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

Loargys 5 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Loargys consists of a cobalt substituted, recombinant human arginase 1 enzyme, produced in *Escherichia coli* cells, that is covalently conjugated to methoxypolyethylene glycol (mPEG).

The strength of Loargys indicates the quantity of the arginase moiety of pegzilarginase without consideration of the mPEG carrier.

Each 0.4 ml vial contains 2 mg of pegzilarginase (5 mg pegzilarginase per ml).
Each 1 ml vial contains 5 mg of pegzilarginase (5 mg pegzilarginase per ml).

The potency of this medicinal product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class (see section 5.1).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion (injection/infusion)

Colourless to slightly yellow or slightly pink, clear to slightly opalescent liquid.

pH: 7.0-7.6
Osmolality: 250-305 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Loargys is indicated for the treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininemia, in adults, adolescents and children aged 2 years and older.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the management of patients with inherited metabolic diseases.

Posology

Loargys is intended for chronic management of patients with ARG1-D in conjunction with individualised disease management such as dietary protein restriction, amino acid supplements and pharmacological treatment including nitrogen scavengers.

Loargys should be administered by intravenous infusion or subcutaneous injection, using the same dose. In clinical trials, treatment was initiated as intravenous administration with subsequent transition to subcutaneous administration after 8 weeks, at the earliest (see section 5.1).

The recommended initial dose of Loargys is 0.1 mg/kg per week. The dose may be increased or decreased in 0.05 mg/kg increments to achieve therapeutic goals. Doses above 0.2 mg/kg per week have not been studied in clinical trials in ARG1-D.

Prior to initiating treatment, a baseline plasma arginine concentration should be obtained. After initiating treatment, the weekly dose should be adjusted based on pre-dose plasma arginine concentrations to maintain plasma arginine within the normal range. To maximise the time within the normal range, dose adjustments should be aimed at achieving a pre-dose level of plasma arginine near the upper limit of normal (ULN) (see section 5.1). The dose adjustment should typically be based on two consecutive measurements, and first such assessment performed after 4 weeks of administration. It is recommended to monitor plasma arginine levels weekly for 2 weeks after any dose adjustment to assess impact of the dose change.

Once the individualised dose level has been established, monitoring of plasma arginine concentration is recommended to be performed in accordance with standard clinical monitoring visits, with no longer intervals than 3-6 months.

Validated methods to monitor arginine levels are to be used in patients treated with Loargys, as standard methods are not adequate to control residual enzyme activity of pegzilarginase after sampling, and may lead to artificially low arginine levels, and incorrect dose adjustments (see section 4.4).

Missed dose

If a dose is missed, administer Loargys as soon as possible. Patients should not be administered 2 doses to make up for the missed dose and should have a minimum of 4 days between doses.

Special population

Elderly population

The safety and efficacy of Loargys in patients older than 65 years have not been established. No data are available.

Hepatic impairment

Hepatic impairment is not expected to impact the recommended Loargys dosing regimen (see section 5.2).

Renal impairment

The safety and efficacy of Loargys in patients with renal impairment have not been established. No data are available. Renal impairment is not expected to impact the recommended Loargys dosing regimen (see section 5.2).

Paediatric population

The posology in the paediatric population aged 2 years and older is the same as in adults.
The safety and efficacy of Loargys in children below 2 years of age have not yet been established. No data are available.

Method of administration

Loargys is intended for intravenous infusion or subcutaneous injection and should be administered by a healthcare professional.

If appropriate, subcutaneous home administration by the patient or caregiver may be considered after at least 8 weeks of treatment, once a stable maintenance dose has been established and the risk for hypersensitivity reactions is assessed as low (see section 4.4). Before self-administration, the patient or caregiver should be adequately trained.

Loargys vial is for single use only.

Determine the total dose and volume of Loargys to be administered (and the number of vials needed) based on the patient's weight (kg) and dose level (mg/kg).

- Calculate the Total dose based on the desired dose level in mg/kg and the patient's weight rounded to a whole number.

Total dose (mg) = Patient weight (kg) x Dose level (mg/kg)

- Calculate the Volume of solution to be administered based on the calculated Total dose and Solution strength. Round the calculated volume to nearest 0.1 ml.

$$\text{Volume of Loargys (ml)} = \frac{\text{Total dose (mg)}}{\text{Solution strength (5 mg/ml)}}$$

- Calculate the number of vials needed based on the calculated Volume of Loargys. One vial of Loargys contains 0.4 ml or 1 ml solution.

For intravenous administration

- For intravenous infusion, Loargys must be diluted and infused over at least 30 minutes.
- For instructions on preparation and dilution of the medicinal product before administration, see section 6.6.

For subcutaneous administration

- For instructions on preparation and administration of the medicinal product, see section 6.6.

4.3 Contraindications

Severe 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 name and the batch number of the administered product should be clearly recorded.

Hypersensitivity reactions

Hypersensitivity reactions (such as facial swelling, rash, flushing) have occurred in Loargys treated subjects. The reactions generally occurred with the first few doses, see section 4.8 for additional details.

The initial administrations of Loargys should be performed under medical observation where proper medical care for hypersensitivity reactions could be provided.

If a hypersensitivity reaction occurs, appropriate medical treatment should be provided and the patient monitored until signs and symptoms are resolved. The management of hypersensitivity reactions may include temporarily interrupting the infusion, lowering the infusion rate, and/or treatment with antihistamines and/or corticosteroids. Pre-medication with an antihistamine and/or corticosteroid should be considered in patients who previously have developed a hypersensitivity reaction in connection with pegzilarginase treatment.

In case of home administration by a non-healthcare professional, the patient should be informed of the early signs of severe hypersensitivity reactions e.g., hives, generalised urticaria, tightness of the chest, wheezing and hypotension. If symptoms of severe hypersensitivity occur, patient should be advised to stop administration immediately and contact their health-care provider or emergency department. Prescription of medication for treatment of a potential severe hypersensitivity reaction should be considered.

