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

Voraxaze 1,000 units powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution with 1 mL of sterile 0.9% sodium chloride solution, each vial contains a nominal 1,000 units of glucarpidase*.

*Produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Voraxaze is indicated to reduce toxic plasma methotrexate concentration in adults and children (aged 28 days and older) with delayed methotrexate elimination or at risk of methotrexate toxicity.

4.2 Posology and method of administration

Glucarpidase is intended for use under medical supervision.

In order to take into account all MTX doses and infusion durations that could be administered to a patient, it is recommended to utilise local treatment protocols or guidelines if available, to determine when glucarpidase should be administered.

Recommendations for intervention with glucarpidase are considered when plasma MTX levels are greater than 2 standard deviations of the mean expected MTX excretion curve. Also, administration of glucarpidase should optimally occur within 60 hours from the start of the HDMTX infusion, because life-threatening toxicities may not be preventable beyond this time point. Clinical data however show that glucarpidase continues to be effective beyond this time window.

Recommendations for intervention with glucarpidase are detailed below:

MTX Dose:	**≤ 1 g/m²**	**1-8 g/m²**	**8-12 g/m²**
Infusion duration:	Over 36-42 hours	Over 24 hours	Over ≤ 6 hours
Hours following start of MTX infusion	Threshold plasma MTX concentration (μM)		
24 hours	-	-*	≥ 50
36 hours	-	≥ 30	≥ 30
42 hours	-	≥ 10	≥ 10
48 hours	≥ 5	≥ 5	≥ 5

*start supportive care when ≥ 120 μM.

As a further guide for patients receiving short infusion MTX regimens, glucarpidase administration may be considered as detailed below:

MTX Dose:	**3-3.5 g/m^2**	**5 g/m^2**
Hours following start of MTX infusion	Threshold plasma MTX concentration (μM)	
24 hours	≥ 20	-
36 hours	-	≥ 10
48 hours	≥ 5	≥ 6

Posology

The recommended dose is a single dose of 50 Units per kilogram (kg) by bolus intravenous (IV) injection over 5 minutes.
Once the diagnosis of delayed methotrexate (MTX) elimination or risk for MTX toxicity is established, glucarpidase should be administered without delay; for patients with delayed MTX elimination the optimal time window for administration is within 48–60 hours from the start of the high dose MTX infusion. Folinic acid, also known as leucovorin, is a competitive substrate of glucarpidase that may compete for the MTX binding sites (see also Section 4.5). It is therefore recommended that folinic acid should not be administered within the 2 hours before or after glucarpidase administration to minimise any potential interaction.
Intracellular MTX will continue to inhibit reduction of folate to its active form following glucarpidase administration thus folinic acid will continue to be needed no earlier than 2 hours post glucarpidase administration in order to replenish the intracellular source of biologically active folate. (see also Section 4.4)

Specific populations
Patients with renal impairment
A study of the pharmacokinetics of glucarpidase in the absence of MTX in 4 subjects with severe renal impairment (CLcr <30 mL/min) showed that the mean pharmacokinetic parameters were similar to those observed in healthy subjects.

On this basis, no dose adjustment of glucarpidase is recommended for patients with renal impairment.

Paediatric population
No dose adjustment is required for the paediatric population. See section 4.4.

Method of administration

Reconstitute each vial of Voraxaze 1,000 units with 1 mL of sterile 0.9% sodium chloride solution before use. Reconstitution should take place immediately prior to use (do not further dilute). It should be administered intravenously by bolus intravenous injection over 5 minutes.
After reconstitution with 1 mL of sterile 0.9% sodium chloride solution each 1 mL will contain 1,000 units of glucarpidase.
A syringe suitable for withdrawing small volumes should be used to remove the solution from the vials. It may not always be possible to withdraw a full 1 mL from the vial but removal of at least 0.90 mL from the vial will provide an adequate amount of glucarpidase for dosing purposes.
Flush intravenous line before and after administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

Paediatric population

No formal evaluation of the effect of age on the pharmacokinetics of glucarpidase has been performed.

No data are available in children aged less than 28 days.

It is important to measure baseline plasma MTX concentations and renal function and to continue to monitor these throughout treatment with high dose MTX therapy, as described below.

