swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Enrylaze

International non-proprietary name: crisantaspase
Pharmaceutical form: solution for injection
Dosage strength(s): 10 mg/vial
Route(s) of administration: intramuscular injection
Marketing authorisation holder: Jazz Pharmaceuticals
Marketing authorisation no.: 69073
Decision and decision date: approved on 18 April 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for crisantaspase in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 14 July 2022.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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 who developed hypersensitivity to *E. coli*-derived asparaginase.
Enrylaze is indicated in patients 1 year of age and older.

2.2.3 Requested dosage

The recommended dosage 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.

* If Enrylaze is administered intravenously on Monday/Wednesday/Friday, asparaginase levels should be checked following the Friday dose. If the target asparaginase activity is not achieved, switching to an alternative dosing regimen should be considered (see section "Warnings and Precautions").

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	25 August 2022
Formal control completed	23 September 2022
List of Questions (LoQ)	19 January 2023
Response to LoQ	19 May 2023
Preliminary decision	17 August 2023
Response to preliminary decision	18 October 2023
Labelling corrections	4 January 2024
Response to labelling corrections	23 January 2024
Final decision	18 April 2024
Decision	approval

3 Medical context

Acute lymphoblastic leukaemia and lymphoblastic lymphoma (ALL/LBL) are common forms of cancer in children but are relatively rare in adults[1]. Therapy improvements in these conditions include treating patients with standardised protocols incorporating asparaginase[2]. One asparaginase product – long-acting PEGylated *E. coli*(-derived) asparaginase – is currently authorised in Switzerland. Approximately 10% of all patients develop hypersensitivity reactions, and around 2-8% develop silent inactivation to *E. coli* asparaginase[3,4], resulting in the premature discontinuation of planned therapy with *E. coli* asparaginase. Patients who discontinue any asparaginase therapy due to toxicity are at risk of having shorter disease-free survival compared to patients who are able to receive all planned asparaginase applications[5]. Expert consensus recommends switching from *E. coli* asparaginase to *Erwinia chrysanthemi*-derived asparaginase in case of grade 2-4 hypersensitivity reactions due to low cross-reactivity between these products[6]. However, there are currently no authorised *Erwinia chrysanthemi* asparaginase products in Switzerland. Therefore, there is an unmet medical need for alternative asparaginase products in patients who develop hypersensitivity to *E. coli* asparaginase.

References:

1. KAF Kline et al. “Acute Lymphoblastic Leukemia and Acute Lymphoblastic Lymphoma: Same Disease Spectrum but Two Distinct Diagnoses”, Current Hematologic Malignancy Reports, DOI: 10.1007/s11899-021-00648-y
2. SE Sallan et al. “Influence of intensive asparaginase in the treatment of childhood non-T-cell acute lymphoblastic leukemia”, Cancer Res. 1983 Nov;43(11):5601-7.
3. Strullu M et al., “Silent hypersensitivity to *Escherichia coli* asparaginase in children with acute lymphoblastic leukemia”, Leuk Lymphoma. 2010 Aug;51(8):1464-72.
4. Tong WH et al. “A prospective study on drug monitoring of PEGasparaginase and *Erwinia* asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia”, Blood. 2014 Mar;123(13):2026-33. Epub 2014 Jan 21.
5. Gupta et al. “Impact of Asparaginase Discontinuation on Outcome in Childhood Acute Lymphoblastic Leukemia: A Report From the Children’s Oncology Group”, DOI: 10.1200/JCO.19.03024
6. W Stock et al. “Prevention and management of asparaginase/perasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel”, Leukemia and Lymphoma, December 2011; 52(12): 2237-2253

4 Quality aspects

The evaluation of the quality data in this application has been carried out in reliance on the previous regulatory decision by the FDA for the product marketed in the United States under the trade name RYLAZE. The available assessment reports were used as a basis for the quality evaluation. However, it should be noted that the FDA has approved RYLAZE for intramuscular administration only.

4.1 Drug substance

INN: crisantaspase

Molecular mass: approximately 140,000 Dalton

Molecular structure:

The drug substance is a recombinant L-asparaginase expressed in *Pseudomonas fluorescens*. The amino acid sequence of crisantaspase is identical with that of the L-asparaginase from *Dicheya dadantii* (previously known as *Erwinia chrysanthemi*). L-asparaginase catalyses L-asparagine to L-aspartic acid and ammonia. Crisantaspase is a non-disulfide bonded, tetrameric enzyme consisting of 4 identical polypeptide subunits. Assembly of the tetramer, which is composed of a dimer of dimers, occurs via noncovalent forces; only the tetramer is active.