Monitoring of plasma arginine

Pegzilarginase will interfere with routine arginine laboratory analysis, resulting in erroneous low measurements due to post-collection degradation of arginine. The testing laboratory should be informed that the patient is treated with a medicinal product that metabolises and reduces arginine levels. Alternative validated sampling procedures to measure arginine must be used in patients treated with Loargys. This includes CE-marked blood collection tubes containing the enzyme-blocker nor-NOHA.

Populations not studied in clinical trials

No data from clinical trials are available in middle-age and elderly patients with long-existing motoric impairment, or in patients with arginine levels near 200 µM on dietary protein restriction alone. Extrapolation of the treatment effects as shown in the clinical trial population is unclear (see section 5.1). The benefit-risk need to be determined on an individual basis in these patients.

Excipients

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

This medicinal product contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially ‘potassium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Pegzilarginase is a recombinant human enzyme and therefore no cytochrome P450 mediated drug-drug interactions are expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of pegzilarginase in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Pegzilarginase is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether pegzilarginase is excreted in human or animal milk.

A risk to the breastfed new-born/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Loargys therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No human data are available. In animal studies, pegzilarginase produced effects on spermatogenesis and reduced female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reaction in patients in clinical trials was hypersensitivity (12.5%).

Tabulated list of adverse reactions

Assessment of adverse reactions was based on exposure in 48 ARG1-D patients (8 adults and 40 children between the ages of 2 and 31 years) with treatment duration of up to approximately 4 years across 3 clinical trials (see section 5.1).

Adverse reactions are listed by MedDRA system organ class and by frequency in Table 1 below. 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); very rare (< 1/10 000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Due to the small size of the medicinal product safety ARG1-D population database (N=48), the adverse reaction frequency for uncommon, rare and very rare could not be reliably estimated.

Table 1. Adverse reactions

System organ class	Very common	Common
Immune system disorders	Hypersensitivity	
General disorders and administration site conditions		Injection site reaction

Description of selected adverse reactions

Hypersensitivity

Hypersensitivity reactions with symptoms including facial swelling, rash and flushing have been reported. In clinical trials, when administered intravenously, 6 of 48 (12.5%) Loargys-treated patients, experienced signs and symptoms either consistent with, or that may be related to a hypersensitivity reaction. The reactions generally occurred with the first few doses. The reactions were mild or moderate and resolved spontaneously, or rapidly after treatment with standard medical care. None of the reactions led to discontinuation of treatment. In the clinical trials, pre-medication with non-sedating antihistamines was considered on an individual basis prior to administration (see section 4.4).

Injection site reactions

Injection site reactions were reported in 8.8% (3/34) of Loargys-treated patients after subcutaneous administration. Signs and symptoms included erythema, swelling, and rash at the injection site. The injection site reactions were mild in severity and resolved spontaneously or with standard medical care without dose interruption.

Immunogenicity

There is potential for immunogenicity to pegylated therapeutic proteins. The observed incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the assay. Across all clinical trials in the pegzilarginase ARG1-D development program, 12 of 48 subjects (25%) tested positive for ADAs against PEG and/or the protein moiety of pegzilarginase, with the majority detected early after the first dose. There was no assay available for detecting neutralising antibodies during the clinical development programme. The ADAs were transient in nature and resolved during continued treatment. The presence of ADAs was associated with transient changes in the pharmacokinetics (PK) and pharmacodynamics (PD) of Loargys in patients with ARG1-D.

Paediatric population

The majority of patients treated with pegzilarginase in the ARG1-D development programme were paediatric patients with 88% (40/48) being children (2-18 years old). The safety profile of pegzilarginase presented in the safety section is therefore considered representative for the paediatric population above 2 years.

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

Potential effects from an overdose would likely be an exaggerated pharmacologic effect of pegzilarginase resulting in abnormally low plasma arginine levels (see section 5.3).

In an oncology Phase 1 trial in subjects with advanced solid tumours, 1 subject inadvertently received 1.6 mg/kg of pegzilarginase (16 × the recommended initial dose of 0.1 mg/kg in ARG1-D patients). The subject developed nausea, vomiting, diarrhoea, and fatigue, and was successfully treated with intravenous supportive care without sequelae.

Patients suspected of receiving an overdose should be closely monitored and general supportive measures should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes.
ATC code: A16AB24

Mechanism of action

ARG1-D is an inherited metabolic disease characterised by deficiency of the arginase 1 enzyme and associated with the persistent elevation of plasma arginine leading to disease manifestations and progression of clinical symptoms.

Pegzilarginase is a cobalt substituted recombinant human arginase 1 enzyme conjugated with 5 kDa mPEG carriers at a degree of substitution of 6-12 moles of mPEG per mole of protein. The molecular mass of the conjugated protein is approximately 224-344 kdA. The mPEG carrier reduces clearance of pegzilarginase resulting in an extended half-life while maintaining the functions of the enzyme. Pegzilarginase is intended to substitute for the deficient human arginase 1 enzyme activity in patients with ARG1-D. Pegzilarginase has been shown to rapidly and sustainably reduce plasma arginine and convert it to urea and ornithine.

Pharmacodynamic effects

The PD effects of pegzilarginase have been evaluated in adults and paediatric subjects with ARG1-D across a range of doses administered both intravenously and subcutaneously.

Intravenous administration of pegzilarginase resulted in early reductions in plasma arginine levels with median time to nadir (lowest arginine level) of 2-5 hours. It is expected that plasma arginine will reach its steady-state on or before Week 8 (see Figure 1). It is not expected for the time to reach these levels to be influenced by the baseline plasma arginine value or the route of administration.

Plasma arginine levels remained controlled after switching from intravenous to subcutaneous administration at the same dose, and subcutaneous administration led to fewer and shorter episodes of pegzilarginase-induced hypoargininaemia.

Corresponding significant increases in plasma ornithine levels and decreases in plasma guanidino compound levels were demonstrated with pegzilarginase treatment.
Treatment with pegzilarginase does not directly target elevated plasma ammonia levels.