A high performance chromatography (HPLC) method is recommended for measuring MTX concentrations following glucarpidase administration. Current immunoassays are unreliable for samples collected following glucarpidase administration due to 4-deoxy-4-amino-N^{10}-methylpteroic acid (DAMPA), an inactive metabolite of MTX formed following glucarpidase administration, interfering with the measurement of MTX concentration. This interference results in an overestimation of the MTX concentration. The effect of DAMPA interference will decline over time as DAMPA is eliminated.

DAMPA concentrations in patients treated with glucarpidase fell within a mean half-life of 8.6 hours. In the majority of patients DAMPA concentrations had fallen to below 1 µmol/l within 48 hours of administration of glucarpidase. In clinical studies, DAMPA concentrations above 1 µmol/L have been observed beyond 3 days in a small minority (≤3%) of patients.

In the absence of more specific HPLC assay it is recommended that the dose of folinic acid used in a 48 hour-period after glucarpidase should be based on the MTX concentration from a sample taken prior to glucarpidase administration. Within 48 hours after glucarpidase administration MTX concentrations determined by immunoassay may not be reliably used to monitor for rebound and confirmatory HPLC data should be considered.

Over 48 hours after glucarpidase administration immunoassay results will be reliable in the majority of patients and so can be used to adjust the folinic acid dose or monitor for rebound. In clinical studies, ~9% patients with baseline MTX concentration ≥ 50µmol/l had DAMPA levels that persisted above 1 µmol/l beyond 4 days.

Routine monitoring of plasma MTX concentrations should be continued in accordance with local guidelines.

Glucarpidase does not reverse pre-existing renal damage or renal failure that occurs as a consequence of MTX administration, but instead removes MTX to reduce the risk of sustaining further renal toxicity. As such, other supportive care, including hydration and alkalinisation of the urine, should be started at the onset of MTX administration and continued in accordance with local treatment guidelines.

Allergic type hypersensitivity reactions are possible following adminstration of glucarpidase see section 4.8.

4.5 Interaction with other medicinal products and other forms of interaction

Glucarpidase can decrease folinic acid concentration, which may decrease the effect of folinic acid rescue unless it is dosed as recommended (see section 4.2).

Glucarpidase may also reduce the concentrations of other folate analogs or folate analog metabolic inhibitors.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of glucarpidase in pregnant women. Glucarpidase is administered in combination with MTX, which is contraindicated in pregnancy. As use of MTX, a genotoxic and teratogenic agent, is a prerequisite for the use of glucarpidase, the medicinal product is not thought to present an additional risk to patients already receiving MTX. Reproductive studies of glucarpidase in animals were not performed. It is unknown whether glucarpidase causes harmful effects during pregnancy and/or on the foetus/newborn child or whether it can affect reproductive capacity. Glucarpidase should only be given to a pregnant woman if clearly needed.

Breast-feeding

It is unknown whether glucarpidase/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from glucarpidase therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There is no or limited amount of data on the impact of glucarpidase on human fertility. Fertility studies in animals were not performed. It is unknown whether glucarpidase affects fertility.

4.7 Effects on ability to drive and use machines

Glucarpidase has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent related adverse reactions were burning sensation (<1%), headache (<1%), paraesthesia (2%), flushing (2%), feeling hot (<1%).

Tabulated summary of adverse reactions

Table 1 gives the adverse reactions observed from the combination of pooled clinical study data (489 patients) and reported adverse reactions during the Post Marketing period. The adverse reactions are presented by system organ class and frequency categories defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Within each frequency grouping undesirable effects are presented in order of decreasing seriousness

Table 1 Adverse reactions reported for glucarpidase

System organ class	Frequency	Adverse reactions
Immune system disorders	Rare	Hypersensitivity
	Very Rare	Anaphylactic reaction
Nervous system disorders	Uncommon	Burning sensation, Headache, Paraesthesia
	Rare	Hypoaesthesia, Somnolence, Tremor
Cardiac disorders	Very Rare	Tachycardia
Vascular disorders	Uncommon	Flushing
	Rare	Hypotension
Respiratory, thoracic and mediastinal disorders	Rare	Pleural effusion, Throat tightness
Gastrointestinal disorders	Rare	Abdominal pain upper, Diarrhoea, Nausea, Vomiting

