ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Enrylaze 10 mg/0.5 mL solution for injection/infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 0.5 mL solution of 10 mg of recombinant crisantaspase*

The amino acid sequence is identical to native L-asparaginase from *Erwinia chrysanthemi* (also known as crisantaspase).

An *in-vitro* activity assay demonstrated that 1 mg of recombinant crisantaspase approximates 1 000 U of native crisantaspase, consistent with the *in-vivo* comparisons from clinical trials. Serum asparaginase activity (SAA) exposures (C_{max}, concentration at 48h & 72h and AUC) have been shown to be comparable for 25 mg/m^2 recombinant crisantaspase and 25 000 U/m^2 native crisantaspase, when administered intravenously or intramuscularly in healthy subjects.

*recombinant *Erwinia chrysanthemi* L-asparaginase produced in *Pseudomonas fluorescens* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear to opalescent, colourless to slightly yellow solution with a pH of 7.0 ± 0.5 and an osmolality: 290–350 mOsmol/Kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Enrylaze is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL) in adult and paediatric patients (1 month and older) who developed hypersensitivity or silent inactivation to *E. coli*-derived asparaginase.

4.2 Posology and method of administration

Enrylaze should be prescribed and administered by physicians and healthcare personnel experienced in the use of antineoplastic products. Appropriate resuscitation equipment and other agents necessary to treat anaphylaxis should be available when administering Enrylaze.

Posology
The recommended dose of Enrylaze is:

- Every 48 hours
    - 25 mg/m^2 intramuscularly or intravenously

Or

- Monday/Wednesday/Friday
    - 25 mg/m^2 intramuscularly on Monday and Wednesday, and 50 mg/m^2 intramuscularly on Friday; or
    - 25 mg/m^2 intravenously on Monday and Wednesday, and 50 mg/m^2 intramuscularly on Friday; or
    - 25 mg/m^2 intravenously on Monday and Wednesday, and 50 mg/m^2 intravenously on Friday

Recommended premedication
A consideration to premedicate patients with paracetamol, an H1 receptor blocker, and an H2 receptor blocker 30–60 minutes prior to administration should be made when Enrylaze is being given intravenously to decrease the risk and severity of infusion related reaction/hypersensitivity reaction.

Recommended monitoring
Asparaginase activity can vary between individuals, therefore trough SAA should be monitored. When administered every 48 hours a trough asparaginase activity measurement should be performed at 48 hours post dose. When dosing on a Monday/Wednesday/Friday schedule, trough SAA should be measured 72 hours after the Friday dose and prior to administration of the following Monday dose. The dosing schedule or route of administration should then be individually adapted (see section 4.4).

Therapy can be further adjusted according to local treatment protocols.

The dose of Enrylaze is administered in mg/m^2 and is not administered in units/m^2, as used for other asparaginase preparations. Enrylaze is not interchangeable with other crisantaspase products to complete a cycle of treatment.

Special populations
Hepatic impairment
Dose adjustment is not required for patients that develop total bilirubin ≤ 3 times the Upper Limit of Normal (ULN) during treatment.

Enrylaze should be withheld if total bilirubin is > 3 times to ≤ 10 times the ULN during treatment, treatment can continue once resolved. In the event of a severe occurrence (total bilirubin > 10 times the ULN), treatment should be stopped and patients not rechallenged (see section 4.4).

Dose adjustment is not required for patients with pre-existing mild or moderate hepatic impairment (total bilirubin > 1 to 3 times the ULN or AST greater than the ULN). There are insufficient data in patients with pre-existing severe hepatic impairment to support a dose recommendation.

Renal impairment
There are insufficient data in patients with mild, moderate or severe renal impairment to support a dose recommendation.

Paediatric population
No dose adjustment is required in paediatric patients.

The safety and efficacy of children aged younger than 1 month has not yet been established.

Elderly
No dose adjustment is required in elderly patients.

Method of administration
Enrylaze is for intramuscular and/or intravenous use.

For intramuscular use, limit the volume of Enrylaze at a single injection site to 2 mL for patients with

a body surface area (BSA) > 0.5 m^2, for patients with a BSA < 0.5 m^2 limit the volume to 1 mL. If the volume to be administered is greater than the mentioned limits, use multiple injection sites.

For intravenous infusion, it is recommended to administer the dose over 2 hours.

For instructions on dilution of the medicinal product before intravenous administration, see section 6.6.

4.3 Contraindications

- History of severe hypersensitivity reactions to the active substance
- Hypersensitivity to any of the excipients listed in section 6.1
- Severe pancreatitis
- History of severe pancreatitis during previous asparaginase therapy
- Severe thrombosis during previous asparaginase therapy
- Severe haemorrhagic events during previous asparaginase therapy

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.