Manufacture:

Crisantaspase is expressed intracellularly and is produced in a bioreactor. The cells are harvested by centrifugation, and the collected cell paste is lysed in a homogeniser. Product purification involves multiple chromatography steps. The enzyme is then concentrated and formulated by use of ultrafiltration and diafiltration.

The fermentation and purification processes for crisantaspase drug substance are both validated with several consecutive batches.

The clinical materials were manufactured using the intended commercial process.

The characterisation of the physicochemical and biological properties of the crisantaspase drug substance and its impurities were performed using state-of-the-art methods.

Specification:

The specifications for drug substance release and stability testing include tests and acceptance criteria, e.g., for identity, quantity, heterogeneity, purity and impurities, bacterial endotoxins, bioburden, and 2 assays for potency. The non-compendial methods have been validated in accordance with international guidelines. Batch analysis data from drug substance batches that were used for non-clinical and clinical supply, process validation, and intended for market supply were provided.

Container closure system:

The drug substance is stored in bottles made of polyethylene terephthalate and closed with a polypropylene screw cap.

Stability:

The drug substance is stored frozen. No significant changes of quality attributes were observed within the proposed shelf life under the proposed storage conditions.

4.2 Drug product

Description and composition:

The drug product is supplied as a sterile, clear to opalescent, colourless to slightly yellow, preservative-free solution for injection or infusion for intramuscular or intravenous administration.
Each single-dose vial contains 10 mg of crisantaspase in 0.5 mL nominal fill.
Prior to intravenous administration, the drug product is diluted with 100 mL of normal saline solution.

Pharmaceutical development:

All of the excipients, i.e. trehalose dihydrate, sodium chloride, anhydrous disodium phosphate, sodium dihydrogen phosphate monohydrate, polysorbate 80, and water for injection, are of compendial grade and commonly used for the formulation of biopharmaceuticals. Sodium hydroxide may be added during manufacture to adjust the pH to pH 7.0.

The same formulation has been developed for drug substance and drug product.

The clinical materials were all manufactured using the intended commercial process and formulation.

Suitability of the container closure system has been demonstrated.

Compatibility studies were conducted to establish the in-use stability of undiluted and diluted drug product with the intended materials and conditions of use.

Manufacture:

The drug product manufacturing process consists of thawing the formulated drug substance, pooling and mixing, sterile filtration and aseptic filling, stoppering and capping, visual inspection, labelling, and secondary packaging.

The drug product manufacturing process is validated with several consecutive batches. The data demonstrated consistent production.

Specification:

The specifications for drug product release and stability testing include tests and acceptance criteria, e.g. for identity, quantity, heterogeneity, purity and impurities, bacterial endotoxins, sterility (stability: container closure integrity), and 2 assays for potency. The non-compendial methods have been validated in accordance with international guidelines. Batch analysis data from drug substance batches that were used for non-clinical and clinical supply, process validation, and intended for market supply were provided.

Container closure system:

The drug product is store in Type I clear glass vials with a 13 mm butyl rubber stopper and crimped with an aluminium seal with a violet plastic flip-off cap. The materials of the glass vial and the rubber stopper meet compendial requirements.

Stability:

The vials are stored at 2°C to 8°C, protected from light. The stability data support a shelf life of 36 months.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

Safety of the product with regard to non-viral contaminants is adequately addressed.

5 Nonclinical aspects

5.1 Nonclinical conclusions

Regarding the marketing authorisation application for Enrylaze (Crisantaspase), the Nonclinical Assessment Division conducted an abridged evaluation based on the assessment report submitted by the FDA (NDA BLA 761179, dated 30 June 2021).

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Enrylaze in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Safety issues that are of concern for human use were identified in the nonclinical studies. The calculated exposure multiples (safety margins) are acceptable taking into account the life-threatening nature of the disease. The Nonclinical Safety Specifications in the RMP adequately address these nonclinical findings and their relevance for clinical use. All nonclinical data that are relevant for safety are also mentioned in the information for healthcare professionals.

There is no safety concern regarding impurities and excipients.

According to the ERA provided, the risk of crisantaspase to the environment is assumed to be low.