Clinical efficacy and safety

The safety and efficacy of pegzilarginase were assessed in a multicentre, double-blind, placebo-controlled trial (CAEB1102-300A, ‘Study 300A’) which included 32 paediatric and adult subjects aged 2 to 29 years with ARG1-D. Subjects were randomised 2:1 to receive pegzilarginase or placebo intravenously once weekly at an initial dose of 0.1 mg/kg and titrated within a range of 0.05 mg to 0.2 mg/kg. All subjects were to continue on any previously prescribed dietary regimen and ammonia scavengers throughout the trial period.

The primary endpoint assessed the reduction from baseline in plasma arginine in subjects treated with pegzilarginase compared to placebo at Week 24. The key secondary endpoints assessing functional mobility were Gross Motor Function Measure Part E (GMFM-E, walking, running, jumping) and the 2-minute walk test (2MWT). Additionally, the proportion of subjects achieving plasma arginine levels below target per treatment guidelines (< 200 µM) and within the normal range as well as the effect on GMFM Part D (GMFM-D, standing) were evaluated as secondary endpoints.

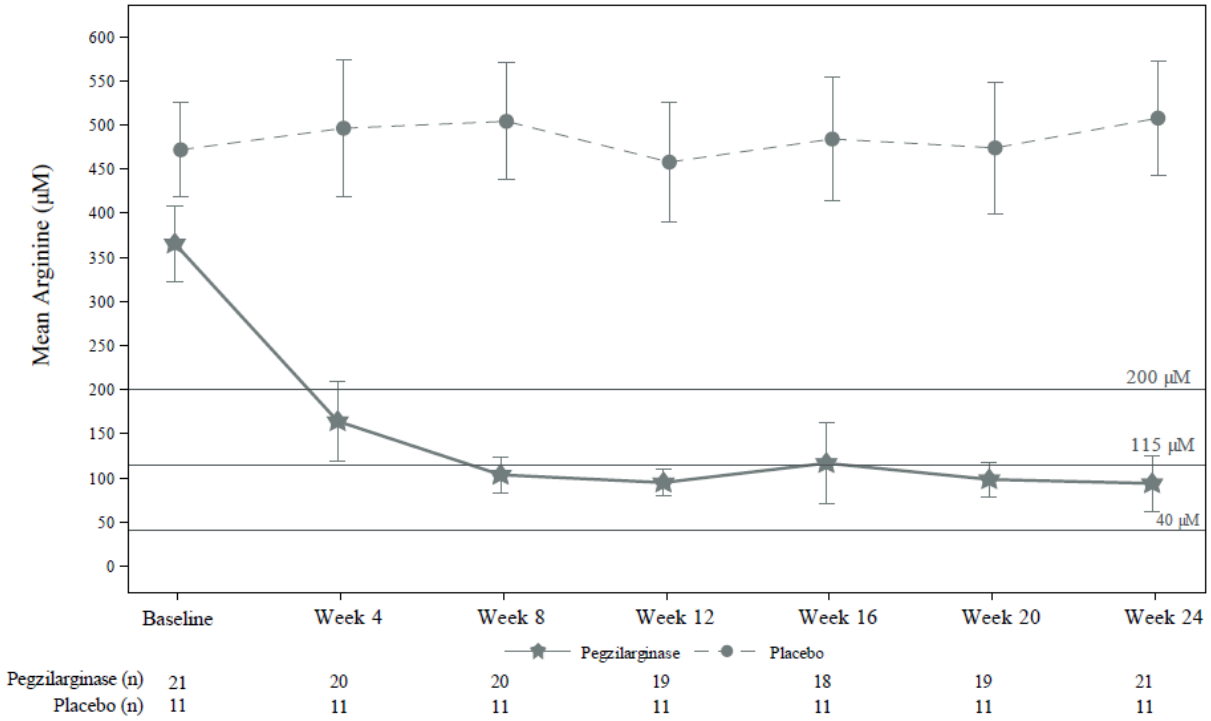
Treatment with pegzilarginase resulted in a statistically significant reduction in plasma arginine compared to placebo ($p< 0.0001$) after 24 weeks of treatment (Table 2 and Figure 1). Plasma arginine levels below guideline recommended target and within normal range were achieved in 90.5% of pegzilarginase-treated subjects compared to 0% of the subjects in the placebo arm (Table 2 and Figure 1).

Table 2: Analysis of plasma arginine endpoints during Study 300A double-blind period

	Pegzilarginase (n=21)		**Placebo (n=11)**	
Primary endpoint: Change from Baseline to week 24 (Log-Transformed)				
	Baseline	**Week 24**	**Baseline**	**Week 24**
n	21	21	11	11
Geometric mean (μM) (CV)[c]	354.0 (0.27)	86.4 (0.50)	464.7 (0.19)	426.5 (0.27)
Week 24 estimated reduction compared to Baseline (95% CI)	76.7% (-146.7%, 300.1%)		0.0% (-234.4%, 232.4%)	
Pegzilarginase Week 24 estimated reduction relative to placebo (95% CI)[a]	76.7% (67.1%, 83.5%)			
p-value[a]	< 0.0001			
Proportion of subjects achieving target levels in plasma arginine at week 24				
Proportion of subjects who achieved guideline recommended target arginine levels (< 200 μM)	19 (90.5%)		0 (0%)	
Proportion of subjects who achieved normal arginine target levels (defined as < 115 μM)	19 (90.5%)		0 (0%)	

[a] Based on an MMRM with visit, randomised trial treatment, and interaction between visit and randomised trial treatment as effects and logged Baseline value included as a covariate. Default covariance structure type=unstructured. Week 24 estimated % reduction was based on geometric mean ratio and accompanying 95% CI;
Abbreviations: CI=confidence interval; CV=coefficient of variation.

Figure 1 Summary of least square mean (95% CI) 168-hour post dose arginine levels (µM) over time in Study 300A double-blind period



Notes: Medical guideline recommendation for plasma arginine: <200 µM; Normal range defined as 40–115 µM in the clinical trial. Last observation carried forward (LOCF) was used for missing values at Week 24.

Treatment with pegzilarginase also resulted in numerical trends of improvement in mobility relative to placebo after 24 weeks as assessed by GMFM-E, 2MWT and GMFM-D performance (Table 3).