Clinical monitoring
Asparaginase activity
SAA varies substantially between patients, when treatment is administered intravenously. The optimal SAA level is ≥ 0.1 U/mL; if this is not observed the dosing schedule should be individually adapted. When administering Enrylaze intravenously on a Monday/Wednesday/Friday schedule, trough SAA levels should be measured 72 hours after the Friday dose and prior to the following Monday administration. If SAA levels ≥ 0.1 U/mL are not observed, administration of intramuscular Enrylaze or switching to a 48-hour dosing interval (intravenous or intramuscular) should be considered. If SAA levels are monitored at 48-hour intervals of intravenous Enrylaze administration and SAA levels ≥ 0.1 U/mL are not observed, administration intramuscularly should be considered (see section 4.2).

Hypersensitivity reactions
Grade 3 and 4 hypersensitivity reactions after the use of Enrylaze have occurred in patients during clinical trials (see sections 4.3 and 4.8). Hypersensitivity reactions may occur more frequently when treatment is administered intravenously in comparison to when treatment is administered intramuscularly.

Because of the risk of serious allergic reactions, Enrylaze should be administered in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. Enrylaze should be discontinued in patients with severe hypersensitivity reactions (see section 4.3).

Pancreatitis
Pancreatitis has been reported in patients treated with Enrylaze in clinical trials (see section 4.8). Patients with symptoms compatible with pancreatitis should be evaluated to establish a diagnosis.

Enrylaze should be discontinued in patients that develop necrotising or haemorrhagic pancreatitis.

In the case of elevations in lipase or amylase > 2 times the ULN or symptomatic pancreatitis, Enrylaze should be withheld until the ULN and symptoms subside. After resolution of pancreatitis, treatment with Enrylaze may be resumed.

Glucose intolerance
Cases of glucose intolerance have been reported in patients receiving Enrylaze in clinical trials (see section 4.8). Glucose levels in patients should be monitored at baseline and periodically during treatment. Insulin therapy should be administered as necessary in patients with hyperglycaemia.

Coagulation disorders
Thrombotic and bleeding events, including sagittal sinus thrombosis and pulmonary embolism have been reported with L-asparaginase therapy. Enrylaze treatment should be held for a thrombotic or haemorrhagic event until symptoms resolve; after resolution, treatment with Enrylaze may be resumed.

Hepatotoxicity
Therapy that includes Enrylaze can cause hepatotoxicity as experienced during clinical trials (see section 4.8).

Patients should be monitored for signs and symptoms of hepatotoxicity. Bilirubin and transaminases should be monitored prior to treatment and as clinically required during treatment with Enrylaze. In the event of severe liver toxicity, treatment with Enrylaze must be discontinued and supportive care provided.

Neurotoxicity
Central nervous system (CNS) toxicity, including encephalopathy, seizures and CNS depression as well as posterior reversible encephalopathy syndrome (PRES) may occur during treatment with any asparaginase therapy.

PRES may occur rarely during treatment with any asparaginase. This syndrome is characterised in magnetic resonance imaging (MRI) by reversible (from a few days to months) lesions/oedema, primarily in the posterior region of the brain. Symptoms of PRES essentially include elevated blood pressure, seizures, headaches, changes in mental state and acute visual impairment (primarily cortical blindness or homonymous hemianopsia).

It is unclear whether the PRES is caused by asparaginase, concomitant treatment or the underlying diseases. PRES is treated symptomatically, including measures to treat any seizures. Discontinuation or dose reduction of concomitantly administered immunosuppressive medicinal products may be necessary. Expert advice should be sought.

Contraception
Contraception should be used during treatment and for 3 months after receiving the final dose of Enrylaze. Women should also undergo pregnancy testing before therapy with Enrylaze is initiated. Since an indirect interaction between oral contraceptives and Enrylaze cannot be ruled out, patients of childbearing potential should use effective non-hormonal contraceptive methods while undergoing treatment (see section 4.6).

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

General
The possibility of interactions with medicinal products whose pharmacokinetics or pharmacodynamics are affected by asparaginase-induced changes in the liver function or plasma protein levels should be taken into account when administering asparaginase. Asparaginase may increase toxicity of other medicinal products through its effect on liver function.

Vincristine
Administration of asparaginase concurrently or immediately before vincristine may be associated with increased toxicity of vincristine. Asparaginase inhibits hepatic clearance of vincristine.

Methotrexate, cytarabine
Non-clinical data indicates that prior or concurrent administration of L-asparaginase attenuates the effect of methotrexate and cytarabine. Administration of L-asparaginase after methotrexate or cytarabine results in a synergistic effect. However, the clinical effect of sequence-dependent L-asparaginase administration on the efficacy of methotrexate and cytarabine is unknown.

