of pegaspargase synergistically. If these substances are given subsequently, the effect of pegaspargase can be weakened antagonistically.

Pegaspargase can interfere with metabolism and clearance of other medicinal products, based on its effects on protein synthesis and hepatic function, as well as from its combined use with other chemotherapy products known to interact with CYP enzymes.

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

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

Immediately preceding or simultaneous treatment with vincristine can increase the toxicity of pegaspargase. Administration of Oncaspar before vincristine may increase the neurotoxicity of vincristine. Therefore, vincristine should be given at least 12 hours prior to administration of Oncaspar in order to minimise toxicity.

An indirect interaction cannot be ruled out between pegaspargase and oral contraceptives due to pegaspargase hepatotoxicity that may impair the hepatic clearance of oral contraceptives. Therefore, the concomitant use of Oncaspar with oral contraceptives is not recommended. Another method than oral contraception should be used in women of childbearing potential (see sections 4.4 and 4.6).

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

4.6 Fertility, pregnancy and lactation

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

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

Breast-feeding
It is not known whether pegaspargase is excreted 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 until after discontinuation of Oncaspar.

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

4.7 Effects on ability to drive and use machines

Oncaspar has major influence on the ability to drive and use machines. The following adverse reactions have been reported in patients treated with Oncaspar along with other chemotherapy medicinal products: somnolence, confusion, dizziness, syncope, seizure.
Patients should be advised not to drive or operate machines while receiving Oncaspar if they experience these or other adverse reactions which can impair their ability to drive or operate machines (see section 4.4).

4.8 Undesirable effects

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

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

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

Tabulated list of adverse reactions
Adverse reactions and their frequencies are reported in Table 1. Frequencies are defined by the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported with Oncaspar therapy

MedDRA standard system organ class	Adverse reaction
Blood and lymphatic system disorders	Very common: Febrile neutropenia Common: Anaemia, coagulopathy Not known: Bone marrow failure
Gastrointestinal disorders	Very common: Pancreatitis, diarrhoea, abdominal pain, nausea Common: Vomiting, stomatitis, ascites Rare: Pancreatitis necrotising, pancreatitis haemorrhagic Not known: Pancreatic pseudocyst, parotitis*
General disorders and administration site conditions	Not known: Pyrexia
Hepatobiliary disorders	Common: Hepatotoxicity, fatty liver Rare: Hepatic necrosis, jaundice, cholestasis, hepatic failure
Immune system disorders	Very common: Hypersensitivity, urticaria, anaphylactic reaction Not known: Anaphylactic shock.
Infections and infestations	Common: Infections, sepsis
Investigations	Very common: Weight decreased, hypoalbuminaemia, alanine aminotransferase increased, aspartate aminotransferase increased, hypertriglyceridaemia, blood fibrinogen decreased, lipase increased,

	amylase increased, activated partial thromboplastin time prolonged, blood bilirubin increased Common: Prothrombin time prolonged. international normalised ratio increased, hypokalaemia, blood cholesterol increased, hypofibrinogenaemia, gamma-glutamyl transferase increased Not known: Blood urea increased, anti-pegaspargase antibodies, neutrophil count decreased, platelet count decreased, hyperammonaemia
Metabolism and nutrition disorders	Very common: Decreased appetite, hyperglycaemia Common: Hyperlipidaemia, hypercholesterolaemia Not known: Diabetic ketoacidosis, hypoglycaemia
Musculoskeletal and connective tissue disorders	Common: Pain in extremities
Nervous system disorders	Common: Seizure, peripheral motor neuropathy, syncope Rare: Posterior reversible leukoencephalopathy syndrome Not known: Somnolence, tremor*
Psychiatric disorders	Not known: Confusional state
Renal and urinary disorders	Not known: Renal failure acute*
Respiratory, thoracic and mediastinal disorders	Common: Hypoxia
Skin and subcutaneous tissue disorders	Very common: Rash Not known: Toxic epidermal necrolysis*
Vascular disorders	Very common: Embolism** Common: Thrombosis*** Not known: Cerebrovascular accident, haemorrhage, superior sagittal sinus thrombosis

*Adverse reactions observed with other asparaginases in the class

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

***Legend: CNS thrombosis

Description of selected adverse reactions

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

Blood and lymphatic system disorders

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

Nervous system disorders

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

Gastrointestinal disorders

About half of patients develop mild to moderate gastrointestinal reactions such as loss of appetite, nausea, vomiting, abdominal cramps, diarrhoea and weight loss.
Acute pancreatitis can occur commonly. There have been isolated reports of formation of pseudocysts (up to four months after the last treatment).

Haemorrhagic or necrotising pancreatitis occurs rarely. One case of pancreatitis with simultaneous acute parotitis has been described with L-asparaginase treatment. In single cases, haemorrhagic or necrotising pancreatitis with fatal outcome has been reported.

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

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

Skin and subcutaneous tissue disorders
Allergic reactions can manifest 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 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 detected; uncommonly they were associated with hypersensitivity reactions. Neutralising antibodies reducing clinical efficacy were also recorded.