6 Clinical aspects

6.1 Clinical pharmacology

PopPK analysis: Serum asparaginase activity (SAA) data, collected from the clinical studies JZP458-101 and JZP458-201, were combined into a population pharmacokinetics (popPK) analysis in order to support the proposed intramuscular dosing schedule for JZP-458. The final popPK database consisted of 4269 observations from 250 subjects. It was determined that a one-compartment model with first-order absorption and first-order elimination was best suited to describe the observed SAA data.

Based on simulations of SAA concentrations using the final parameter values and PK model, the proposed intramuscular dosing schedules of either 25 mg/m^2 every 48 hours or 25/25/50 mg/m^2 Monday/Wednesday/Friday (MWF) were identified to ensure that the lower bound of the 95% confidence interval (CI) of the proportion of NSAA levels $\geq$ 0.1 IU/mL meets the efficacy threshold of 90.0% or higher.

The calculated 95% confidence interval is 95.6 – 97.4% for the intramuscular dosing schedule of 25 mg/m^2 every 48 hours prior to the next dose.

For the MWF schedule the timing of the Friday dose may vary within the time window of 52 to 56 hours following the Wednesday morning dose:

- 52 hours after the Wednesday morning dose: 95% CI of 90.6 – 93.0%
- 56 hours after the Wednesday dose (i.e. 68 hours prior to the Monday morning dose): 95% CI of 90.4 – 92.8%.

In addition, following the proposed BSA-based dosing regimens, subgroup analyses suggested that no clinically significant difference is expected in the probability of achieving the NSAA $\geq$ 0.1 IU/mL threshold based on race or age, i.e. no dose adjustments are required in regard to race or age.

6.2 Dose finding and dose recommendation

Phase 1 study JZP458-101 was a randomised, single-centre, open-label study to evaluate the safety, tolerability, and pharmacokinetics (PK) of a single dose of JZP-458 (Enrylaze®) in healthy adult participants via either intravenous infusion or intramuscular drug administration. Another asparaginase product derived from *E. chrysanthemi* was included for reference (as a separate study arm). Based on the gathered Phase 1 study data, popPK modelling, and simulations, the applicant assumed that an intramuscular dose of 25 mg/m² of Enrylaze should achieve 72-hour nadir serum asparaginase activity (NSAA) levels ≥ 0.1 IU/mL in all adult and paediatric patients. The applicant used the data generated from this study to substantiate the dose rationale for the subsequent dose confirmation and pharmacokinetic (PK) Phase 2 study JZP458-201 (see below).

6.3 Efficacy

The applicant submitted results from the Phase 2 clinical study JZP458-201. This study investigated Enrylaze using different administration forms (intramuscular or intravenous) and included paediatric and adult ALL/LBL patients who developed hypersensitivity or silent inactivation to *E. coli* asparaginase therapy. The study treatment was intended to replace the remaining *E. coli* asparaginase doses according to patient's original ALL/LBL treatment protocol. The primary efficacy endpoint was the proportion of patients with 72-hour nadir serum asparaginase activity (NSAA) ≥ 0.1 IU/mL during the first cycle of intramuscular administration of Enrylaze. The efficacy threshold for the primary endpoint was met when the lower bound of the 95% confidence interval (CI) exceeded 90%. It has been demonstrated in the past that persistent NSAA levels ≥ 0.1 IU/mL correlate with clinical efficacy outcomes[1]. The applicant provided an interim clinical study report (CSR) from the July

2021 data cut-off (DCO) and a final CSR from the November 2022 database-lock (DBL). The application was assessed as part of Project Orbis.

Study JZP458-201 consisted of the following intramuscular dose cohorts:

- Cohort 1a was initiated at an intramuscular dose of 25 mg/m^2 on Mondays, Wednesdays, and Fridays (MWF) schedule over 2 weeks (further abbreviated as 25 mg/m^2 MWF). The weekly dose of this regimen is 75 mg/m^2.
- Cohort 1b was initiated at an intramuscular dose of 37.5 mg/m^2 on a MWF schedule over 2 weeks (further abbreviated as 37.5 mg/m^2 MWF). The weekly dose of this regimen is 112.5 mg/m^2.
- Cohort 1c was initiated to evaluate an intramuscular dose of 25 mg/m^2 on Mondays and Wednesdays and a dose of 50 mg/m^2 on Fridays over 2 weeks (further abbreviated as 25/25/50 mg/m^2 MWF). The weekly dose of this regimen is 100 mg/m^2.