Glucocorticoids
Administration of asparaginase with or immediately before glucocorticoids (e.g. prednisone) may change coagulation parameters, such as a decrease in fibrinogen and antithrombin III levels.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Men and women should use contraception during treatment with Enrylaze containing chemotherapy. Because the time period following treatment with asparaginase when it is safe to become pregnant or father a child is unknown, effective contraception should be used in men and women for at least 3 months after discontinuation. Since an indirect interaction between oral contraceptives and Enrylaze cannot be ruled out, patients of childbearing potential should use effective non-hormonal contraceptive methods while undergoing treatment (see section 4.4).

Pregnancy
There are no data on the use of recombinant crisantaspase in pregnant women. Based on studies with *Erwinia chrysanthemi* L-asparaginase in pregnant animals, recombinant crisantaspase can cause embryonic and foetal harm when administered to a pregnant woman (see section 5.3).

Women of childbearing potential should undergo pregnancy testing before initiation of Enrylaze. Enrylaze should not be used during pregnancy, unless the clinical condition of the woman requires treatment and justifies the potential risk to the foetus. If the medicinal product is used during pregnancy, or if the patient becomes pregnant while receiving Enrylaze, the woman should be informed of the potential hazard to the foetus.

Breast-feeding
It is not known whether recombinant crisantaspase is excreted in human milk. Because of the potential for serious adverse reactions in breast-feeding infants/children, mothers should be advised not to breast-feed during Enrylaze therapy and for a period of two weeks after the last dose.

Fertility
No human data on the effect of recombinant crisantaspase on fertility are available. In a fertility and early embryonic development study in rats with *Erwinia chrysanthemi* crisantaspase, there were no effect on female or male fertility (margins of human exposure < 1) (see section 5.3).

4.7 Effects on ability to drive and use machines

Enrylaze has minor influence on the ability to drive and use machines. This influence is based on the adverse reactions that may occur during treatment (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Serious adverse reactions occurred in 59% of patients who received Enrylaze in a clinical trial. The most frequent serious adverse reactions were febrile neutropenia (29%), pyrexia (10%), vomiting (8%), sepsis (7%), medicinal product hypersensitivity (6%), nausea (6%), and pancreatitis (5%).

The most common adverse reactions were anaemia (52%), vomiting (49%), thrombocytopenia (42%), neutropenia (41%), nausea (38%), febrile neutropenia (32%), fatigue (32%), pyrexia (32%), decreased appetite (29%), transaminase increased (29%), abdominal pain (27%), white blood cell count decreased (27%), headache (25%), diarrhoea (22%), and lymphocyte count decreased (20%).

Tabulated list of adverse reactions

Adverse reactions reported in clinical trial are listed in Table 1 by system organ class and by frequency. The frequencies identified are from patients (n=228) who received 6 doses of Enrylaze, along with a multi-agent chemotherapeutic regimen. Certain adverse reactions listed below, such as reactions resulting from bone marrow suppression, and infections, are known to be associated with multi-agent chemotherapeutic regimens, and the contributory role of Enrylaze is not clear. In individual cases of adverse reactions, other medicinal products of the regimen may have contributed.

Frequencies are defined as: 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); 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 in patients receiving Enrylaze with multi-agent chemotherapy (Study JZP458-201)

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Sepsis
Blood and lymphatic system disorders	Very common	Anaemia, Thrombocytopenia, Neutropenia, Febrile neutropenia
Immune system disorders	Very common	Drug hypersensitivity
	Common	Anaphylactic reaction, Hypersensitivity
Metabolism and nutrition disorders	Very common	Decreased appetite, Hyperglycaemia, Hypoalbuminemia
	Common	Hypertriglyceridemia, Hypoglycaemia, Hyperammonaemia
Psychiatric disorders	Very common	Anxiety
	Common	Irritability
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Superior sagittal sinus thrombosis
Vascular disorders	Common	Hypotension
	Uncommon	Jugular vein thrombosis, Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	Common	Pulmonary embolism
Gastrointestinal disorders	Very common	Vomiting, Nausea, Abdominal pain, Diarrhoea
	Common	Pancreatitis
Skin and subcutaneous tissue disorders	Common	Rash maculo-papular, Pruritus, Rash, Urticaria, Rash erythematous,
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity

General disorders and administration site conditions	Very common	Fatigue, Pyrexia
	Common	Injection site pain, Injection site reaction
Investigations	Very common	Transaminases increased, White blood cell count decreased, Lymphocyte count decreased, Weight decreased, Blood bilirubin increased
	Common	Blood creatinine increased , Activated partial thromboplastin time prolonged, Blood fibrinogen decreased, Antithrombin III decreased
Injury, poisoning and procedural complications	Very common	Contusion
	Common	Infusion-related reaction

Description of selected adverse reactions

Hypersensitivity

Hypersensitivity reactions were reported adverse reactions in the Enrylaze clinical trial. The incidence of medicinal product hypersensitivity was 11% and it was severe in 8% of patients. The incidence of anaphylactic reaction was 2%, and it was severe in all patients. Overall hypersensitivity reactions observed more frequently in patients who received Enrylaze intravenously. The frequency of hypersensitivity reactions leading to discontinuation was 10% (see section 4.4).