Skin and subcutaneous tissue disorders	Rare	Pruritus, Rash
	Very Rare	Drug eruption, Skin reaction
Renal and urinary disorders	Very Rare	Crystalluria*
General disorders and administration site conditions	Uncommon	Feeling hot
	Rare	Pyrexia, Rebound effect
	Very Rare	Infusion site reaction

*Crystalluria is the preferred term; the adverse reaction refers to DAMPA crystalluria

Description of selected adverse reactions
As with any intravenous protein product, infusion-related reactions or hypersensitivity reactions are possible.
It is recommended that patients are monitored for signs and symptoms of anaphylaxis and an acute allergic reaction. Medical support must be readily available when glucarpidase is administered.
As with all therapeutic proteins, there is potential for immunogenicity. 205 patients who received one (n=176), 2 (n=27), or 3 (n=2) doses of glucarpidase were evaluated for anti-glucarpidase antibodies. Forty-three of these 205 patients (21%) had detectable anti-glucarpidase antibodies following administration, of which 32 received 1 dose and 11 received 2 or 3 doses of glucarpidase. Antibody titers were determined using a bridging enzyme-linked immunosorbent assay (ELISA) for anti- glucarpidase antibodies. Neutralizing antibodies were detected in 22 of the 43 patients who tested positive for anti-glucarpidase binding antibodies.

Paediatric population

The incidence of adverse events related to glucarpidase did not differ between paediatric and adult patients.

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

The safety profile of the nine patients who have received the highest doses of Voraxaze in clinical studies (single dose range of 90.9 – 188.7 U/kg and/or cumulative dose range of 150.0 – 201.8 U/kg) was similar to the safety profile of all patients.

In case of overdose, it is recommended to stop glucarpidase dosing, patients should be observed and appropriate supportive care should be provided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agent for antineoplastic treatment, ATC code: V03AF09.

Mechanism of action and pharmacodynamic effects

Glucarpidase is a recombinant bacterial enzyme that hydrolyses the carboxyl-terminal glutamate residue from folic acid and structurally related molecules such asMTX. Glucarpidase converts MTX to its inactive metabolites DAMPA and glutamate. Because both DAMPA and glutamate are metabolised by the liver, glucarpidase provides an alternative route for MTX elimination in patients with renal dysfunction during high-dose MTX treatment.

Due to its large molecular size, glucarpidase does not cross the cellular membrane and therefore does not counteract the intracellular antineoplastic effects of high-dose MTX.

Clinical efficacy

The efficacy of glucarpidase has been evaluated in four open-label multi-center, compassionate use, single arm, open label studies in patients with delayed MTX elimination due to renal dysfunction. The primary endpoint in the clinical studies was referred to as a clinically important reduction (CIR) in MTX concentration and was based on central MTX HPLC data. A patient was considered to have achieved a CIR if all central MTX HPLC plasma concentrations after the first dose of glucarpidase were ≤1 μmol/L.

In Study 001, 44 male and female patients were in the Safety population (median age 53.0; range 10 – 78 years) and received a median dose of 50 U/kg (range 9.80 to 58.14 U/kg). Of the 28 patients with central HPLC data, 85.7% (95% CI: 68.5% to 94.3%) achieved a CIR.

In Study 002, 214 male and female patients were in the Safety population (median age 17.0; range 0 - 82 years) and received a median dose of 49.23 U/kg (range 10.87 to 63.73 U/kg). Of the 84 patients with central HPLC data, 54.8% (95% CI: 44.2% to 65.0%) achieved a CIR.

In Study 003, 69 male and female patients were in the Safety population (median age 15.0; range 0 - 71 years) and received a median dose of 50 U/kg (range 16.64 to 100 U/kg). Of the 30 patients with central HPLC data, 66.7% (95% CI: 48.8% to 80.8%) achieved a CIR.

In Study 006, 149 male and female patients were in the Safety population (median age 18.0; range 10 – 78 years) and received a median dose of 48.73 U/kg (range 17.86 to 98.04 U/kg). Of the 27 patients with central HPLC data, 51.9% (95% CI: 34.0% to 69.3%) achieved a CIR.