In the intramuscular dose cohorts, a total of 167 patients received at least 1 dose of the study drug as of the final analysis, with results from the 22 November 2022 database-lock (DBL). At the final database-lock, 77.2% of patients treated via the intramuscular route had completed all planned study treatments and 22.8% of intramuscular patients had discontinued study treatment. The most common reasons for study drug discontinuation were adverse events (13.8%), physician decision (5.4%), and progressive disease (1.8%).

Thirty-three patients received at least 1 dose of Enrylaze in the 25 mg/m^2 MWF dose cohort, 83 in the 37.5 mg/m^2 MWF dose cohort, and 51 in the 25/25/50 mg/m^2 MWF dose cohort.

Regarding the 25/25/50 mg/m^2 MWF dose schedule, the lower confidence interval for the proportion of patients who achieved NSAA ≥ 0.1 IU/mL at last 72 hours was below the prespecified threshold. However, the PK simulations showed that if the Friday dose of this schedule is administered in the afternoon, the predefined threshold for efficacy can be reached. See the information for healthcare professionals for the applicant's final popPK results in the respective adapted dosing schedule.

The authorisation for the intramuscular dose of 25 mg/m² every 48 hours is based on simulated data. According to the applicant's final popPK model, the lower confidence interval for the proportion of patients who achieved NSAA ≥ 0.1 IU/mL at last 48 hours was >90%. See the information for healthcare professionals for the applicant's final popPK results in the respective dosing schedule. Further, clinically evaluated intramuscular 25/25/50 mg/m^2 MWF and 25 mg/m^2 MWF dosing schedules demonstrated that CI95% lower bounds of 48-hour NSAA were >90%.

Reference:

1. IM Van der Sluis et al. "Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation", Haematologica 2016 Volume 101(3):279-285.

6.4 Safety

The most common relevant adverse events in all patients treated with Enrylaze via the intramuscular administration route were hypersensitivity, pancreatitis, hyperglycaemia, thrombosis, and hepatotoxicity, and were consistent with known published asparaginase-related adverse events. Further details on safety signals and undesirable effects can be found in the attached information for healthcare professionals.

The updated safety results from the pivotal study of the intravenous cohort were mostly consistent with known safety signals for asparaginase. However, in the intravenous dose cohort, 52.5% of patients experienced allergic reactions and 21.3% of patients discontinued treatment due to allergic reactions. Overall, the study drug discontinuation rate due to treatment emergent adverse events was more than 2-fold higher in the intravenous dose cohort than in the intramuscular cohorts (32.8% vs 13.8%).

6.5 Final clinical benefit-risk assessment

Asparaginase is essential in treatment of ALL/LBL with curative intent. However, patients who receive *E. coli* asparaginase frequently develop allergic reactions and are unable to complete all prespecified asparaginase treatment cycles, which is associated with inferior survival outcomes. Enrylaze is a recombinant *Erwinia chrysanthemi*-derived asparaginase developed as an alternative for patients who are hypersensitive to *E. coli* asparaginase.

The pivotal study JZP458-201 evaluated the nadir serum asparaginase activity of Enrylaze. Given that the anti-leukemic effect of asparaginase is based on asparagine depletion, and that publications describe the correlation between serum asparaginase activity and asparagine depletion, the absence of a comparator arm in the pivotal study, the overall small study population size, and the selection of a pharmacokinetic endpoint as the primary efficacy endpoint in this setting are acceptable. Additional evidence to support the requested dosing schedules is generated from pre-planned modelled and simulated popPK data. The final popPK analysis demonstrated that the authorised doses met the prespecified efficacy threshold.

The reported adverse events were consistent with known published safety results for other asparaginase products. No new safety signals were identified.

The benefit-risk ratio is positive for the intramuscular 25 mg/m^2 every 48 hours and for the adapted intramuscular 25/25/50 mg/m^2 MWF dosing schedules.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Enrylaze was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

ENRYLAZE®

Composition

Active substances

crisantaspase*
The amino acid sequence is identical to native L-asparaginase from *Erwinia chrysanthemi* (also known as crisantaspase).
*recombinant *Erwinia chrysanthemi* L-asparaginase produced in *Pseudomonas fluorescens* by recombinant DNA technology.