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

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

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

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

The type of adverse reactions of Oncaspar is similar with that of native non-pegylated L-asparaginase (e.g., native *E. coli* asparaginase).

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

In Study CCG-1962, PD effect of Oncaspar was assessed through serial measurements of asparagine in serum (n=57) and CSF (n=50) of newly diagnosed paediatric patients with standard-risk ALL who received three intramuscular doses of Oncaspar (2,500 Units/m^2 BSA), one each during induction and two during delayed intensification treatment phases. A reduction in serum asparagine concentration was evident by the 4th day after the first Induction dose and reached an apparent nadir by the 10th day after the dose. Serum asparagine concentrations of approximately 1 µM persisted for approximately 3 weeks. Asparagine concentration fell to <3 µM when asparaginase activity was >0.1 U/mL. CSF asparagine of 2.3 µM pre-treatment fell to 1.1 µM on Day 7 and 0.6 µM on Day 28 of Induction (see Clinical efficacy and safety).

In Study AALL07P4, the PD effect of Oncaspar was assessed in 47 evaluable subjects with high risk B-precursor ALL who received IV doses of Oncaspar 2,500 U/m^2 BSA during the Induction and Consolidation phases. Plasma L-asparagine concentrations were depleted to below the assay limit of quantification within 24 hours following the Induction and first Consolidation dose of Oncaspar and depletion was sustained for approximately two weeks. CSF asparagine concentrations were reduced by the 4th day following the Induction dose, and remained largely undetectable by the 18th day after dosing.

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

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

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

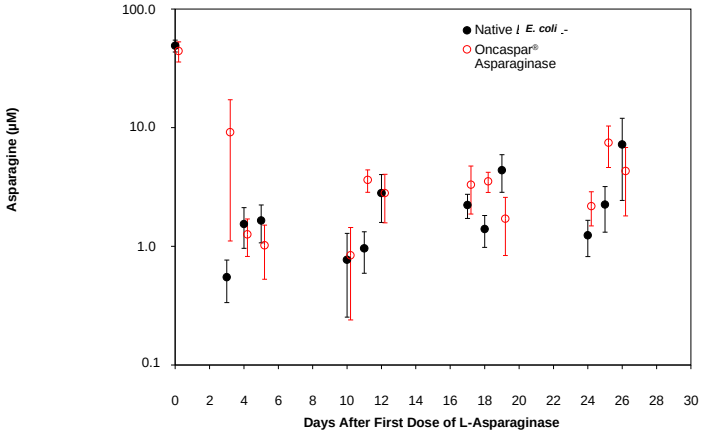
First-Line (ALL patients non-hypersensitive to native E. coli L-asparaginase)
The safety and efficacy of Oncaspar was evaluated in an open-label, multicentre, randomised, active-controlled study (StudyCCG-1962). In this study, 118 paediatric patients aged 1 to 9 years with previously untreated standard-risk ALL were randomised 1:1 to Oncaspar or native *E. coli* L-asparaginase as part of combination therapy. Oncaspar was administered intramuscularly at a dose

of 2,500 Units/m^2 BSA on Day 3 of the 4-week Induction phase and on Day 3 of each of two 8-week Delayed Intensification (DI) phases. Native *E. coli* L-asparaginase was administered intramuscularly at a dose of 6,000 Units/m^2 BSA three times weekly for a total of 9 doses during induction and for a total of 6 doses during each delayed intensification phase.

The primary determination of efficacy was based on demonstration of similar asparagine depletion (magnitude and duration) in the Oncaspar and native *E. coli* L-asparaginase arms. The protocol-specified goal was achievement of asparagine depletion to a serum concentration of ≤1 µM. The proportion of patients with this level of depletion was similar between the 2 study arms during all 3 phases of treatment at the protocol-specified time points.

In all phases of treatment, serum asparagine concentrations decreased within 4 days of the first dose of asparaginase in the treatment phase and remained low for approximately 3 weeks for both Oncaspar and native *E. coli* L-asparaginase arms. Serum asparagine concentrations during the induction phase are shown in Figure 1. The patterns of serum asparagine depletion in the 2 delayed intensification phases are similar to the pattern of serum asparagine depletion in the induction phase.

Figure 1: Mean (± standard error) serum asparagine during Study CCG-1962 induction phase



Note: Oncaspar (2,500 Units/m^2 BSA intramuscular) was administered on Day 3 of the 4-week induction phase. Native *E. coli* L-asparaginase (6,000 Units/m^2 BSA intramuscular) was administered 3 times weekly for 9 doses during induction.

CSF asparagine concentrations were determined in 50 patients during the induction phase. CSF asparagine decreased from a mean pre-treatment concentration of 3.1 µM to 1.7 µM on Day 4 ± 1 and 1.5 µM at 25 ± 1 days after administration of Oncaspar. These findings were similar to those observed in the native *E. coli* L-asparaginase treatment arm.