Pancreatitis

Cases of pancreatitis including life threatening cases have been reported in the Enrylaze clinical trial. The incidence of pancreatitis was 7%; the incidence of serious events of pancreatitis was 5%; the incidence of life-threatening pancreatitis was 1%. One patient developed pancreatic pseudocyst after acute pancreatitis, which resolved without sequelae. The frequency of pancreatitis in Study JZP458-201 which led to discontinuation was 5% (see section 4.4).

Adults and other special populations

Although the safety profile of adults above 25 years of age has not been studied, some adverse reactions, such as hepatotoxicity, thrombosis, and pancreatitis, have been reported more frequently in adults with acute lymphoblastic leukemia receiving other asparaginases than in paediatric patients.

Immunogencity

It has been reported that there is no to little cross reactivity between crisantaspase and other *E. coli* derived asparaginase.

As with all therapeutic proteins, there is a potential for immunogenicity. Immunogenicity assays are highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as assay methodology, sample handling, timing of sample collection, concomitant treatment, and underlying disease. For these reasons, comparison of the incidence of antibodies to Enrylaze with the incidence of antibodies to other products may be misleading.

Analysis of patients receiving Enrylaze by either intramuscular injection (n=167) or intravenous infusion (n=61) showed that 116 of 228 (51%) patients had confirmed positive anti-drug antibodies (ADA) toward Enrylaze, 8 (7%) of these were ADA positive at pre dose 1.

A total of 23 (20%) patients who had ADAs experienced hypersensitivity reactions of which 6 (5%) had neutralising antibodies. Of the negative ADA patients 7/112 (6%) experienced a hypersensitivity reaction.

During the course of treatment 73 (63%) patients became ADA negative at least once.

Intravenous infusion

- A total of 34 (56%) patients were found to be ADA positive.
- 1 patient was ADA positive at pre dose 1.
- 33 patients developed ADA toward Enrylaze following administration of Enrylaze. 18 of these patients subsequently became ADA negative at least once during the study.
- 12 (35%) experienced hypersensitivity reactions during the study, and of these patients 2 had neutralising antibodies. Of the negative ADA patients 4/27 (15%) experienced a hypersensitivity reaction.

Intramuscular injection

- A total of 82 (49%) patients were found to be ADA positive.
- 7 patients were ADA positive at pre dose 1.
- 75 patients developed ADA toward Enrylaze following administration of Enrylaze. 55 of these patients subsequently became ADA negative at least once during the study.
- 11 (13%) patients experienced hypersensitivity reactions, and of these patients 4 had neutralising antibodies. Of the negative ADA positive patients 7/85 (8%) experienced a hypersensitivity reaction.

The presence of ADA does not appear to correlate with the occurrence of hypersensitivity reactions. SAA levels were not impacted for applicable ADA positive patients as they maintained SAA levels ≥ 0.1 U/mL at all available 48- and 72-hour time points during Course 1. No impact on the pharmacokinetics of Enrylaze was observed and ADA status was not found to be a significant factor in population pharmacokinetic analysis.

Paediatric population

The majority of the patients in Study JZP458-201 were children < 18 years old 197/228 (86%) and therefore a comparison of frequency and severity in adverse reactions versus other age groups is not suitable.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of Enrylaze overdose with clinical symptoms has been reported and there is no specific antidote. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents ATC code: L01XX02.

Mechanism of action

Asparaginase is an enzyme that catalyses the conversion of the amino acid L-asparagine into L-aspartic acid and ammonia. The pharmacological effect of Enrylaze is based on the killing of leukemic cells due to depletion of plasma asparagine. Leukemic cells with low expression of asparagine synthetase have a reduced ability to synthesize asparagine, and therefore is dependent on an exogenous source of asparagine for survival.

Clinical efficacy and safety

The efficacy and safety of Enrylaze was determined in the clinical trials, an open-label, two-part, multi-cohort, multi-centre, multi-agent chemotherapeutic trial that treated 228 adult and paediatric

patients with ALL or LBL who developed hypersensitivity to a long-acting *E. coli*-derived asparaginases. The median age of patients was 10 years (range, 1 to 25 years).

Prior long-acting *E. coli*-derived asparaginase treatments included pegaspargase for all patients apart from one who received other type of *E. coli*-derived asparaginase. In Study JZP458-201, 190 (83%) patients experienced a hypersensitivity (Grade ≥ 3) to a long-acting *E. coli*-derived asparaginases, 15 (7%) patients experienced silent inactivation, and 23 (10%) patients experienced an allergic reaction with inactivation. The number of courses of Enrylaze received ranged from 1 to 15.

