Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Loargys 5 mg/ml solution for injection/infusion

pegzilarginase

PLGB 53487/0007

Immedica Pharma AB

LAY SUMMARY

Loargys 5 mg/ml solution for injection/infusion
pegzilarginase

This is a summary of the Public Assessment Report (PAR) for Loargys 5 mg/ml solution for injection/infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Loargys in this lay summary for ease of reading.

This product has been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 15 December 2023 (EMEA/H/C/005484/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended).

For practical information about using Loargys, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Loargys and what is it/they 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 1. This enzyme helps the body control levels of arginine, an amino acid needed by the 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 the body.

How does Loargys work?
Pegzilarginase, the active substance in Loargys, acts similarly to the natural enzyme arginase 1, which is lacking or not working properly in patients with ARG1-D. This lowers arginine levels in the blood, thereby reducing the disease symptoms.

How is Loargys used?
The pharmaceutical form of this medicine is solution for injection/infusion and the route of administration is subcutaneous, or intravenous use.

Loargys will be given to the patient by a healthcare professional.

The doctor will decide the amount of Loargys given to the patient.

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

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

The doctor may decide if their patient can be given Loargys at home, as an injection under the skin. After being trained by the doctor or nurse, the patient can inject themselves with Loargys.

For further information on how Loargys is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

Administration by a healthcare professional (usually first doses)
The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

Self-administration (when appropriate training has been given)
The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Loargys have been shown in studies?
Loargys was compared with placebo (a dummy treatment) in a study involving 32 adults and children with hyperargininaemia. The main measure of effectiveness was the change in the blood level of arginine after 24 weeks of treatment. The study showed that the arginine levels were reduced by 77% and normalised in patients treated with Loargys, while there was no reduction in arginine levels in patients given placebo.

Although the study also suggested that Loargys may improve motor function compared with placebo, the difference was not statistically significant (i.e. it may be due to chance). However, preliminary longer-term data collected beyond the 24-week treatment period indicated that motor function (walking and standing) may stabilise or gradually improve with long-term use of the medicine.

What are the possible side effects of Loargys?
The most common side effects with Loargys (which may affect more than 1 in 10 people) is:

- Allergic reaction (hypersensitivity). Symptoms may include swelling of the face, skin rash and sudden redness of the skin (flushing).

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can

be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Loargys approved?
MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Loargys has been authorised under "exceptional circumstances". This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. Any new information on Loargys will be reviewed every year and this report will be updated as necessary. Loargys has also been authorised with the condition to provide additional measures to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Loargys?".

Loargys has been authorised as a GB Orphan medicine. Orphan medicines are intended for use against rare conditions that are life-threatening or chronically debilitating. To qualify as an orphan medicine, certain criteria, for example concerning the rarity of the disease and the lack of currently available treatments, must be fulfilled.

What measures are being taken to ensure the safe and effective use of Loargys?
As for all newly-authorised medicines, an Risk Management Plan (RMP) has been developed for Loargys. The RMP details the important risks of Loargys, how these risks can be minimised, any uncertainties about Loargys (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Loargys:

Summary of safety concerns	
Important identified risks	None
Important potential risks	Severe hypersensitivity reactions Prolonged hypoargininaemia and its clinical sequelae Medication errors during administration by a non-healthcare professional
Missing Information	Safety in pregnancy and lactation Long-term safety

Prior to launch of Loargys in Great Britain and in each applicable member state of the EU, the Marketing Authorisation Holder (MAH) must have agreed an educational 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 minimise the potential risk of severe hypersensitivity reaction. The MAH shall ensure that in Great Britain and in each applicable member state of the EU where Loargys is marketed, that 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 toreduce 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.

Product information
The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Loargys are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Loargys
A marketing authorisation was granted in Great Britain on 20 December 2023

The full PAR for Loargys follows this summary.

This summary was last updated in February 2024.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Loargys 5 mg/ml solution for injection/infusion (PLGB 53487/0007) could be approved.