At Week 24, more subjects treated with pegzilarginase met the defined response criteria for arginine and across multiple mobility domains. Eight out of 17 evaluable subjects treated with pegzilarginase met the criteria for response in ≥ 2 neuromotor function assessments in conjunction with normalisation of plasma arginine levels, with 6 of the responders having no worsening in any assessments. Without treatment with pegzilarginase, no subjects met clinical response criteria on 2 or more clinical outcomes.

Table 3: **Analysis of secondary mobility endpoints from Study 300A double-blind period**

	Pegzilarginase (n=21)	**Placebo (n=11)**
GMFM Item E (Change from baseline to week 24)		
n	20	11
Mean (SD)	4.2 (7.69)	-0.4 (6.2)
LS Mean	4.2	-0.4
95% CI for LS Mean	0.8, 7.6	-4.9, 4.2
LS Mean Difference (Pegzilarginase – Placebo) (95% CI)	4.6 (-1.1, 10.2)	
2MWT (Change from baseline to week 24)		
n	19	10
Mean (SD)	7.3 (30.64) meters	2.7 (19.66) meters
LS Mean	7.4	1.9
95% CI for LS Mean	-5.0, 19.8	-15.2, 19.1
LS Mean Difference (Pegzilarginase – Placebo) (95% CI)	5.5 (-15.6, 26.7)	
GMFM Item D (Change from baseline to week 24)		
n	20	10
Mean (SD)	2.7 (3.88)	0.4 (0.97)
LS Mean	2.7	0.4
LS Mean Difference (Pegzilarginase – Placebo) (95% CI)	2.3 (-0.4, 4.9)	

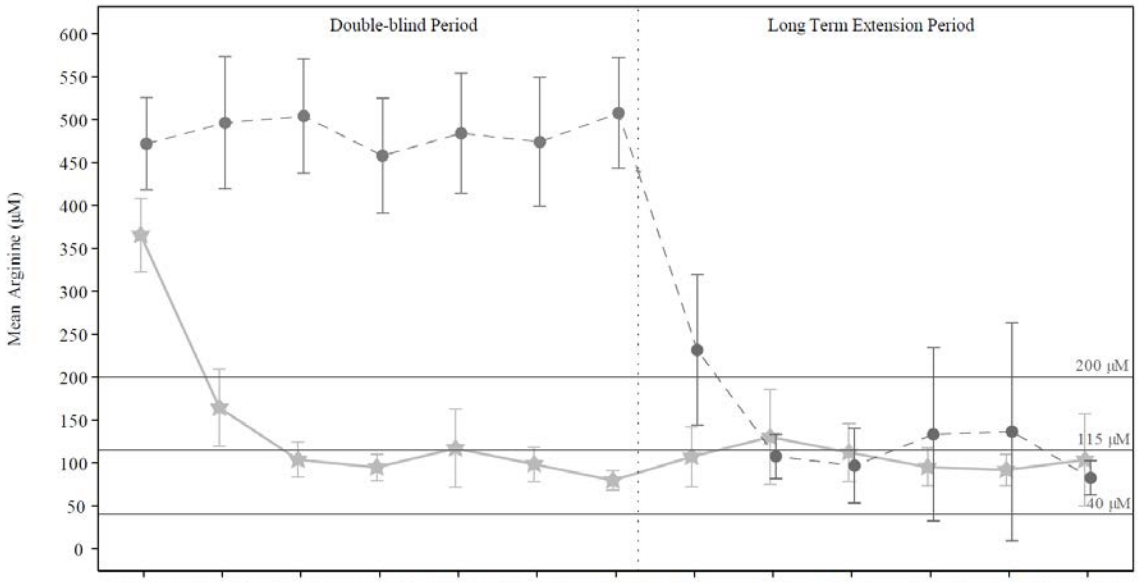
Abbreviations: 2MWT=2-minute walk test; CI=confidence interval; GMFM=Gross Motor Function Measure; LS=least squares, MMRM=mixed model repeated measures; SD=standard deviation; SE=standard error.
Note: Unless noted otherwise, model-based estimates (LS means, differences, 95 % CIs, and p-values) are based on an MMRM analysis with visit, randomised trial treatment, and interaction between visit and randomised trial treatment and baseline value as covariates. Default covariance structure type=unstructured.

Long-term treatment in ARG1-D

Paediatric and adult subjects who participated in the double-blind period of Study 300A were eligible to continue treatment in an open -label extension period with once weekly pegzilarginase treatment. Thirty-one (n=20 pegzilarginase and n=11 placebo) of the 32 subjects entered the extension period. Subjects previously receiving pegzilarginase were transitioned to subcutaneous administration at the earliest after 8 weeks of intravenous treatment. The median duration of pegzilarginase exposure was 31 weeks (range: 1 to 102 weeks).

During the open -label extension, subjects who previously received pegzilarginase demonstrated sustained improvements in plasma arginine levels, GMFM-E and GMFM-D scores and 2MWT. Subjects randomised initially to placebo and treated with pegzilarginase in the open -label extension period also showed similar reductions from baseline in mean plasma arginine levels (Figure 2).

Figure 2 Summary of mean 168-hour post dose arginine levels (µM) over time in Study 300A double-blind and long-term extension periods



Pegzilarginase (n)	21	20	20	19	18	19	20	16	15	14	13	12	10
Placebo/Pegzilarginase (n)	11	11	11	11	11	11	11	7	7	7	5	7	5

Notes: 95% confidence interval of mean is displayed; Medical guideline recommendation for plasma arginine: <200 µM; Normal range defined as 40–115 µM in the clinical trial.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Loargys in one or more subsets of the paediatric population in treatment of hyperargininaemia (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease 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 pharmacokinetic (PK) properties of pegzilarginase were evaluated following intravenous and subcutaneous administration in adults and paediatric subjects with ARG1-D. Population PK analysis has been used to characterise the pharmacokinetics of pegzilarginase.

The following PK parameters at steady state were derived using the final population PK model (Table 4). The final PK model was based on data obtained from 20 female and 17 male subjects, aged 2-31 years old with body weights 12.2-76.7 kg. In the clinical trials, the dose range was 0.015-0.2 mg/kg. Simulated dose in the model was 0.1 mg/kg for 5 weeks.