Patients received 6 doses of Enrylaze, either intramuscularly at 25 mg/m^2 or 37.5 mg/m^2 three times a week (Monday/Wednesday/Friday), or 25 mg/m^2 on Monday and Wednesday then 50 mg/m^2 on Friday by intravenous infusion or an intramuscular injection as a replacement for each dose of *E. coli* derived asparaginase remaining on a patient's treatment plan.

The determination of efficacy was based on demonstration of the achievement and maintenance of nadir serum asparaginase activity (NSAA) levels ≥ 0.1 U/mL. Serum trough asparaginase activity ≥ 0.1 U/mL has been demonstrated to correlate with asparagine depletion that predicts clinical efficacy (see section 5.2).

Observed NSAA levels during the clinical trials for indicated dosing schedules are presented in Table 2.

Table 2: Observed NSAA levels ≥ 0.1 U/mL during the clinical trials

Time Point	**Intramuscularly 25 (MW)/ 50 (F) mg/m^2**	**Intravenously 25 (MW)/ 50 (F) mg/m^2**
Last 48-hour	95.9% [90.4%, 100.0%]	89.8% [82.1%, 97.5%]
Last 72-hour	89.8% [81.3%, 98.3%]	40.0% [26.4%, 53.6%]

MW=Monday, Wednesday
MWF=Monday, Wednesday, Friday

The other recommended dosing schedules are based on interpolation from pharmacokinetic (PK) and response rates observed with the very similar investigated regimens.

Paediatric population
No clinically significant difference is expected in probability of achieving a therapeutic NSAA ≥ 0.1 U/mL based on age (1 month to 39 years) following the proposed Body surface area (BSA)-based dosing regimens.

5.2 Pharmacokinetic properties

The PK of Enrylaze was determined based on SAA. Patients received 6 doses of Enrylaze at various doses intramuscularly on Monday, Wednesday and Friday or 25 mg/m^2 administered intramuscularly or intravenously on Monday and Wednesday and 50 mg/m^2 on Friday as a replacement for each dose of a long-acting *E. coli*-derived asparaginase remaining on their original treatment plan. Recombinant crisantaspase maximum SAA (C_{max}) and area under the SAA-time curve (AUC) increase approximately proportionally over a dose range from 12.5 to 50 mg/m^2. The trough SAA at 48-hour ($C_{trough,48}$) or 72-hour ($C_{trough,72}$) post the last dose for recombinant crisantaspase are summarised in Table 3.

Table 3: Enrylaze pharmacokinetic parameters based on SAA

PK Parameter[a]	Mean (95% CI) after last dose			
	25/25/50 mg/m^2 Monday, Wednesday, Friday		25/25/50 mg/m^2 Monday, Wednesday, Friday	
	Intramuscularly		Intravenously	
$C_{trough,48}$ (U/mL)	N =49	0.66 (0.54-0.77)	N = 59	0.25 (0.20-0.29)
$C_{trough,72}$ (U/mL)	N=49	0.47 (0.35-0.59)	N =50	0.10 (0.07-0.13)

[a]: $C_{trough,48}$: Trough SAA at 48 hour post the last 25 mg/m^2 dose in cycle 1; $C_{trough,72}$: Trough SAA at 72 hour post the last 50 mg/m^2 dose in cycle 1.

Absorption
The median T_{max} of recombinant crisantaspase is 16 hours following intramuscular administration. The mean absolute bioavailability for intramuscular administration is 38%.

Distribution
Following intravenous administration, the geometric mean (%CV) volume of distribution of recombinant crisantaspase is 1.75 L/m^2 (14%).

Biotransformation
Recombinant crisantaspase is expected to be metabolized into small peptides by catabolic pathways.

Elimination
Following intravenous administration, the geometric mean (%CV) clearance of recombinant crisantaspase is 0.14 L/hour/m^2 (20%).

The geometric mean (%CV) half-life is 8.6 hours (13%) following intravenous administration and 18.8 hours (11%) following intramuscular administration.

Special populations
Renal and hepatic impairment
There was no dedicated study on renal or hepatic impairment with Enrylaze.

During treatment dose adjustment is not required for patients with total bilirubin ≤ 3 times the Upper Limit of Normal; there is limited data with Enrylaze in patients with total bilirubin > 3 times to ≤ 10 times the ULN.

Dose adjustment is not required for patients with pre-existing mild or moderate hepatic impairment (total bilirubin > 1 to 3 times the ULN or AST > than the ULN). There are insufficient data in patients with pre-existing severe hepatic impairment to support a dose recommendation.There are insufficient data in patients with mild, moderate or severe renal impairment to support a dose recommendation.