The product is approved for the following indications:
For the treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininemia, in adults, adolescents and children aged 2 years and older.

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.

This product has been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 15 December 2023 (EMEA/H/C/005484/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).
For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended).

This application was evaluated for fulfilment of orphan designation criteria. It was concluded that fulfilment of the criteria for approval as an orphan medicinal product was satisfactorily demonstrated. Please see Annex 1 for a summary of the orphan approval.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) MHRA-101071-PIP01-23-M01 (update). At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation was granted on 20 December 2023.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

The SmPC is in line with current guidelines and was satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

V. CLINICAL ASPECTS

MHRA considered that the clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance and risk minimisation measures have been proposed, this is acceptable.

Important potential risk: Severe hypersensitivity reactions	
Evidence for linking the risk to the medicine	Hypersensitivity reactions can occur with enzyme therapy and this risk is supported by epidemiologic evidence and literature reports which also note significant variation in the frequency and severity across different therapies. Furthermore, hypersensitivity reactions were reported in clinical studies. These were solely following IV dosing and there were no reports following SC dosing.
Risk factors and risk groups	Patients with known hypersensitivity to PEG or any of the excipients.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.3, 4.4 and 4.8 PL section 2 and 4 Restricted medical prescription **Additional risk minimisation measures:** Educational material
Additional pharmacovigilance activities	Pegzilarginase registry-based PASS (IMM-PEG-002) Open-label extension study (Study CAEB1102-102A) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Prolonged hypoargininaemia and its clinical sequelae	
Evidence for linking the risk to the medicine	No risks related to prolonged hypoargininaemia have been observed in the clinical development program. In the nonclinical general and developmental and reproductive toxicology studies, pegzilarginase was well tolerated, with adverse

	findings associated with exaggerated pharmacology characterized by marked and sustained arginine depletion below the normal range. These findings were reversible and likely the result of exaggerated pharmacology in normal animals at baseline and, as such, are a low risk to patients with ARG1-D that have elevated basal levels of arginine.
Risk factors and risk groups	Paediatric patients that are still under development and risk to the foetus during pregnancy.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 4.2 and 4.4 PL section 3 Restricted medical prescription **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Pegzilarginase registry-based PASS (IMM-PEG-002) Open-label extension study (Study CAEB1102-102A) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Medication errors during administration by a non-healthcare professional	
Evidence for linking the risk to the medicine	No evidence of risk available from the clinical study programme. The potential risk is based on the theoretical possibility of medication errors when the product is handled by a non-healthcare professional.
Risk factors and risk groups	Patients for whom home administration by the patient or their caregiver will be performed.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 4.2 PL section 3 and 7 Restricted medical prescription **Additional risk minimisation measures:** Educational material
Additional pharmacovigilance activities	Pegzilarginase registry-based PASS (IMM-PEG-002) See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Safety in pregnancy and lactation	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6 PL section 2 Restricted medical prescription **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Pegzilarginase registry-based PASS (IMM-PEG-002)

	See section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Long-term safety	
Risk minimisation measures	**Routine risk minimisation measures:** Restricted medical prescription **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Pegzilarginase registry-based PASS (IMM-PEG-002) Open-label extension study (Study CAEB1102-102A) See section II.C of this summary for an overview of the post-authorisation development plan.

* Section II.C can be viewed in the RMP located on the EMA website.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product for the treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininemia, in adults, adolescents and children aged 2 years and older.