A total of 169 patients were included in the pooled central MTX HPLC population and received a median initial dose of 50 Units/kg (range 11 to 60 Units/kg). A CIR was achieved by 61.5% (95% CI: 54.0% to 68.5%) of patients in the central MTX HPLC population that was sustained for up to 8 days. Amedian reduction of > 98% in MTX concentration occurred within 15 minutes following glucarpidase administration.

Rebound (defined as MTX concentration increase of at least 1 μmol/L and at least two times the post-glucarpidase nadir) occurred in 19.4% of patients in the central MTX HPLC population. Overall half of the patients with rebound had a maximum absolute increase in MTX concentration of between 1 and 2 μmol/L, and only 1 patient had an increase of >10 μmol/L (this patient had a pre-glucarpidase MTX concentration of 165.86 μmol/L and received a glucarpidase dose of 10.53 U/kg). Of the 4 patients who had rebound after their first glucarpidase dose and received a second glucarpidase dose, there was a median reduction of MTX concentration of 84% and 2 achieved a CIR.

Of the 410 patients in the pooled renal evaluable population (patients who had at least one post-glucarpidase renal function assessment) who developed serum creatinine (sCr) common toxicity criteria grade ≥2 at pre-glucarpidase baseline, 262 (63.9%) recovered to grade 0 or 1. In the renal evaluable population there was a 3.5-fold increase in mean sCr concentration from pre-MTX to pre-glucarpidase baseline (0.79mg/dL to 2.79 mg/dL). After administration of glucarpidase, sCr continued to rise (mean increase of 0.24 mg/dL over three days), then began to decrease. The mean sCr value at day 22 was 1.27 mg/dL. For the 258 patients for whom days to recovery could be calculated, the median time to recovery was 12.5 days (range 1–213 days).

Paediatric population

The pooled clinical safety database for glucarpidase includes data for 232 patients up to 17 years of age. Within the central MTX HPLC population 0% (0/1) patient aged ≥28 days to <2 years (Infant Subgroup), 31.3% (5/16) patients aged ≥2 to <12 years (Child Subgroup) and 49.1% 27/55 patients

aged ≥12 to <18 years of age achieved a CIR. A median reduction of ≥ 95% in MTX concentration occurred within 15 minutes following glucarpidase administration in all paediatric subgroups.
This medicinal product has been authorised under "Exceptional Circumstances". This means that due to the rarity of the disease and for ethical reasons it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of glucarpidase in the absence of MTX were studied in 8 healthy subjects following glucarpidase 50 Units/kg administered as an intravenous injection over 5 minutes. Serum glucarpidase activity levels were measured by an enzymatic assay and serum total glucarpidase concentrations were measured by enzyme linked immunosorbent assay (ELISA). The mean maximum serum concentration (C_{max}) was 3.3 µg/mL and the mean area under the curve ($AUC_{0\text{-}INF}$) was 23.3 µg·h/mL. The pharmacokinetic parameters derived from the serum total glucarpidase concentrations were similar to those generated by serum glucarpidase activity levels except for elimination half-life as described below.

A clinically relevant accumulation of glucarpidase after a repeat injection within a MTX cycle has not been observed.

Distribution

The mean volume of distribution (V_d) was 3.55 L.

Biotransformation

The product is an enzyme, and therefore a protein. The metabolism of such products entails the degradation to small peptides and individual amino acids and therefore, the metabolic pathways are generally understood. Classical biotransformation studies are therefore not required and have not been conducted.
The ability of the main metabolite produced by the action of glucarpidase on MTX (DAMPA) to induce or inhibit CYP450 metabolising isoenzymes has been investigated *in vitro*, which revealed possible enzyme induction with CYP1A2 and CYP2C9. Modest induction would only be expected in a minority of patients who have the highest DAMPA exposure.

Elimination

Serum glucarpidase activity levels declined with a mean elimination half-life ($t_{1/2}$) of 5.6 hours and serum total glucarpidase concentration declined with a mean $t_{1/2}$ of 9 hours. The mean systemic clearance (CL) was 7.5 mL/min.

Specific populations

Patients with renal impairment
A study of the pharmacokinetics of glucarpidase in the absence of MTX in 4 subjects with severe renal impairment (CLcr <30 mL/min) showed that the mean pharmacokinetic parameters were similar to those observed in healthy subjects.
On this basis, no dose adjustment of glucarpidase is recommended for patients with renal impairment.

