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 starting dose of Loargys is 0.1 mg/kg once weekly. 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) × 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, dyspnoea) have occurred in Loargys treated subjects with intravenous and subcutaneous administration. The reactions generally occurred with the first few doses, but may also occur later in treatment, see section 4.8 for additional details.

The initial administrations of Loargys should be performed under medical observation.

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 administration or lowering the infusion rate and/or treatment with antihistamines and/or corticosteroids. In severe cases stopping the administration and adrenaline treatment may be necessary. 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. Prescription of medication for treatment of a potential severe hypersensitivity reaction should be considered. Patients should also be advised what to do if symptoms of severe hypersensitivity occur which includes seeking immediate medical support.

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 reactions in patients in clinical trials were injection site reactions (13.6%) and 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 at enrolment) with treatment duration of up to approximately 5 years across 3 clinical trials.

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**
Immune system disorders	Hypersensitivity
General disorders and administration site conditions	Injection site reactions

Description of selected adverse reactions

Hypersensitivity

Hypersensitivity reactions with symptoms including facial swelling, rash, flushing and dyspnoea 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).

Post-marketing, hypersensitivity reactions were reported, even involving patients treated by subcutaneous administration who were pre-medicated with antihistamines.

Injection site reactions

Injection site reactions were reported in 13.6% (6/44) of Loargys-treated patients after subcutaneous administration. Signs and symptoms included pain, erythema, swelling, irritation 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 at enrolment 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).

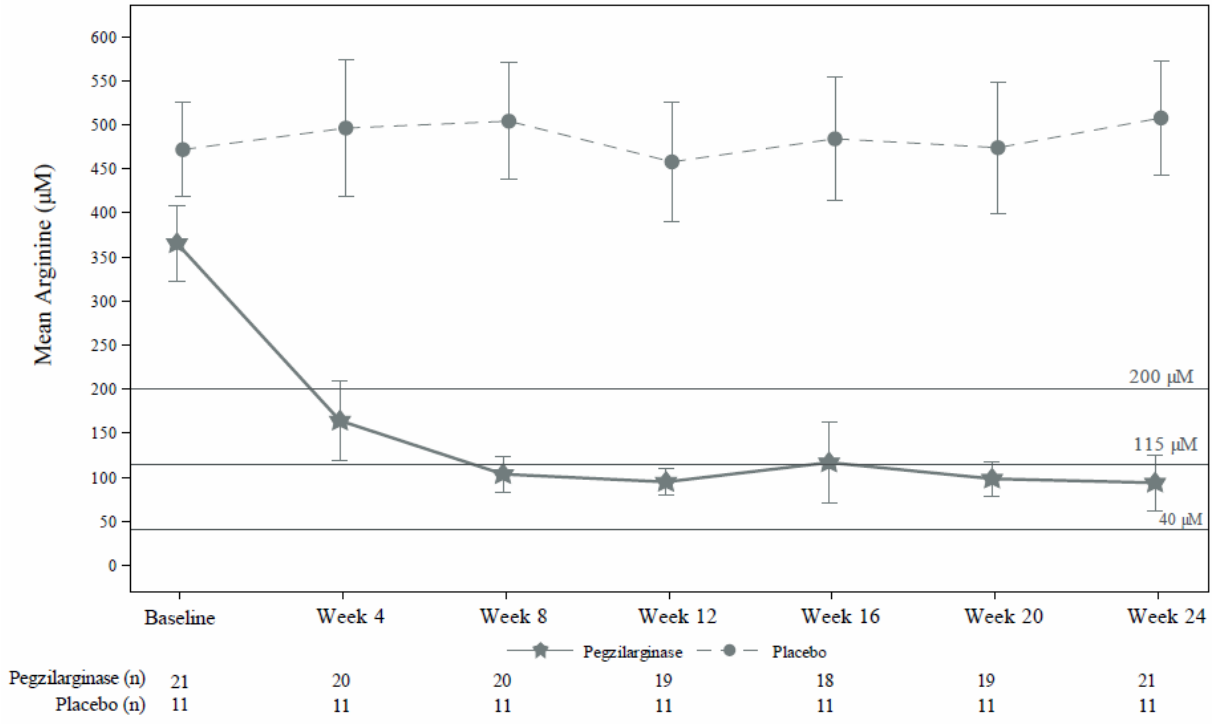
Table 2: Analysis of plasma arginine endpoints during Study 300A double-blind period