As comprehensive data on the product are not available, Loargys has been authorised under "exceptional circumstances". The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	**Due date**
Non-interventional Post authorisation safety study (PASS): In order to further characterise the long-term safety and efficacy 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.	31/12/2024 (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).	31/03/2024
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.	31/12/2024 Annually (with Annual re-assessment)

Postauthorisation 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.	31/12/2024 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 CAEB1102-102A, 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).	31/03/2024

Loargys has been authorised with the condition to provide additional measures to minimise the risk. The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	**Due date**
Prior to launch of Loargys in each Member State and in GB, 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 MHRA. 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. 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 an Injection guide for patients and caregivers. For the key messages to be included in the guide - please see the RMP.	N/A (pre—product launch)

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

IX. TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**

Annex 1
Summary of fulfilment of the criteria for orphan drug designation

Product: ***Loargys 5 mg/ml solution for injection/infusion***
Active substance: ***pegzilarginase***

Orphan Designation Number: *PLGB 53487/0007/OD1*

Evaluation:

Orphan condition
The orphan condition is hyperargininaemia (also known as arginase I deficiency). This is acceptable and in line with the guidance on what constitutes a valid condition. ARG1-D is an autosomal recessive disorder of amino acid metabolism caused by mutation in the Arginase I gene with recognisable pathophysiological and clinical characteristics.

Orphan indication
The proposed therapeutic indication for pegzilarginase is for the treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininemia, in adults, adolescents and children aged 2 years and older.

Life threatening/ debilitating condition
ARG1-D is a debilitating, progressive, inherited, neurotoxic, metabolic disease associated with increased arginine and its metabolites, with significant reductions in quality of life, increased morbidity, and premature mortality. Most ARG1-D patients are asymptomatic at birth through early infancy, developing initial symptoms at 2 to 3 years of age.

The clinical presentation of ARG1-D is distinct from the other urea cycle disorders (UCDs) and is characterized by highly elevated plasma, liver, and cerebrospinal fluid levels of neurotoxic arginine and guanidino compounds. Clinical manifestations include progressively worsening spastic diplegia, gait disorders, developmental delays, intellectual disability, and seizures. Those who survive into adulthood are increasingly impacted by neurological complications and have challenges caring for themselves due to deteriorating mobility, including wheelchair dependence, and increasing intellectual disability. The condition is life-threatening and seriously debilitating.

Prevalence of the Condition in Great Britain (GB)
Suitable evidence has been provided that demonstrates that, at the time of orphan designation, the condition affects 0.014 in 10,000 people in GB. This does not exceed the upper limit of prevalence for orphan designation, which is 5 in 10,000 people in GB.

Existing methods of diagnosis/prevention/ treatment
Current international guidelines for ARG1-D[1] focus on reduction of plasma arginine to levels of <200µM, and ideally to within the normal range, as the primary treatment goal. However, there are no pharmacologic agents known to effectively reduce arginine levels in patients

[1] Häberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019;42(6):1192-230.

with ARG1-D, and no agents have been approved that specifically target the enzyme deficiency.

Current management approaches for ARG1-D include individualized combinations of protein restriction to reduce arginine, essential amino acid supplementation, and concomitant medications to manage other clinical symptoms such as ammonia scavengers to help control ammonia levels. Other treatment options have included red blood cell exchange or liver transplant, but these are limited by availability, associated morbidities, and cost. Dietary modification can produce modest reductions in plasma arginine levels, but reducing plasma arginine to the guideline-recommended level of <200 μM is difficult to achieve via dietary restriction alone as arginine flux is largely dependent on whole body protein turnover and is minimally affected by dietary intake.

Patients with ARG1-D require a range of continuous therapies and ongoing monitoring to try and manage manifestations of the disease and are often hospitalised multiple times annually for extended stays, most often related to hyperammonaemia, infection, or gastrointestinal-related illness. Common medical interventions/procedures include physical and occupational therapy, CT scans, and laboratory assessments. Patients often require surgical intervention to manage contractures. Common medications include antiepileptics, antispasmodics, and medical foods. Additionally, the use of medical devices including ankle-foot orthoses, arm crutches, canes, walkers, and wheelchairs is common. A subset of patients may require high-cost interventions, including dialysis and/or liver transplantation to lower plasma arginine levels that have demonstrated positive clinical impact.