Table 4: Pharmacokinetic parameters at steady state

	Pegzilarginase	
	Intravenous	Subcutaneous
Steady state exposure [C_{max} (µg/ml)]*	2.48 (19.9%)	0.579 (19.9%)
Steady state exposure [AUC_{0-168} (h*µg/ml)]*	108 (18.3%)	61.3 (18.3%)
T_{max} (h)**	0.25^	34 (22.0 - 46.0)

Abbreviations: AUC_{0-168}=area under the concentration-time curve from time 0 to 168 hours; C_{max}=maximum observed concentration; $t_{½}$=half-life; T_{max}=time to maximum concentration
* Data displayed are geometric mean and geometric coefficient of variation (%)
** Data displayed as [median (range)]
^ For intravenous dosing, the Tmax corresponds to the time of the first measured PK sample. In these simulations the first PK sample was set at the end of infusion (0.25 h post-dose) for all subjects with no variability.
Simulations were performed for a patient with a body weight of 31kg.

Absorption

Following subcutaneous administration, the mean absolute bioavailability was 57 % and the maximum concentration was reached approximately 34 hours post-dose. Exposure to pegzilarginase increase in an approximately dose-proportional manner with linear PK over a dose range of 0.04 to 0.2 mg/kg intravenous and 0.06 to 0.2 mg/kg subcutaneous. Negligible accumulation was observed after weekly dosing.

Distribution

Pegzilarginase is mainly distributed in the vascular system, with a total volume of distribution of approximately 47 ml/kg, which is similar to human serum volume. The pharmacokinetics was best described with a population-PK model which comprised two-compartments (central and peripheral).

Elimination

Pegzilarginase is a pegylated recombinant human enzyme. To allow once-weekly administration, PEG has been used as a carrier to prolong the half-life of pegzilarginase compared to endogenous arginase. Based on population PK analysis; pegzilarginase has a half-life of approximately 50 hours. The enzyme is expected to be metabolised into small peptides and amino acids by catabolic pathways. Pegzilarginase utilizes a 5 kDa PEG which is eliminated via renal glomerular filtration in patients with normal renal function.

Special populations

Age and sex were not found to be significant covariates once body weight was taken into account. Anti-PEG ADAs were considered an important covariate on clearance, however, this effect was observed with initial doses and it is expected that exposure at steady-state will not be affected.

Renal impairment

Pegzilarginase has not been studied in patients with renal impairment. It cannot be excluded that elimination of PEG is decreased in patients with impaired renal function.

Hepatic impairment

Pegzilarginase has not been studied in patients with hepatic impairment. Changes in the clearance of the enzyme are expected as pegzilarginase is metabolised by catabolic pathways.

Body weight

Overall, body weight had a minimal impact (< 20%) on the exposure of pegzilarginase, when dosing is weight based.

5.3 Preclinical safety data

Animal toxicology and/or pharmacology

Dose-dependent and adverse loss of appetite and reductions in body weight gain attributed to marked and sustained arginine depletion below the normal range in normal animals (mice, rats, rabbits and monkeys) was observed in single and repeat dose toxicology studies as well as developmental and reproductive toxicity studies with pegzilarginase. These findings were reversible following cessation of dosing.

In the long-term studies with pegzilarginase, male reproductive toxicities were noted in a single species, healthy juvenile rats. The principal adverse findings at dose levels ≥0.3 mg/kg, included decreased weights of testes, seminal vesicles, epididymides and prostate, atrophy was observed in the seminiferous tubules. The male rat organ weight findings were reversible. Histopathology confirmed findings in the testes and epididymides, which were not reversible in the recovery period of 6 weeks; however, it is worth noting that the normal sperm cycle is 9 weeks. These effects could be due to exaggerated pharmacology in normal animals with normal circulating arginine levels at baseline. However, the relevance for humans is unclear.

Reproductive and developmental toxicology

Studies conducted with pegzilarginase in rats and rabbits with normal circulating arginine levels demonstrated maternal reproductive toxicity that is associated with sustained decreases in plasma arginine concentrations below the normal range during gestation. Toxicities associated with the prolonged exaggerated pharmacology in pregnant animals were decreased maternal body weights, food consumption, and mean gravid uterine weights and associated secondary fetal growth retardation.

In pre- and postnatal development toxicology studies in rats with normal circulating arginine levels, male rat offspring of nursing animals dosed with 1 mg/kg pegzilarginase (approximately 7 times human exposure based on AUC) revealed deficits possibly due to secondary effects related to exaggerated pharmacology in animals with normal circulating arginine levels (see section 4.6).

Fertility

During fertility assessments conducted in normal animals with normal circulating arginine levels, male rats dosed at 1 mg/kg showed decreased sperm production and motility. Additionally, in naïve female rats paired with males treated at 1 mg/kg/dose for 8 weeks prior to mating, pegzilarginase-related effects included a significant reduction in uterine implantation sites and increased pre-implantation loss.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Potassium dihydrogen phosphate
Dipotassium phosphate
Glycerol

Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

2 years

Once removed from the refrigerator, Loargys can be stored for 2 hours at room temperature up to 25 °C.

After preparation

Chemical and physical stability has been demonstrated for 2 hours when stored at room temperature up to 25 °C or up to 4 hours if stored refrigerated at 2 °C to 8 °C. If the product is not used within these time frames, it must be discarded. From a microbiological point of view, the product should be used immediately after preparation.

6.4 Special precautions for storage

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

Do not freeze.

Store in the original carton in order to protect from light.

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

6.5 Nature and contents of container

Each pack contains 1 vial with 0.4 ml or 1 ml solution for injection/infusion.

0.4 ml solution for injection/infusion in a 3 ml type 1 glass vial with a Fluorotec coated chlorobutyl rubber stopper, aluminium seal and a blue flip-off cap.

1 ml solution for injection/infusion in a 5 ml type 1 glass vial with a Teflon coated chlorobutyl rubber stopper, aluminium seal and a white flip-off cap.