Excipients

Trehalose dihydrate
Sodium chloride
Sodium hydroxide (pH adjustment)
Sodium phosphate dibasic anhydrous
Sodium phosphate monobasic monohydrate
Polysorbate 80
Water for injection
Contains approx. 1 mg sodium per vial.

Pharmaceutical form and active substance quantity per unit

Solution for injection
Clear to opalescent, colourless to slightly yellow solution.
One vial contains 0.5 mL solution of 10 mg of recombinant crisantaspase.
Enrylaze is for intramuscular injection.

Indications/Uses

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 who developed hypersensitivity to *E. coli*-derived asparaginase.
Enrylaze is indicated in patients 1 year of age and older.

Dosage/Administration

Usual dosage

It is recommended that Enrylaze be prescribed and administered only by physicians and other healthcare professionals familiar with the use of antineoplastic drugs. It should only be administered in a hospital where adequate resuscitation equipment is available. Patients should be closely monitored throughout the period of use and carefully observed for adverse effects (see "Warnings and Precautions").

Enrylaze is usually administered as part of combination chemotherapy protocols together with other antineoplastic agents (see "Interactions").

The recommended dosages of Enrylaze are:
Every 48 hours:

- 25 mg/m^2 administered intramuscularly every 48 hours;

Monday/Wednesday/Friday:

- 25 mg/m^2 intramuscularly on Monday morning and Wednesday morning, and 50 mg/m^2 intramuscularly on Friday afternoon. Administer the Friday afternoon dose 52 to 56 hours after the last Wednesday morning dose (e.g., 8:00 am on Monday and Wednesday, and 12:00 pm to 4:00 pm on Friday)

Recommended premedication
A consideration to premedicate patients with acetaminophen, an H-1 receptor blocker (such as diphenhydramine), and an H-2 receptor blocker (such as famotidine) 30-60 minutes prior to administration of Enrylaze should be made to decrease the risk and severity of hypersensitivity reactions (see “Warnings and Precautions”).

The dose of Enrylaze is administered in mg/m^2 and is not administered in units/m^2 as used for other asparaginase preparations.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

If an adverse reaction occurs, modify treatment according to the table below (Table 1)

Table 1 Dosage modifications

Adverse Reaction	Severity*	Action
Hypersensitivity Reaction *[see Warnings and Precautions]*	Grade 2	• Treat the symptoms.
	Grade 3 to 4	• Discontinue Enrylaze permanently.
Pancreatitis *[see Warnings and Precautions]*	Grade 2 to 4	• Hold Enrylaze for elevations in lipase or amylase > 2 times the ULN**, or for symptomatic pancreatitis. • Resume treatment when lipase and amylase are < 1.5 times the ULN and symptoms are resolved. • Discontinue Enrylaze permanently if clinical necrotizing or haemorrhagic pancreatitis is confirmed.
Thrombosis *[see Warnings and Precautions]*	Uncomplicated thrombosis	• Hold Enrylaze. • Treat with appropriate antithrombotic therapy. • Upon resolution of symptoms, consider resuming Enrylaze, while continuing antithrombotic therapy.
	Severe or life-threatening thrombosis	• Discontinue Enrylaze permanently. • Treat with appropriate antithrombotic therapy.
Hemorrhage *[see Warnings and Precautions]*	Grade 3 to 4	• Hold Enrylaze. • Evaluate for coagulopathy and consider clotting factor replacement as needed. • Resume Enrylaze with the next scheduled dose if bleeding is controlled.
Hepatotoxicity *[see Warnings and Precautions]*	Total bilirubin > 3 times to ≤ 10 times the ULN	• Hold Enrylaze until total bilirubin levels decrease to ≤ 1.5 times the ULN.
	Total bilirubin > 10 times the ULN	• Discontinue Enrylaze and do not make up missed doses.

* Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

** Upper limit of normal

Patients with hepatic disorders

Withhold Enrylaze if total bilirubin >3 times to ≤10 times the ULN, 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 “Warnings and precautions”).

Patients with renal disorders

No dose adjustment is required in patients with renal disorders. Concomitant medications including chemotherapy regimen may aggravate renal impairment.

Elderly patients

There were no elderly patients (>65 years of age) during the clinical study and therefore no dose recommendation can be made for this population.

Children and adolescents

No dose adjustment is required in paediatric patients.
The available data can be found in the "Properties/Effects", “Paediatric population”.
The youngest patient in the clinical study was 1 year of age.