Ammonia scavengers, including sodium phenylbutyrate (Pheburane, Ammonaps), glycerol phenylbutyrate (Ravicti), or sodium benzoate, are indicated as adjunctive therapy for the chronic management of a broad classification of UCDs, specifically by reducing the probability and frequency of the sporadic hyperammonaemic crises through control of plasma ammonia levels. However, only Ravicti is an approved medicine indicated for the treatment of ARG1-D. The active substance in Ravicti, glycerol phenylbutyrate, is a ‘prodrug’ of phenylbutyrate. It consists of three molecules of phenylbutyrate linked together. Ravicti is hydrolysed by pancreatic lipases to yield, phenylbutyrate (PBA), which is converted by beta oxidation to phenylacetic acid (PAA), the active moity. Phenylacetate conjugates with the amino acid glutamine, which contains nitrogen, to form a substance that can be removed from the body by the kidneys. This allows the levels of nitrogen in the body to decrease, reducing the amount of ammonia produced. Ravicti improves the symptoms of high ammonia levels in ARG1-D patients but does not act on lowering arginine levels and increasing ornithine levels, with no potential to improve the efficiency of the urea cycle. There were subjects with ARG1-D in the clinical development program with glycerol phenylbutyrate and their arginine levels were not reduced during the trial. In contrast to the other UCDs, in ARG1-D elevated plasma ammonia is not universally present in patients and is unlikely to be the main cause of disease pathogenesis.

Conclusion on current management

Current management approaches for ARG1-D include individualized combinations of protein restriction to reduce arginine, essential amino acid supplementation, and concomitant medications to manage other clinical symptoms such as ammonia scavengers to help control ammonia levels.

Justification of significant benefit
The clinical presentation of ARG1-D is distinct from other UCDs and is characterized by highly elevated plasma, liver, and CSF levels of neurotoxic arginine and guanidino compounds.

Currently, the only approved medicine indicated for the treatment of ARG1-D in GB is the ammonia scavenger glycerol phenylbutyrate (Ravicti). Arginine levels were not improved in the few ARG1-D patients included in the glycerol phenylbutyrate clinical trials and mobility was not examined.

The data from Study 300A demonstrated a clinically relevant advantage of pegzilarginase vs placebo (see section A.3.2 above). This study was designed to assess the effect of pegzilarginase in combination with subjects' Individualised Disease Management plans, which typically included a prescribed diet with severe protein restriction and essential amino acid supplementation, and pharmacological symptomatic treatments (including ammonia scavengers).

Overall, all 32 subjects (100%) received concomitant medications during the study. The most frequently used concomitant medications were ammonia scavengers (sodium benzoate and glycerol phenylbutyrate). The proportion of subjects who used glycerol phenylbutyrate was similar between treatment groups: 47.6% (n=10) in the pegzilarginase group and 45.5% (n=5) in the placebo group, hence the clinical data supports significant benefit of pegzilarginase. Overall, almost all subjects in the pegzilarginase-treated group (95.2%, n=20) and in the placebo group (81.8%, n=9) received ammonia scavengers during the study.

Pegzilarginase represents a novel targeted treatment option to address the unmet medical need for patients affected by ARG1-D. The totality of the efficacy data, ranging from 24 to over 120 weeks in duration, demonstrates a clinically meaningful and consistent benefit with pegzilarginase treatment compared to placebo for patients affected by this rare, progressive and debilitating

Justification of significant benefit conclusion
Significant benefit over existing methods has been demonstrated. Clinical study data demonstrated a significant reduction of hyperarginaemia to the level of normal ranges observed with pegzilarginase, which cannot be achieved with Ravicti (the only approved treatment for ARG1-D in GB at present) or a protein restricted diet alone. The clinical relevance of this reduction of hyperarginaemia was supported by improvement of gross motor function.

Conclusion on acceptability of orphan designation
The applicant has demonstrated fulfilment of the criteria for approval as an orphan medicinal product.

All medicines that gain an orphan marketing authorisation from the UK Licensing Authority are listed on its publicly available Orphan Register until the end of the market exclusivity period. The authorised orphan indication defines the scope of orphan market exclusivity.

Decision: Grant

Date: *20/12/2023*