Pack size of 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not shake.

Loargys is intended for intravenous infusion or subcutaneous injection and should be administered by a healthcare professional. If appropriate, subcutaneous home administration by the patient or caregiver may be considered (see section 4.2).

Use aseptic technique when preparing and administering Loargys.

Instruction for preparation

- Determine the total volume of Loargys to be administered (and the number of vials needed) based on the patient's weight and dose level (see section 4.2).
- Remove the vial(s) from the refrigerator to reach room temperature.
- Inspect the vial visually for particulate matter and discoloration prior to administration. Loargys is a colourless to slightly yellow or slightly pink, clear to slightly opalescent liquid, essentially free of visible foreign particles. Discard any vial(s) not consistent with this appearance.
- Withdraw the intended dose into the syringe. See section 6.3 for storage conditions.

For intravenous administration

- Dilute with sodium chloride 9 mg/ml (0.9 %) solution for injection to achieve the desired volume of infusion (maximum pegzilarginase concentration 0.5 mg/ml).
- Administer the intravenous infusion over at least 30 minutes.
- Do not mix other medicinal products with Loargys or infuse other medicinal products concomitantly via the same intravenous access line.

For subcutaneous administration

- Administer the undiluted solution as subcutaneous injection into the abdomen, lateral part of the thigh, or the side or back of the upper arms. Rotate injection sites between doses. Do not inject into scar tissue or areas that are reddened, inflamed, or swollen.
- If injecting into the abdomen, avoid the area directly surrounding the navel.
- If more than 1 injection is needed for a single dose of Loargys, the injection sites should be at least 3 cm apart.

Discard unused portion of the medicinal product.

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Immedica Pharma AB
113 63 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1774/001
EU/1/23/1774/002

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(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)

Fujifilm Diosynth Biotechnologies U.S.A. Inc.
6051 George Watts Hill Drive
27709 North Carolina
United States

Name and address of the manufacturer(s) responsible for batch release

Unimedic AB
Storjordenvägen 2
864 31 Matfors
Sweden

Immedica Pharma AB
Solnavägen 3H
113 63 Stockholm
Sweden

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (MAH) shall submit the first PSUR 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.

- **Additional risk minimisation measures**

Prior to launch of Loargys in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to provide instructions to non-healthcare professionals (patients and caregivers) for proper administration techniques to address the potential risk of medication errors as well as to minimize the potential risk of severe hypersensitivity reaction.

The MAH shall ensure that in each Member State where Loargys is marketed, all patients or caregivers who are expected to administer Loargys as a subcutaneous injection in the home-setting are provided with the following educational material:

- Injection guide for patients and caregivers

This educational material, for patients and caregivers, shall contain the following key messages:

- Instructions on importance of proper handling, preparation and administration of Loargys to reduce the risk of medication errors.
- A detailed description on how to prepare and administer Loargys.
- A description of the signs and symptoms of severe hypersensitivity reactions.
- A description of the recommended course of action if signs and symptoms of hypersensitivity occur.
- Information on the importance of reporting of side effects including hypersensitivity and medication errors.

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
Post-authorisation efficacy study (PAES): In order to collect information on the long-term effectiveness/clinical outcomes in patients with arginase 1 deficiency (ARG1-D) treated with pegzilarginase, the MAH should conduct and submit the results of a study in patients, based on data from a registry.	Annually (with annual re-assessment)
Non-interventional post-authorisation safety study (PASS): In order to further characterise the long-term safety of pegzilarginase, the MAH should conduct and submit the results of a study in patients with arginase 1 deficiency (ARG1-D) based on data from a registry.	Annually (with annual re-assessment)
In order to further characterise the long-term efficacy and safety of pegzilarginase, the MAH should submit the final results of study CAEB1102-300A, a Phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of pegzilarginase in adults, adolescents and children with arginase 1 deficiency (ARG1-D).	31 March 2024
In order to further characterise the long-term efficacy and safety of pegzilarginase, the MAH should submit the final results of study CAEB1102-102A, an open-label extension study to evaluate the long-term safety, tolerability, and efficacy of pegzilarginase in adults, adolescents and children with arginase 1 deficiency (ARG1-D).	31 March 2024
In order to ensure adequate monitoring of safety and efficacy of pegzilarginase in the treatment of arginase 1 deficiency (ARG1-D) in adults, adolescents and children, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of pegzilarginase.	Annually (with annual re-assessment)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Loargys 5 mg/ml solution for injection/infusion
pegzilarginase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution contains 5 mg of pegzilarginase.

3. LIST OF EXCIPIENTS

Also contains: sodium chloride, potassium dihydrogen phosphate, dipotassium phosphate, glycerol, hydrochloric acid, sodium hydroxide, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection/infusion

1 vial of 0.4 ml
2 mg/0.4 ml

1 vial of 1 ml
5 mg/1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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.
Store in the original carton in order to protect from light.

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

Immedica Pharma AB
113 63 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1774/001
EU/1/23/1774/002

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

Loargys 5 mg/ml injection/infusion
pegzilarginase
SC, IV use

2. METHOD OF ADMINISTRATION

Subcutaneous use, intravenous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mg/0.4 ml
5 mg/1 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Loargys 5 mg/ml solution for injection/infusion
pegzilarginase

▼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 or nurse.
- If you get any side effects, talk to your doctor, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Loargys is and what it is used for

Loargys contains the active substance pegzilarginase, which is a modified human enzyme produced by recombinant DNA technology. The medicine is used to treat arginase 1 deficiency (ARG1-D), also known as hyperargininemia, in adults, adolescents and children aged 2 years and older.

Patients with ARG1-D have low levels of an enzyme called arginase. This enzyme helps the body control levels of arginine, an amino acid needed by your body to make proteins. If arginine is not controlled it can build up in the body and cause symptoms, like problems with muscle control.

Loargys is used in combination with other ways to manage the disease. These may include;
- a diet that is low in protein
- food supplements with essential amino acids
- medicines to manage other symptoms of the disease, such as medicines that lower levels of ammonia in your body.