Age, weight, body surface area and sex
There were no clinically significant differences in the pharmacokinetics of Enrylaze based on weight (9 to 131 kg) or sex (n=138 male; n=88 female) after the dose was adjusted by body surface area (BSA).

The volume of distribution and clearance of recombinant crisantaspase increase with increasing BSA (0.44 to 2.53 m^2).

Age impacts absorption rate constant whereas younger subjects have higher absorption rate constant value, leading to earlier T_{max}.

Race
Black or African American patients (n=24) had 25% lower clearance which may increase SAA exposure compared to population average (n=226). No dose adjustment is needed in African American population. There were no clinically significant differences in clearance between Hispanic (n=73) and Non-Hispanic (n=139) patients.

Neutralising antibodies
As with other asparaginase preparations, development of specific neutralising antibodies were identified with repeated dosing.

5.3 Preclinical safety data

In a study, recombinant crisantaspase was administered intravenously to groups of rats for up to 14 consecutive days. Adverse effects in naïve animals, which were typical for asparaginases, were noted at exposures greater than 3.6 times the maximum human exposure.

Carcinogenicity, mutagenicity, and reproductive toxicity studies have not been conducted with Enrylaze.

In embryofoetal development studies in rats and rabbits, *Erwinia chrysanthemi* L-asparaginase produced maternal toxicity, increased resorptions, post implantation loss, embryofoetal toxicity, and/or gross abnormalities at exposures lower than those observed clinically (margins of exposure < 1).

In rat fertility and pre- and post-natal development studies with *Erwinia chrysanthemi* L-asparaginase, there were no adverse effects on fertility or development, but the exposures were lower than those observed clinically (margins of exposure < 1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
Sodium chloride
Sodium hydroxide (for pH adjustment)
Disodium phosphate
Sodium dihydrogen phosphate monohydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. This includes infusion of other medicinal products using the same infusion line as Enrylaze.

6.3 Shelf life

Unopened vial
3 years.

In-use stability data
From a microbiological point of view, unless the method of opening/dilution 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.

Intramuscular preparation
Chemical and physical in-use stability for intramuscular preparations in a polypropylene syringe has been demonstrated for up to 8 hours at room temperature (15 °C–25 °C) or 24 hours when refrigerated (2 °C–8 °C).

Intravenous preparation
Chemical and physical in-use stability for intravenous preparations has been demonstrated for up to 12 hours at room temperature (15 °C–25 °C) or 24 hours when refrigerated (2 °C–8 °C). The storage times start from withdrawing the required volume from the unopened vials. The storage time in the polyethylene inner lined intravenous bag includes the 2-hour administration time (see section 6.6).

6.4 Special precautions for storage

Store in a refrigerator (2 °C–8 °C) in an upright position.

Keep the vial in the outer carton in order to protect from light.

Do not freeze.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 mL Type 1 clear borosilicate glass vial sealed with a halobutyl rubber stopper and aluminium overseal and a violet plastic cap.

Pack size: 3 vials.

6.6 Special precautions for disposal and other handling

Precautions
Compatibility has been demonstrated in the following materials. No other materials have been studied.
- Syringes made of polypropylene
- Intravenous infusion sets made of PVC, polyolefin, polyamide, and ethylene vinyl acetate

Preparation instructions
- Determine the posology, and number of vials of Enrylaze based on the individual patient's BSA as outlined in section 4.2. More than one vial may be needed for a full dose
- Remove the appropriate number of vials of Enrylaze from the refrigerator
    - Do not shake the vials
    - Each vial should be inspected for particles. If particles are observed and/or the liquid in the vial is not clear, the vial must not be used
- Withdraw the required volume of Enrylaze into a syringe

Subsequent steps for intravenous infusion preparation
- The prepared dose of Enrylaze in the syringe should be further diluted in an infusion bag containing 100 mL of sodium chloride 9 mg/mL (0.9%) solution for injection
- The intravenous infusion prepared dose should be a clear liquid free from visual particulates.
    - If particles are observed in the intravenous infusion prepared dose, the solution must not be used
    - The start of storage mentioned starts from withdrawing the required volume from the vial (see section 6.3)
    - The 12- or 24-hour storage time includes the recommended 2-hour infusion time

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

7. MARKETING AUTHORISATION HOLDER

Jazz Pharmaceuticals Ireland Ltd
5th Floor
Waterloo Exchange
Waterloo Road
Dublin 4
D04 E5W7
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1747/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer of the biological active substance

AGC Biologics, Inc. (legal name CMC Biologics, Inc.)
Vandtaarnsvej 83B Soeborg
Copenhagen DK-2860
Denmark

Name and address of the manufacturer responsible for batch release

Jazz Pharmaceuticals Ireland Ltd
5th Floor
Waterloo Exchange
Waterloo Road
Dublin 4
D04 E5W7
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European Medicines web-portal.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Enrylaze 10 mg/0.5 mL solution for injection/infusion
recombinant crisantaspase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 0.5 mL solution of 10 mg of recombinant crisantaspase.