Mode of administration

Enrylaze is for intramuscular (IM) use.
Limit the volume of Enrylaze at a single injection site to 2 mL. If the volume to be administered is greater than 2 mL, use multiple injection sites.

Contraindications

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

Warnings and precautions

Hypersensitivity Reactions
Grade 3 and 4 hypersensitivity reactions after the use of Enrylaze have occurred in patients during clinical trials (see “Contraindications” and “Undesirable Effects”).
Because of the risk of serious allergic reactions, administer Enrylaze in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. Discontinue Enrylaze in patients with severe hypersensitivity reactions (see “Contraindications”).

Pancreatitis
Pancreatitis has been reported in patients treated with Enrylaze in clinical trials (see “Undesirable Effects”).

Evaluate patients with symptoms compatible with pancreatitis to establish a diagnosis.
Discontinue Enrylaze in patients with severe or haemorrhagic pancreatitis. In the case of elevations in lipase or amylase >2 times the ULN or symptomatic pancreatitis, withhold Enrylaze until the ULN and symptoms subside. After resolution of asymptomatic pancreatitis, treatment with Enrylaze may be resumed.

Hyperglycaemia

Cases of hyperglycaemia have been reported in patients receiving Enrylaze in clinical trials (see "Undesirable Effects"). Monitor glucose levels in patients at baseline and periodically during treatment. Administer insulin therapy as necessary in patients with hyperglycaemia.

Thrombosis

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

Haemorrhage

Bleeding events have been reported with L-asparaginase therapy. Hold Enrylaze treatment for a 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 "Undesirable Effects").
Patients should be monitored for signs and symptoms of hepatotoxicity. Monitor bilirubin and transaminases prior to treatment and as clinically required during treatment with Enrylaze. In the event of severe liver toxicity, discontinue treatment with Enrylaze and provide supportive care.

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.

Immunosuppression and infections

Animal data has shown asparaginase therapy may cause immunosuppression, consideration should therefore be taken in humans as asparaginase is routinely used with other immunosuppressive agents.

Sodium content

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

Interactions

No interaction studies have been performed, Enrylaze should therefore not be mixed with any other medicinal products prior to administration.

Pregnancy, lactation

Women of childbearing potential / Contraception in males and females

Men and women should use contraception during treatment and for at least 3 months after discontinuation. Since an indirect interaction between oral contraceptives and Enrylaze cannot be ruled out, patients of childbearing/procreative potential should use effective non-hormonal contraceptive methods while undergoing treatment.

Pregnancy

There are no data on the use of recombinant crisantaspase in pregnant women. Animal studies have shown reproductive and developmental toxicity. (see "Preclinical data").
The use of Enrylaze during pregnancy and in women of childbearing age who are not using contraception is not recommended.
If a patient becomes pregnant while receiving Enrylaze, the woman should be informed of the potential hazard to the foetus.

Lactation

It is not known whether recombinant crisantaspase is excreted in human milk. Because of the potential for serious adverse reactions in breastfeeding infants/children, mothers should be advised not to breastfeed during Enrylaze therapy and for a period of one week 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 asparaginase *Erwinia chrysanthemi*, no effect on fertility was identified although decreased sperm count was observed at all doses in males. (see "Preclinical data").

Effects on ability to drive and use machines

Based on the adverse effects Enrylaze has a minor influence on the ability to drive and use machines (see "Undesirable effects").

Undesirable effects

Summary of the safety profile

Serious adverse effects occurred in 59% of patients who received Enrylaze. The most frequent serious adverse effects were febrile neutropenia, pyrexia, vomiting, nausea, and drug hypersensitivity. The most common adverse effects were anaemia, vomiting, thrombocytopenia, neutropenia, nausea, febrile neutropenia, fatigue, pyrexia, decreased appetite, transaminase increased, abdominal pain, white blood cell count decreased, headache, diarrhoea, and lymphocyte count decreased.

List of adverse effects

The safety of Enrylaze was determined in Study JZP458-201, an open-label, two-part, multi-cohort, multi-centre, multi-agent chemotherapeutic trial that treated 228 patients with ALL or LBL who developed hypersensitivity to a long-acting *E. coli*-derived asparaginase. In the study, all grades of adverse events were prospectively and systematically collected. Patients received 6 doses of Enrylaze, by either intravenous infusion or an intramuscular injection as a replacement for each dose of *E. coli*-derived asparaginase remaining on a patient's treatment plan.
Certain adverse effects listed below (Table 2), such as effects 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 effects, 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).