How Loargys works
Pegzilarginase, the active substance in Loargys, acts similarly to the natural enzyme arginase, which is lacking or not working properly in patients with ARG1-D. This lowers arginine levels in the blood, thereby reducing the disease symptoms.

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

You must not be given Loargys
- if you have had a severe allergic reaction to pegzilarginase or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Loargys may cause allergic reactions. This is most likely to occur after the first few doses.

Stop the injection immediately and contact your health care provider or emergency department if you experience any of the following symptoms of a severe allergic reaction: hives, generalised itching, tightness of the chest, difficulty breathing or low blood pressure. Your doctor may decide you need additional medical treatment to either prevent or treat an allergic reaction.

During your treatment, your doctor will do blood tests to check what dose of Loargys is right for you.

Children and adolescents
The medicine should not be used in children under 2 years of age, because it is not known if Loargys is safe and effective in this age group.

Other medicines and Loargys
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Loargys is not recommended for use if you are pregnant.

It is not known if the medicine passes into breast milk. If you are breast-feeding, ask your doctor for advice before taking this medicine. Your doctor will help you decide whether to stop breast-feeding or to stop treatment.

Driving and using machines
Loargys has no or negligible influence on the ability to drive and use machines.

Loargys contains sodium and potassium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. This medicine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.

3. How Loargys is given

Loargys will be given to you by a healthcare professional. Your doctor will decide the amount of Loargys given to you.

The recommended starting dose of Loargys is 0.1 mg per kilogram of your body weight taken once per week. The dose may be increased or decreased by your doctor to keep your blood arginine levels under control. Your doctor will do regular blood tests to check your blood arginine levels and change your dose if needed.

Loargys is given as an infusion (drip) directly into your vein or as an injection under the skin, as considered appropriate by your doctor.

Your doctor may decide you can be given Loargys at home, as an injection under the skin. After being trained by the doctor or nurse, you can inject Loargys yourself, see instructions in section 7 below.

Always use this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

If you are given more Loargys than you should
Your doctor will ensure that you receive the right amount of Loargys. If you have been given too much Loargys, your blood arginine level may become too low. Symptoms may include nausea, vomiting, diarrhoea and tiredness. If you or your doctor suspects that you have been given more Loargys than you should, you should be closely monitored and given treatment as needed.

If you forget to use Loargys
If you have missed a dose of Loargys, contact your doctor to schedule the next dose as soon as possible. You should not be given a double dose to make up for a forgotten dose and there should be at least 4 days between doses.

If you stop using Loargys
Your doctor will decide if you should stop using Loargys. If you stop using Loargys, your blood arginine level is likely to increase again.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

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

Very common (may affect more than 1 in 10 people)
- Allergic reaction (hypersensitivity). Symptoms may include swelling of your face, skin rash and sudden redness of the skin (flushing).

Common (may affect up to 1 in 10 people)
- Injection site reaction. Symptoms may include swelling, redness and rash around the site of injection.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. 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 to store Loargys

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 label. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Store in the original carton in order to protect from light.

Once removed from the refrigerator, Loargys can be stored for 2 hours at room temperature up to 25 °C.

Do not throw away any medicines via wastewater or household waste. These measures will help protect the environment.

6. Contents of the pack and other information

What Loargys contains

- The active substance is pegzilarginase.
- Each 0.4 ml vial contains 2 mg pegzilarginase.
- Each 1 ml vial contains 5 mg pegzilarginase.
- The other ingredients are sodium chloride, potassium dihydrogen phosphate, dipotassium phosphate, glycerol, hydrochloric acid, sodium hydroxide and water for injections. Loargys contains sodium and potassium, see section 2.

What Loargys looks like and contents of the pack
Loargys is a colourless to slightly yellow or slightly pink, clear to slightly opalescent (pearly) liquid, in a clear glass vial.

Each pack contains 1 vial with either 0.4 ml or 1 ml solution for injection/infusion.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Immedica Pharma AB
113 63 Stockholm
Sweden

Manufacturer
Unimedic AB
Storjordenvägen 2
864 31 Matfors
Sweden

This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

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.

You can find the information also when scanning the QR code below with a smartphone or via the website http://www.loargyspatient.eu

7. Instructions for use

The steps below describe how to prepare and give Loargys at home, as an injection under the skin. If you are injecting this medicine yourself, you will be trained how to prepare and inject Loargys by your doctor or nurse.

Do not inject this medicine yourself unless you have received training and you understand the steps.

Your doctor will prescribe your correct dose and will tell you what volume (in ml) to inject. You may need more than one vial to get the correct dose and you may need to divide the total dose into more than one injection. Your doctor or nurse will tell you exactly what is right for you.

Each vial is for single use only, always use new vial(s) for each dose.
Loargys should not be mixed with other solutions for injection or infusion.
Do not shake.

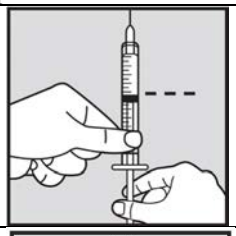
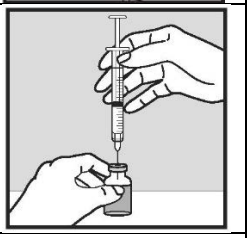
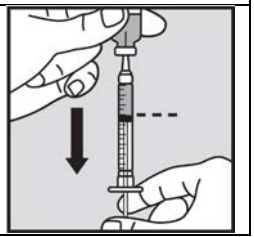
Preparation:

Make sure you have everything you need for the injection(s):

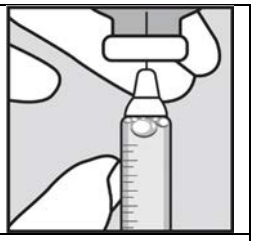
- Loargys vial(s)
- A graduated syringe
- 1 large needle (e.g. 18 Gauge) per vial, to withdraw the dose
- 1 small needle (e.g. 26-27 Gauge) per injection
- Alcohol wipes
- Gauze pad
- Plaster, if required
- Sharps container

1.	Check the name and the strength of the package to make sure it contains the correct medicine. Check the expiry date on the carton. Do not use if the product has expired.
2.	Take the unopened Loargys vial(s) out of the refrigerator **15 to 30 minutes** before the planned injection to allow the solution to reach room temperature. Do not use external heat.
3.	Wash your hands.
4.	The solution in the vial should be colourless to slightly yellow or slightly pink, clear to slightly opalescent (pearly). Do not use if the solution is cloudy or contains visible particles.
5.	Place the vial on a clean flat surface. Remove the plastic flip-off cap from the vial.
6.	Wipe the top of the vial with an alcohol swab and allow to air dry. Do not touch the top of the vial or allow it to touch anything else once wiped.