Paediatric population
No formal evaluation of the effect of age on the pharmacokinetics of glucarpidase has been performed.

5.3 Preclinical safety data

Generally, effects in non-clinical studies were observed at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

The carcinogenic, genotoxic and reproductive toxicity potential of glucarpidase have not been studied. Decreased platelets were reported in a 14 day dog study and intravenous human equivalent doses of 278 and 1389 Units/kg were associated with increasing severe dose related toxicity which resulted in deaths or premature euthanasia.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Trometamol
Zinc acetate dihydrate

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products (see section 6.6).

6.3 Shelf life

Unopened vials: 5 years

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

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C).
Do not freeze.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 mL type 1 glass vials (Ph Eur) with a bromobutyl stopper and standard blue flip off seal.

Pack size of 1 vial.

6.6 Special precautions for disposal

Each vial should be reconstituted with 1 mL of sterile 0.9% sodium chloride solution. Reconstitution should take place immediately prior to use (do not further dilute). It should be administered intravenously by bolus intravenous injection over 5 minutes.

After reconstitution with 1 mL of sterile 0.9% sodium chloride solution each 1 mL will contain 1,000 units of glucarpidase. A syringe suitable for withdrawing small volumes should be used to remove the solution from the vials. It may not always be possible to withdraw a full 1 mL from the vial but removal of at least 0.90 mL from the vial will provide an adequate amount of glucarpidase for dosing purposes.

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

7. MARKETING AUTHORISATION HOLDER

SERB SAS
32 rue de Monceau
75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1586/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 January 2022

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(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) 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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

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

Name and address of the manufacturer(s) of the biological active substance(s)
Kaneka Eurogentec S.A
Liege Science Park
Rue du Bois Saint Jean 14
4102 Seraign
Belgium

Name and address of the manufacturer(s) responsible for batch release
Almac Pharma Services Limited
Seagoe Industrial Estate,
Portadown,
Craigavon,
BT63 5UA, UK (Northern 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The 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.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	**Due date**
In order to further characterise the efficacy and safety of glucarpidase indicated to reduce toxic plasma methotrexate concentration in adults and children (aged 28 days and older) with delayed methotrexate elimination or at risk of methotrexate toxicity, the MAH should conduct and submit the results of a study from a glucarpidase patient registry to be conducted on patients with impaired methotrexate clearance according to an agreed protocol.	Annual updates to be submitted at the time of the annual reassessment.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Voraxaze 1,000 units powder for solution for injection
Glucarpidase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1,000 units of glucarpidase produced in *Escherichia coli* cells by recombinant DNA technology.

3. LIST OF EXCIPIENTS

Contains also : lactose, trometamol and zinc acetate dihydrate

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use
Reconstitue with 1 ml sodium chloride 9 mg/ml solution for injection immediately prior to use (do not further dilute)

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.

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

SERB SAS, 32 rue de Monceau, 75008 Paris, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1586/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted.>

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier to be 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

Voraxaze 1,000 units powder for injection
Glucarpidase
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

after reconstitution: 1,000 units in 1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Voraxaze 1000 units powder for solution for injection
glucarpidase

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

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

What is in this leaflet

1. What Voraxaze is and what it is used for
2. What you or your child need to know before you are given Voraxaze
3. How Voraxaze will be given
4. Possible side effects
5. How to store Voraxaze
6. Contents of the pack and other information

1. What Voraxaze is and what it is used for

The active substance in this medicine is glucarpidase, an enzyme that breaks down the cancer medicine methotrexate.

Voraxaze is used in adults and children older than 28 days if they are being given methotrexate for cancer treatment but their body is not able to get rid of the methotrexate fast enough and they are at risk of severe side effects. The medicine breaks down the methotrexate in the bloodstream, reducing methotrexate levels and so helping to control side effects and stop them worsening. It works very quickly and can reduce the amount of methotrexate in the bloodstream by more than 90% in 15 minutes. The medicine does not enter cells, so it does not prevent any methotrexate that has already entered the cancer cells from working to treat the cancer.

2. What you or your child need to know before you are given Voraxaze

Do not take Voraxaze
- if you are allergic to glucarpidase or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before you are given Voraxaze.
You will be given this medicine as soon as possible after your doctor decides you need it in order to prevent serious side effects from methotrexate.