Table 2: Adverse Effects in Patients Receiving Enrylaze with Multi-Agent Chemotherapy (Study JZP458-201)

System Organ Class	Frequency	ADR
Infections and infestations	Common	Sepsis
Blood and lymphatic system disorders	Very common	Anaemia*(52%), Febrile neutropenia (32%), Neutropenia* (41%), Thrombocytopenia* (42%)
Immune system disorders	Very common Common	Drug hypersensitivity (11%) Anaphylactic reaction
Metabolism and nutrition disorders	Very common Common	Decreased appetite (29%), Hyperglycaemia (17%), Hypoalbuminemia (11%) Hypertriglyceridemia, Hypoglycaemia, Hyperammonaemia
Psychiatric disorders	Very common Common	Anxiety (10%) Irritability
Nervous system disorders	Very common Common Uncommon	Headache (25%) Dizziness Superior sagittal sinus thrombosis
Vascular disorders	Common Unommon	Hypotension Jugular vein thrombosis, Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	Common	Pulmonary embolism
Gastrointestinal disorders	Very common Common	Vomiting (49%), Nausea (38%), Abdominal pain* (27%), Diarrhoea (22%) Pancreatitis*
Skin and subcutaneous tissue disorders	Common	Pruritis
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity (18%)
General disorders and administration site conditions	Very common Common	Fatigue* (32%), Pyrexia (32%) Injection site pain, Injection site reaction
Investigations	Very common	Transaminases increased* (29%), White blood cell count decreased (27%), Lymphocyte count decreased* (20%), Weight decreased (13%), Blood bilirubin increased* (10%)

	Common	Activated partial thromboplastin time prolonged, Antithrombin III decreased, Blood fibrinogen decreased, Blood creatinine increased
Renal and Urinary disorders	Uncommon	Acute Kidney Injury
Injury, poisoning and procedural complications	Very common Common	Contusion (10%) Infusion-related reaction

* Grouped terms: Abdominal pain: Abdominal pain, Abdominal pain upper; Anaemia: Anaemia, Haematocrit decreased, Haemoglobin decreased and Red blood cell count decreased; Blood bilirubin increased: Blood bilirubin increased, Bilirubin conjugated increased; Fatigue: Fatigue, Asthenia; Lymphocyte count decreased: Lymphocyte count decreased, CD4 lymphocytes decreased; Neutropenia: Neutropenia, Neutrophil count decreased; Pancreatitis: Pancreatitis, Pancreatitis acute; Thrombocytopenia: Thrombocytopenia, Platelet count decreased; Transaminases increased: Transaminase increased, Alanine aminotransferase increased and Aspartate aminotransferase increased; Hypoalbuminaemia: Blood albumin decreased and Hypoalbuminaemia.

Description of specific adverse reactions and additional information

Hypersensitivity

Hypersensitivity reactions were reported ADRs in the Enrylaze clinical study. The incidence of drug 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 were observed more frequently in patients who received Enrylaze intravenously. The frequency of hypersensitivity reactions leading to discontinuation was 10%. No fatal hypersensitivity reactions were observed (see “Warnings and precautions”).

Pancreatitis

Cases of pancreatitis including life threatening cases have been reported in the Enrylaze clinical study. 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 “Warnings and precautions”).

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 effects versus other age groups is not suitable.

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse effects online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Treatment

Treatment is symptomatic and supportive.

Properties/Effects

ATC code:

L01XX02 (other antineoplastic agents)

Mechanism of action / Pharmacodynamics

Crisantaspase 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.

Pharmacodynamics

See above

Clinical efficacy

The efficacy and safety of Enrylaze was determined in Study JZP458-201, 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, , 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 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 IU/mL. Serum trough asparaginase activity ≥0.1 IU/mL has been demonstrated to correlate with asparagine depletion that predicts clinical efficacy (see "Pharmacokinetics").

Paediatrics

The safety and efficacy in paediatric patients aged 1 year and above was determined in Study JZP458-201 for the treatment of ALL and LBL in patients who developed hypersensitivity to E. coli-derived asparaginase.

Pharmacokinetics

The pharmacokinetics (PK) of Enrylaze was determined based on serum asparaginase activity (SAA). Patients received 6 doses of Enrylaze intramuscularly on Monday, Wednesday and Friday as a replacement for each dose of a long-acting *E. coli*-derived asparaginase remaining on their original treatment plan.
Population PK modelling and simulation results for the determination of efficacy are summarised in Table 3.