	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)	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)	

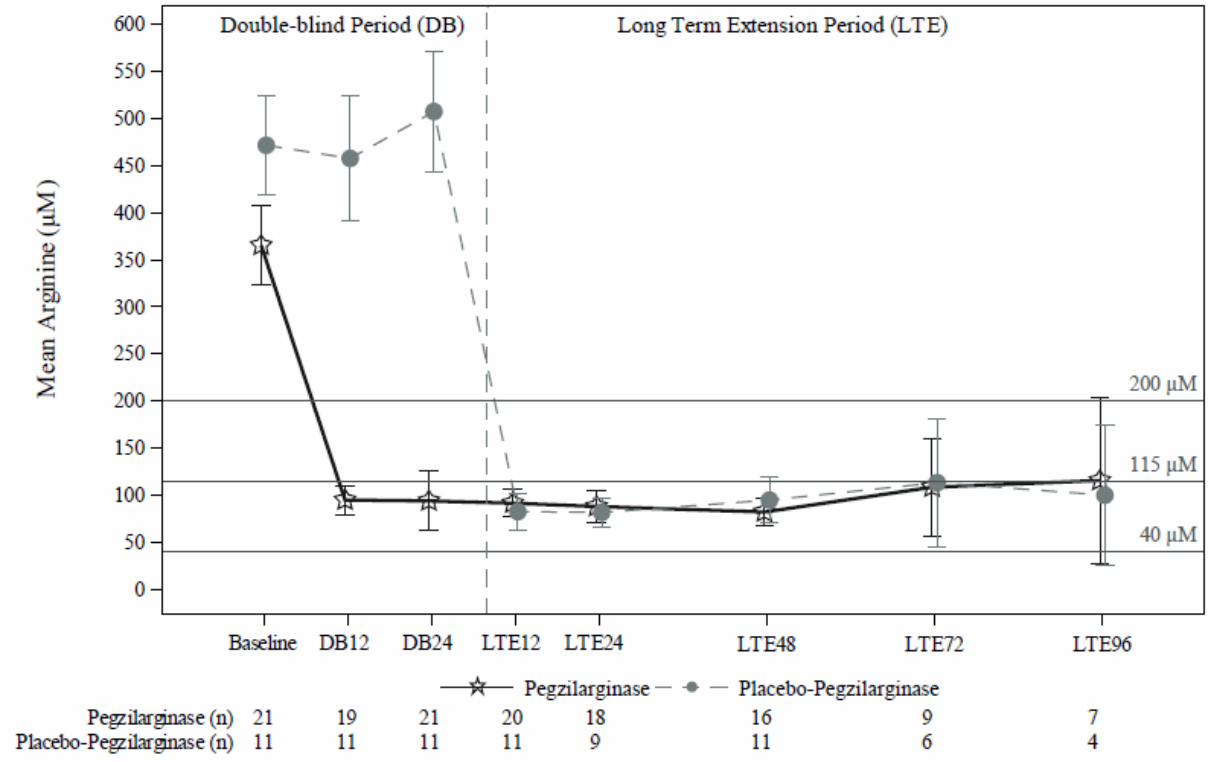
Abbreviations: 2MWT=2-minute walk test; CI=confidence interval; GMFM=Gross Motor Function Measure; LS=least squares, MMRM=mixed model repeated measures; SD=standard deviation; SE=standard error.
Note: Unless noted otherwise, model-based estimates (LS means, differences, 95 % CIs, and p-values) are based 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 in the long-term extension period, excluding the double-blind period of 24 weeks was 94 weeks (range: 62 to 152 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 period



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. Last observation carried forward (LOCF) was used for missing values at Week 24 (DB24).
Abbreviations: DB = Double-blind period, LTE = Long Term Extension Period.

Paediatric population

The Medicines and Healthcare products Regulatory 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).

Exceptional circumstances

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 Medicines and Healthcare products Regulatory 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 t_{max} 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 31 kg.

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

3 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

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)

PLGB 53487/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/12/2023

10 DATE OF REVISION OF THE TEXT

11/11/2025