Withdrawing solution from the vial:

1.	Attach a large needle to the empty graduated syringe. Remove the needle cap.
2.	Pull the plunger back to draw air into the graduated syringe, equal to your dose (in ml). 
3.	Keep the vial on a flat surface, slowly insert the needle through the rubber seal into the vial. Avoid having the tip of the needle touching the solution. 
4.	Slowly push the plunger in completely to inject the air into the vial.
5.	Keep the needle in the vial and turn it upside down. With the needle in the solution, slowly pull the plunger to the mark equal to your dose. 

6. Before removing the needle from the vial, check the solution in the syringe for air bubbles. If there are bubbles, continue to hold the vial upside down with the needle pointing upwards. Gently tap the barrel of the syringe with your finger. Once all the air bubbles are at the top, gently push the plunger to push out the bubbles through the needle.



7. Check your dose again (in ml) against the markings on the syringe. Repeat the process if required. You may need to use several vials to withdraw the complete volume.
8. Pull the syringe and needle from the vial and put the needle cap back on.
9. Remove the needle from the syringe and dispose it in your sharps container.

Giving the dose:

1. Place a small needle on the filled syringe, do not remove the needle cap. Ensure the needle sits tight.

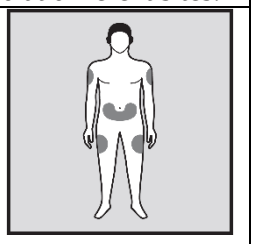
   Note: If the solution is not to be used immediately, the syringe cap should be carefully put back on the syringe tip. Do not touch the syringe tip or the inside of the cap. Protect the syringe from light.

   After preparation, Loargys can be stored at room temperature (up to 25 °C) for up to 2 hours before administration. After this time, the prepared Loargys cannot be used anymore and must be discarded.
2. Remove the needle cap. Hold the syringe with the needle pointing up and tap the barrel of the syringe with your finger to remove any air bubbles.

   Control visually that the volume contained in the syringe is correct. The volume per injection should not exceed 1 ml. If it is the case, multiple injections should be injected at different sites.
3. Choose an injection site (abdomen, side of the thigh, or the side or back of the upper arms). Rotate injection sites between doses.

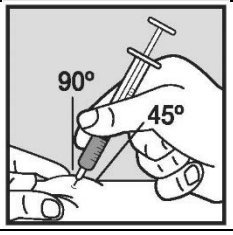
   Do not inject into scar tissue or areas that are reddened, inflamed, or swollen. If injecting into the abdomen, avoid the area directly surrounding the navel.

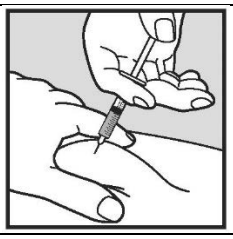
   If more than 1 injection is needed for a single dose of Loargys, the injection sites should be at least 3 cm apart.



4. Clean the injection site using an alcohol swab and allow the skin to dry.
5. Gently pinch the skin of the chosen injection site between your thumb and index finger.

6. Hold the syringe like a pencil or dart. Insert the needle into the raised skin at a 45° to 90° angle.



7. While continuing to pinch the skin, slowly push the plunger until the syringe is empty.	
8. Remove the syringe by pulling it straight out. Release the pinched skin and gently press a gauze pad over the injection site for a few seconds. Apply a plaster if needed.	
9. Put your used syringe, needles and caps in the sharps container. Used vials, even if not empty, should be discarded according to your local guidelines.	
Reminder: If you need more than one injection for your total prescribed dose, the injection sites should be at least 3 cm apart, repeat the procedure above as needed. Always use a new small needle for each injection.	

Note the date of the injection and all the sites where you have injected. This helps you to use a different injection site for the next injection.

The following information is intended for healthcare professionals only:

Loargys is intended for intravenous infusion or subcutaneous injection.
Use aseptic technique when preparing and administering Loargys.

Do not shake.

Instruction for preparation

- Determine the total volume of Loargys to be administered (and the number of vials needed) based on the patient's weight and dose level.
- Remove the vial(s) from the refrigerator to reach room temperature.
- Inspect the vial visually for particulate matter and discoloration prior to administration.
    - Loargys is a colourless to slightly yellow or slightly pink, clear to slightly opalescent liquid, essentially free of visible foreign particles.
    - Discard any vial(s) not consistent with this appearance.
- Withdraw the intended dose into the syringe.
- Chemical and physical stability for the prepared dose has been demonstrated for 2 hours when stored at room temperature up to 25 °C or up to 4 hours if stored refrigerated at 2 °C to 8 °C. If the product is not used within these time frames, it must be discarded. From a microbiological point of view, the product should be used immediately after reconstitution.

For intravenous administration

- Dilute with sodium chloride 9 mg/ml (0.9 %) solution for injection to achieve the desired volume of infusion (maximum pegzilarginase concentration 0.5 mg/ml).
- Administer the intravenous infusion over at least 30 minutes.
- Do not mix other medicines with Loargys or infuse other medicines concomitantly via the same intravenous access line.

For subcutaneous administration

- Administer the undiluted solution as subcutaneous injection into the abdomen, lateral part of the thigh, or the side or back of the upper arms. Rotate injection sites between doses.
- Do not inject into scar tissue or areas that are reddened, inflamed, or swollen.
- If injecting into the abdomen, avoid the area directly surrounding the navel.

- If more than 1 injection is needed for a single dose of Loargys, the injection sites should be at least 3 cm apart.

Discard unused portion of the medicine.

No special requirements for disposal.

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.