The exposures for recombinant crisantaspase are summarised in Table 4. Recombinant crisantaspase maximum SAA (C_{max}) and area under the SAA-time curve (AUC) increase proportionally over a dosage range from 12.5 to 50 mg/m^2.

Table 3: Proportion (95% CI) of patients modelled and simulated with NSAA levels ≥0.1 IU/mL

Enrylaze Dosage	Trough Sampling Time	Proportion with NSAA ≥ 0.1 IU/mL (95% CI)[a]
25 mg/m^2 intramuscularly every 48 hours	48 hours	96.7% (95.9%, 97.4%)
25/25/50 mg/m^2 intramuscularly Monday morning/Wednesday morning/Friday afternoon	Friday afternoon: 56 hours after 25 mg/m^2 Wednesday morning dose[b]	91.8 (90.6, 93.0)

	Monday morning: 68 hours after 50 mg/m^2 Friday afternoon dose[c]	91.6 (90.4, 92.8)

[a] Based on 2,000 virtual subjects.

[b] Based on maximum interval of 56 hours between the Wednesday morning and Friday afternoon doses.

[c] Based on maximum interval of 68 hours between the Friday afternoon and Monday morning doses.

Table 4: Enrylaze - Pharmacokinetic Parameters Based on SAA

PK Parameter	Geometric Mean (% Geometric CV) After Last Dose		
	25 mg/m^2 Every 48 Hours	25/25/50 mg/m^2 Monday, Wednesday, Friday	
		Last 25 mg/m^2	Last 50 mg/m^2
	Intramuscularly	Intramuscularly	
C_{max} (IU/mL)	1,36 (79%)	1,37 (79%)	2,30 (78%)
C_{trough} (IU/mL)	0,48 (99%)	0,34 (105%)[a]	0,33 (104%)[b]

[a] C_{trough} at maximum interval of 56 hours after the last 25 mg/m^2 Wednesday morning dose.

[b] C_{trough} at maximum interval of 68 hours after the last 50 mg/m^2 Friday afternoon dose

Absorption

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

Distribution

Following IM administration, the geometric mean (%CV) of individual predicted V/F of recombinant crisantaspase is 1.75 L/m^2 (13%).

Metabolism

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

Elimination

Following IM administration, the geometric mean (%CV) of individual predicted CL/F of Recombinant crisantaspase is 0.13 L/h/m^2 (21%) and the t½ is 18.76 hours (11%).

Kinetics in specific patient groups

Impaired renal or Hepatic function

There was no dedicated study on renal or hepatic impairment with Enrylaze.

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 Tmax.

Race

Black or African American patients (n=24) had 2925% 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.

Preclinical data

In a Good Laboratory Practice (GLP)-compliant study, recombinant crisantaspase was administered intravenously to groups of rats for up to 14 consecutive days. Adverse effects were noted only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Genotoxicity / Carcinogenicity

Carcinogenicity and genotoxicity studies have not been conducted with Enrylaze.

Reproductive toxicity

Reproductive toxicity studies have not been conducted with Enrylaze.
Four GLP-compliant reproductive and developmental toxicity studies were conducted with the native *Erwinia chrysanthemi* asparaginase and are summarized below.
In GLP-compliant 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 GLP-compliant 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).

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Chemical, and physical in-use stability for IM preparations in a polypyrene 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).
For microbiological reason, the Enrylaze solution in the syringe should be used immediately unless the preparation has been carried out under controlled and validated aseptic conditions.
If the solution is not used immediately, the duration of storage and the conditions are the responsibility of the user.

Special precautions for storage

Store in the refrigerator (2-8°C) in an upright position.
Do not shake or freeze.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

Preparation instructions

- Determine the posology, and number of vials of Enrylaze based on the individual patient's BSA as outlined in section "Dosage/Administration". 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 vial.
    - 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.

Authorisation number

69073 (Swissmedic)

Packs

Pack size: 3 vials each containing 0.5mL of Enrylaze (A).
Type 1 clear borosilicate glass vial with a capacity of 2 mL sealed with a halobutyl rubber stopper and aluminium overseal and a violet plastic cap.

Marketing authorisation holder

Jazz Pharmaceuticals Switzerland GmbH, Zug

Manufacturer

Jazz Pharmaceuticals Ireland Ltd., Dublin (IRL)

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