3. LIST OF EXCIPIENTS

Trehalose dihydrate, sodium chloride, sodium hydroxide (for pH adjustment), disodium phosphate, sodium dihydrogen phosphate monohydrate, polysorbate 80, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection/infusion
3 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous or intramuscular use.
Do not shake.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Store in an upright position.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jazz Pharmaceuticals Ireland Ltd
5th Floor
Waterloo Exchange
Waterloo Road
Dublin 4
D04 E5W7
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1747/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

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

Enrylaze 10 mg/ 0.5 mL injection/infusion
recombinant crisantaspase
IV or IM IV/IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Enrylaze 10 mg/0.5 mL solution for injection/infusion
recombinant crisantaspase

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

Read all of this leaflet carefully before you start receiving this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Enrylaze is and what it is used for
2. What you need to know before you are given Enrylaze
3. How Enrylaze is given
4. Possible side effects
5. How Enrylaze is stored
6. Contents of the pack and other information

1. What Enrylaze is and what it is used for

Enrylaze contains the active substance recombinant crisantaspase. It is a medicine used alongside other medicines to treat acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL). Enrylaze can be given to patients aged 1 months of age or older.
Enrylaze contains a protein made in the laboratory by recombinant DNA technology. This protein works by decreasing the amount of a protein called asparagine. This protein is needed by the ALL and LBL cancer cells to survive.

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

You should not receive Enrylaze
- if you have a severe allergic reaction to Enrylaze.
- if you have an allergic reaction to any of the other ingredients of this medicine (listed in section 6).
- if you are currently experiencing severe pancreatitis (inflammation of the pancreas).
- if you have experienced severe pancreatitis after being treated with asparaginase therapies.
- if you have experienced serious blood clots after being treated with asparaginase therapies.
- if you have experienced serious bleeding events after being treated with asparaginase therapies.

Warnings and precautions
Talk to your doctor or pharmacist before you receive Enrylaze.

The following problems may occur during treatment with Enrylaze:
- serious allergic reactions that may be life threatening. The hospital will ensure they are prepared to address any allergic reactions that may occur during treatment.

- inflammation of your pancreas. Discomfort or pain in your stomach or back area may be a sign of pancreatitis and should be reported to your doctor straight away.
- changes in your body's ability to manage blood sugar levels. Your doctor should monitor your glucose levels whilst on treatment and provide insulin if necessary.
- unusual bleeding events or blood clots. If either of these events occur treatment will be paused by your doctor until they are resolved.
- issues with your liver. Your doctor will monitor you to identify if you are experiencing any issues with your liver and treat you as necessary.
- central nervous system toxicity, such as seizures and impaired neurological function. Also, instances of posterior reversible encephalopathy syndrome (characterised by headache, confusion, seizures and loss of vision) may require blood-pressure lowering medicines and in case of seizure, treatment with anti-epileptic medicines.

Monitoring during treatment with Enrylaze
You will be monitored during and after treatment with Enrylaze for:
- allergic reactions
- functioning of your pancreas and liver
- blood sugar levels

Other medicines and Enrylaze
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular inform your doctor or pharmacist if you have or are receiving:
- methotrexate or cytarabine, used in cancer treatment. Use of these medicines immediately before Enrylaze may increase their effect.
- vincristine, used in cancer treatment. Use of vincristine with Enrylaze may increase the toxicity of vincristine.
- glucocorticoids, used as anti-inflammation medicines. Use of these medicines immediately before Enrylaze may increase the formation of blood clots.

Pregnancy
Enrylaze should not be used during pregnancy, and women should check they are not pregnant prior to starting therapy. If you are pregnant or think you may be pregnant, ask your doctor or pharmacist for advice before receiving this medicine.

Breast-feeding
You should not breast-feed during treatment and for two weeks following treatment with Enrylaze, as there may be a risk to the breast-feeding child.

Family planning
Both men and women should use a form of contraception and avoid conceiving a child during treatment with Enrylaze and for 3 months after you last receive Enrylaze. Hormonal contraceptives are not recommended for use in women when being treated with Enrylaze.

Women should undergo pregnancy testing before starting treatment.

Driving and using machines
Enrylaze can cause you to feel sick and have a headache. This may impact your ability to drive and operate machines.

Enrylaze contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose unit, that is to say essentially 'sodium free'.

3. How Enrylaze is given

Your doctor will determine what dose you are given and whether it will be given to you by an infusion into your veins or an injection into your muscle. You may also be given some other medicines before you start receiving Enrylaze, such as paracetamol, H1 and H2 blocker.