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

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

	Oncaspar	native *E. coli* L-asparaginase
3-Year EFS Rate, % (95% CI)	83 (73, 93)	79 (68, 90)
5-Year EFS Rate, % (95% CI)	78 (67, 88)	73 (61, 85)
7-Year EFS Rate, % (95% CI)	75 (63, 87)	66 (52, 80)

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

A pilot study was conducted for newly diagnosed patients from 1 to <31 years of age with high risk B-precursor ALL (Study AALL07P4). This was an open label, controlled, randomised study comparing an investigational pegylated asparaginase product to Oncaspar as a component of multi-agent chemotherapy in the first line treatment of ALL. White blood cell (WBC) criteria were: a) Age 1-10 years: WBC ≥50,000/μL; b) Age 10-30 years: Any WBC; c) Prior steroid therapy: Any WBC. Patients were not allowed prior cytotoxic chemotherapy with the exception of steroids and intrathecal cytarabine. A total of 166 patients were enrolled in this study; 54 patients were randomised to treatment with 2,500 U/m^2 BSA Oncaspar and 111 patients were randomised to the investigational pegylated asparaginase product. Oncaspar was administered intravenously at the dose of 2,500 Units/m^2 BSA during Induction, Consolidation, Delayed Intensification, and Interim Maintenance phases in patients with high-risk ALL receiving augmented Berlin-Frankfurt-Münster therapy. The percentage of patients in the Oncaspar treatment arm with evaluable minimal residual disease (MRD) negative status (<0.1% leukaemia cells in bone marrow) at Day 29 of Induction was 80% (40/50). At 4-years, the EFS and overall survival (OS) for the Oncaspar treatment arm were 81.8% [95% CI 62.9-91.7%] and 90.4% [95% CI 78.5-95.9%], respectively. Overall, in the group receiving Oncaspar, the rate of all grade hypersensitivity was 5.8%, anaphylactic reactions was 19.2%, and pancreatitis 7.7%. Grade 3 or higher febrile neutropenia was 15.4%.

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

ALL patients hypersensitive to native E. coli L-asparaginase

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

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

5.2 Pharmacokinetic properties

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

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

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

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

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

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

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

Patients with newly diagnosed ALL received a single IM injection of Oncaspar (2,500 U/m² BSA) or native asparaginase from *E. coli* (25,000 U/m² BSA) or from *Erwinia* (25,000 U/m² BSA). The plasma elimination half-life of Oncaspar was statistically significantly longer (5.7 days) than the plasma elimination half-lives of the native asparaginases from *E. coli* (1.3 days) and *Erwinia* (0.65 days). The immediate cell death of leukaemic cells *in vivo*, measured by rhodamine fluorescence, was the same for all three L-asparaginase preparations.

ALL patients with several relapses were treated either with Oncaspar or with native asparaginase from *E. coli* as part of an induction therapy. Oncaspar was given IM in a dose of 2,500 U/m² BSA on days 1 and 15 of induction. The mean plasma half-life of Oncaspar was 8 days in non-hypersensitive patients (AUC 10.35 U/ml/day), and 2.7 days in hypersensitive patients (AUC 3.52 U/ml/day).

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

The impact of renal and hepatic impairment on the PK of Oncaspar has not been evaluated. As pegaspargase is a protein with a high molecular weight, it is not excreted renally, and no change of pharmacokinetic of Oncaspar in patients with renal impairment is foreseen.

Since the proteolytic enzymes responsible for Oncaspar metabolism are ubiquitously distributed in tissues the exact role of the liver is unknown: however any decrease in liver function is not expected to present clinical relevant problems in the use of Oncaspar.

There are no data available for elderly patients.

5.3 Preclinical safety data

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

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

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

Repeated dose toxicity
A 4-week study in rats treated with a dose of pegaspargase of 400 U/kg/day 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 temporary suppression in body weight gains and a temporary reduction in total leukocyte counts were observed in dogs which were treated with pegaspargase 1200 U/kg weekly for 2 weeks. Increased serum glutamic pyruvic transaminase activity also occurred in one out of four dogs.

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

Disodium phosphate heptahydrate
Sodium dihydrogen phosphate monohydrate
Sodium chloride
Sucrose
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

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

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

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

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

Pack size of 1.

6.6 Special precautions for disposal and other handling

This medicinal product can cause irritation on contact. The powder must therefore be handled and administered with particular caution. Inhalation of the vapour and contact with the skin and mucous membranes, especially the eyes, must be avoided; if the medicinal product comes in contact with eyes, skin or mucous membranes, rinse immediately with plenty of water for at least 15 minutes.

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

Instructions for handling

1. Staff should be trained in how to handle and transfer the medicinal product (pregnant staff should be excluded from working with this medicinal product).
2. Aseptic technique must be used.
3. Procedures for proper handling of antineoplastic agents should be observed.
4. The use of disposable gloves and protective garments is recommended when handling Oncaspar.
5. All items for administration or cleaning, including gloves, should be placed in high-risk waste disposal bags for high-temperature incineration.

Reconstitution

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

Administration

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

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

SINXXXXP

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