This medicine alone cannot prevent or stop all of the side effects of high-dose methotrexate, and you will also be given other treatments and supportive care as required.

It is important that your doctor knows how much methotrexate is in your blood and how well your kidneys are working. You will have tests to check this before and after treatment with this medicine.

Children and adolescents
This medicine can be given to children from 28 days of age. The safety and efficacy of this medicine in children aged less than 28 days has not been established.

Other medicines and Voraxaze

This medicine can affect the amount of folinic acid in your body, another product that you may be given by your doctor to reduce methotrexate toxicity. As a precaution, your doctor will adjust the timing of your folinic acid and doses of Voraxaze to ensure that there is at least 2 hours between the two medicines. Your doctor will restart folinic acid administration no earlier than 2 hours after glucarpidase administration.

No other interactions between this and other medicines have been reported during clinical studies.

Pregnancy and breast-feeding
Talk to your doctor if you are pregnant or breastfeeding or you are planning to have a baby.

As this medicine is only used in people who have already been given methotrexate, which is known to cause harmful effects to a developing baby, no studies have been done to determine whether this medicine alone can cause harmful effects to a developing baby during pregnancy or whether it is excreted in breast milk.

Driving and using machines

This medicine has no or negligible effect on the ability to drive or use machines

3. How this medicine will be given

This medicine is given as an injection into a vein, over a 5-minute period. Your doctor will work out the right dose for you, based on your weight. The recommended dose is 50 Units per kilogram of body weight.

As the medicine is given under medical supervision, it is unlikely that you will be given too much. If you think you have been given more than you should, talk to your doctor or nurse.

You will be monitored for changes in the amount of methotrexate in your blood after treatment with this medicine.

4. Possible side effects

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

Tell your doctor or one of the medical staff immediately if you experience any of the following:

- Swelling of the throat, tightness in the chest, difficulty breathing
- Swelling of the hands, feet, face, lips or mouth
- Rash, with or without flushing and swelling of the face
- Shaking or chills without fever

If you have any of the symptoms listed above, you may be having a serious allergic reaction and may need urgent medical attention. These side effects (allergic reactions) are very rare and if they do occur, usually occur on the day of treatment.

You should tell your doctor or one of the medical staff as soon as possible if you experience any of the following side effects which are also rare but have been reported during treatment with this medicine:

- Fever
- Headache
- A tingling or pricking sensation on the skin (“pins and needles”)
- A burning sensation on the skin

If you experience any other side effects not mentioned in this leaflet, inform your doctor or one of the medical staff.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Voraxaze

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.

You will be given this medicine under medical supervision. It is stored between 2 and 8°C and should not be stored in a freezer.

Use by Date**:** This medicine will not be used after the expiry date stated on the vial and outer carton. The pharmacist will check this before it is dispensed.

6. Contents of the pack and other information

What Voraxaze contains

The active substance is glucarpidase.

Voraxaze contains Lactose, Trometamol, and Zinc acetate dihydrate

What Voraxaze looks like and contents of the pack
Each pack contains one vial which is a white or off-white lyophilised powder, to be reconstituted with 1 mL of sterile 0.9% sodium chloride solution (not included).

Marketing Authorisation Holder and Manufacturer
Name and address of the marketing authorisation holder
SERB SAS
32 rue de Monceau
75008 Paris
France

Name and address of the manufacturer(s) responsible for batch release
Almac Pharma Services Limited
Seagoe Industrial Estate,
Portadown,
Craigavon,
BT63 5UA, UK (Northern Ireland)

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.

The following information is intended for healthcare professionals only:

Each vial of Voraxaze should be reconstituted with 1 mL of sterile 0.9% sodium chloride solution. Reconstitution should take place immediately prior to use (do not further dilute). It should be administered intravenously by bolus intravenous injection over 5 minutes.

After reconstitution with 1 mL of sterile 0.9% sodium chloride solution each 1 mL will contain 1,000 Units of glucarpidase. A syringe suitable for withdrawing small volumes should be used to remove the solution from the vials. It may not always be possible to withdraw a full 1 mL from the vial but removal of at least 0.90 mL from the vial will provide an adequate amount of glucarpidase for dosing purposes.

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

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.