The dose and how it is given may vary depending on your specific condition, body surface area and response to therapy.

If you are given Enrylaze into your veins, this will be given over a 2-hour period. If you are given Enrylaze into a muscle, several injection sites may be used.

If you think you have been given more Enrylaze than you should
If you have any concerns, contact your doctor or any healthcare professional immediately.

If you think you have missed a dose of Enrylaze
If you have any concerns, contact your doctor or any healthcare professional immediately.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. For patients treated with Enrylaze the following side effects were reported.

Serious side effects
Tell your doctor immediately if you experience:
Symptoms of a serious allergic reaction, including swelling of the face, shortness of breath, hay fever like symptoms, rash, chills, wheezing, flushing, vomiting, high or low blood pressure. In severe cases anaphylaxis (a sudden, severe allergic reaction with breathing difficulty, swelling, light-headedness, fast heartbeat, sweating and loss of consciousness) can also occur.

Symptoms of blood clots, including in the blood vessels of the lung which could present as sudden shortness of breath, chest pain, or coughing up blood and the blood vessels of the brain which could present with symptoms such as weakness/numbness, seizure, trouble speaking, or severe headache.

Symptoms of pancreatitis, including abdominal pain, nausea, vomiting, back pain, or loss of appetite.

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

Very common side effects (may affect more than 1 in 10 people):
- allergic reaction, including rash, itching, and hives
- infections
- low levels of red blood cells (anaemia)
- low levels of blood platelets (thrombocytopenia)
- low levels of white blood cells (white blood cell count decreased)
- low levels of neutrophils, a type of white blood cell that fights off infection (neutropenia)
- low levels of white blood cells (neutrophils) with fever due to infection (febrile neutropenia)
- low levels of lymphocytes, a type of white blood cell that fights off infection (lymphocyte count decreased)
- pain in your stomach (abdominal pain)
- diarrhoea
- feeling sick (nausea)
- vomiting
- tiredness (fatigue)
- fever (pyrexia)

- high blood sugar levels (hyperglycaemia)
- pain in limbs (pain in extremity)
- weight loss (weight decreased)
- headache
- decreased appetite
- abnormal liver function test (transaminases increased, blood bilirubin increased)
- decreased albumin (a blood protein) level (hypoalbuminaemia)
- anxiety
- bruising (contusion)

Common side effects (may affect up to 1 in 10 people):
- blood poisoning (sepsis)
- sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating and loss of consciousness (anaphylactic reaction)
- skin rash characterized with flat, discolored patches (macules) and raised, reddened bumps (papules) (rash maculo-papular)
- skin rash with redness and inflamation (rash erythematous)
- hives (urticaria)
- itchy skin (pruritus)
- inflammation of the pancreas (pancreatitis)
- injection site pain
- injection site reaction
- infusion related reactions
- abnormal blood clotting factor levels (prolonged activated partial thromboplastin time, decreased antithrombin III, decreased blood fibrinogen)
- abnormal kidney function (increased blood creatinine)
- low blood sugar levels (hypoglycaemia)
- low blood pressure (hypotension)
- blood clots, including in the blood vessels of the lung and brain
- irritability
- dizziness

Uncommon side effects (may affect up to 1 in 100 people)
- blood clot in a major brain vein (superior sagittal sinus thrombosis)
- blood clot in the neck vein (jugular vein thrombosis)
- blood clot in extremity veins (deep vein thrombosis)

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

5. How Enrylaze will be stored

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

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

Store the unopened vials in a refrigerator (2 °C–8 °C) in an upright position. Do not freeze. Keep the vial in the outer carton in order to protect from light.

After preparing a dose in a syringe, Enrylaze can be stored for up to 8 hours at room temperature

(15 °C–25 °C) or 24 hours when refrigerated (2 °C–8 °C).

After dilution in an intravenous bag, Enrylaze can be stored for up to 12 hours at room temperature (15 °C–25 °C) or 24 hours when refrigerated (2 °C–8 °C). Storage time starts once the solution has been withdrawn from the unopened vials.

Do not use this medicine if you notice any particles in the solution.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enrylaze contains

- The active substance is recombinant crisantaspase. Each vial contains 10 mg of recombinant crisantaspase in 0.5 mL solution.
- The other ingredients are trehalose dihydrate, sodium chloride (see section 2 "Enrylaze contains sodium"), sodium hydroxide (for pH adjustment), disodium phosphate, sodium dihydrogen phosphate monohydrate, polysorbate 80 and water for injections.

What Enrylaze looks like and contents of the pack
Enrylaze is a clear to slightly yellow solution for injection/infusion, free from particulate matter.

One carton contains 3 glass vials, each with 0.5 mL of solution for injection/infusion.

Marketing Authorisation Holder and Manufacturer
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This leaflet was last revised in:

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.