15 December 2023
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Loargys (pegzilarginase)
Treatment of hyperargininaemia
EU/3/16/1701

Sponsor: Immedica Pharma AB

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Product and administrative information

Product	
Designated active substance	Poly (oxy-1,2-ethanediyl), alpha-(carboxymethyl)-omega-methoxy-,amide with arginase 1 [cobalt cofactor] (synthetic human) (1:10), trimer
Other name	-
International Non-Proprietary Name	Pegzilarginase
Tradename	Loargys
Orphan condition	Treatment of hyperargininaemia
Sponsor's details:	Immedica Pharma AB Solnavagen 3 H 113 63 Stockholm Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	ERA Consulting GmbH
COMP opinion	16 June 2016
EC decision	14 July 2016
EC registration number	EU/3/16/1701
Post-designation procedural history	
Transfer of sponsorship	Transfer from ERA Consulting GmbH to Yes Pharmaceutical Development Services GmbH – EC decision of 2 August 2021 2nd transfer from Yes Pharmaceutical Development Services GmbH to Immedica Pharma AB – EC decision of 9 November 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Peter Mol / Ewa Balkowiec Iskra
Applicant	Immedica Pharma AB
Application submission	26 July 2022
Procedure start	18 August 2022
Procedure number	EMEA/H/C/005484
Invented name	Loargys
Proposed therapeutic indication	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. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Loargys
CHMP opinion	12 October 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Ingeborg Barisic
Sponsor's report submission	17 May 2023
COMP discussion	3-5 October 2023
COMP opinion (adoption via written procedure)	13 October 2023

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2016 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing poly(oxy-1,2-ethanediyl), alpha-(carboxymethyl)-omega-methoxy-, amide with arginase 1 [cobalt cofactor] (synthetic human) (1:10), trimer was considered justified based on preliminary pre-clinical in vivo data in a model of the condition showing a reduction in hyperargininaemia;
- the condition is life-threatening and chronically debilitating due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage;
- the condition was estimated to be affecting approximately 0.06 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing poly(oxy-1,2-ethanediyl), alpha-(carboxymethyl)-omega-methoxy-, amide with arginase 1 [cobalt cofactor] (synthetic human) (1:10), trimer will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a reduction in hyperargininaemia which is an important characteristic of the condition. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing poly(oxy-1,2-ethanediyl), alpha-(carboxymethyl)-omega-methoxy-, amide with arginase 1 [cobalt cofactor] (synthetic human) (1:10), trimer as an orphan medicinal product for the orphan indication: treatment of hyperargininaemia".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Hyperargininaemia, also known as Arginase I deficiency (ARG1-D), is a rare, debilitating, progressive, inherited, neurotoxic, metabolic disease. ARG1-D is characterised by deficiency of the arginase 1 enzyme and associated with the persistent elevation of plasma arginine leading to progressive neurodegenerative symptoms (Diez-Fernandez 2018; Schlune 2015; Summar 2013; Waisbren 2018).

Hyperargininaemia belongs to one of the eight urea cycle disorders (UCD), a group of inborn errors of metabolism that affect the transfer of nitrogen into urea. UCDs are associated with a defect in the genes encoding each urea cycle enzyme, co-factors or transporters. The common characteristic of these diseases is hyperammonaemia, which is highly toxic to the central nervous system – albeit that hyperammoniaemia is generally milder for ARG1-D patients, as compared to other UCDs.

Arginine and its derivates are also neurotoxic when present at increased concentrations. Typically for ARG1-D, patients present with the development of progressive spasticity with greater severity in the lower limbs. They may also develop seizures and gradually lose intellectual attainments. Growth is usually retarded. Other symptoms that may present early in life include episodes of irritability, anorexia and vomiting, and moderate hyperammonaemia. Severe episodes of hyperammonaemia with seizures and coma are seen infrequently with this disorder but can be fatal.

Diagnosis is made by the elevated levels of arginine in the blood, followed by analysis of enzymatic activity in red blood cells, and/or genetic testing.

The approved therapeutic indication "treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininaemia, in adults, adolescents and children aged 2 years and older" falls within the scope of the designated orphan condition "treatment of hyperargininaemia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor argued that there are no known changes in the chronically debilitating or life-threatening nature of the condition, since the initial orphan designation in 2016.

ARG1-D remains a debilitating, progressive, neurodegenerative, metabolic disease associated with increased arginine and its toxic metabolites, with significant reductions in quality of life, increased morbidity, and premature mortality (Diez-Fernandez 2018; Schlune 2015; Summar 2013; Waisbren 2018). Most ARG1-D patients are asymptomatic at birth through early infancy, developing initial symptoms at 2 to 3 years of age, typically with spastic diplegia of the lower limbs.

Although survival data for ARG1-D is limited, and there has been no systematic natural history study, the available data indicates that ARG1-D is generally associated with premature mortality (Terheggen 1969; Schlune 2015; Cederbaum 1977; Cederbaum 1979; Grody 1989; Grody 1993; Peralta 1965; Mizutani 1983; Sakiyama 1984; Antonozzi 1987; Romano 1987; De Deyn 1997; Endres 1984; Jordá 1986; Fuchshuber 1993; Prasad 1997; Picker 2003). Some individual cases have been reported of patients surviving into their forties, but suffering from severe contractures, and poor metabolic condition.

The sponsor has provided an adequate discussion on the mortality and morbidity of the condition. The COMP has previously established that the condition is chronically debilitating and life threatening due

to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage. The condition therefore remains chronically debilitating and life-threatening in nature.

Number of people affected or at risk

At time of initial orphan designation in 2016, the COMP concluded that the condition was estimated to be affecting approximately 0.06 in 10,000 persons in the European Union.

In the maintenance application, the sponsor proposed a prevalence of 0.014 in 10,000 persons. The sponsor referred to publication entitled 'Arginase 1 Deficiency: using genetic databases as a tool to establish global prevalence' (Catsburg 2022). In this report, global population prevalence estimates of 0.014 in 10,000 persons, based on genetic sources and mathematical modelling (Table 1).

Table 1. Calculated ARG1-D case number and population prevalence by country (Catsburg 2022)

Country	Population 2021 (1000 s)	Estimated ARG1-D cases	ARG1-D population prevalence (cases/ million)
Argentina	45,914	70	1.53
Australia	25,700	14	0.56
Austria	8801	5	0.60
Bahrain	1744	5	3.02
Belgium	11,669	9	0.73
Brazil	215,278	312	1.45
Canada	37,924	37	0.97
Chile	18,605	31	1.67
Colombia	50,576	95	1.88
Croatia	4092	2	0.47
Czech Republic	10,634	5	0.47
Denmark	5819	5	0.80
Finland	5599	3	0.48
France	65,955	51	0.77
Germany	82,591	52	0.64
Ireland	4926	3	0.59
Israel	8842	34	3.90
Italy	59,038	36	0.61
Japan	126,109	306	2.43
South Korea	51,667	44	0.85
Kuwait	4361	28	6.49
Mexico	135,384	193	1.43
Netherlands	17,230	9	0.51
New Zealand	4876	3	0.52
Norway	5500	3	0.46
Poland	37,847	22	0.59
Portugal	10,183	9	0.90
Qatar	2840	25	8.74
Russia	143,637	93	0.65
Saudi Arabia	35,263	258	7.32
Spain	46,450	81	1.73
Sweden	10,188	6	0.60
Switzerland	8731	5	0.60
Taiwan	23,873	38	1.58
Turkey	84,515	267	3.16
UAE	9937	64	6.40
UK	67,699	39	0.58
United States	333,783	250	0.75
Total (38 countries)	**1,823,780**	**2511**	**1.38**

The COMP considered that, based on the rarity of the disease and the limited prevalence calculations published, the proposed prevalence is acceptable and concluded that an estimated prevalence of less

than 0.02 in 10,000 better reflects uncertainty of the prevalence estimate, than the proposed exact figure.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Current management consist of dietary protein restriction, often with essential amino acid (EAA) supplementation. However, in the vast majority of patients, a stringent protein-restricted diet does not lead to a sufficient reduction of arginine below the target levels. Arginine is endogenously produced in the body from proteins, and only partially dependent on dietary intake of arginine. It has been estimated that about 20-25% of the natural human arginine is derived from the diet (Zhou M, Martindale RG. J Nutr. 2007;137(6 Suppl 2):1687S-1692S). Moreover, the diet is poorly palatable and difficult to manage. Thus, the protein dietary restrictions are not considered entirely satisfactorily.

Liver transplantation has been reported to lead to the normalisation of arginine and amelioration of cognitive and motor function delay, and hepatic impairment in individual cases. However, due to the limited availability of donors, the high associated risks of this procedure and requirement of life-long immune-suppressants, liver transplantation is not considered a satisfactory method, to be taken on board for the significant benefit assessment.

The sponsor identified Ravicti which is authorized in EU for the treatment of arginase I deficiency:

Ravicti (glycerol phenylbutyrate) is indicated for use as adjunctive therapy for chronic management of patients with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate synthetase I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Ravicti must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).

The COMP considered Ravicti to be a satisfactory method.

Significant benefit

The sponsor received EMA protocol assistance, dated 28 March 2019, with regards to the evidence needed to justify significant benefit of pegzilarginase compared to current individualised disease management defined as a protein-restricted diet in conjunction with essential amino acids and ammonia scavengers used for the treatment of patients with arginase I deficiency. As set out during protocol assistance, "*the sponsor anticipates at least 40% of patients in the study will be on Ravicti. To ensure balance across treatment arms, the sponsor should consider stratification for the use of Ravicti. If the sponsor can show a clinically relevant improvement in patients on top of standard of care (including a representative number of patients on Ravicti) compared to placebo, these data could be sufficient to demonstrate significant benefit*".

The safety and efficacy of pegzilarginase were assessed in an exploratory dose-finding study CAEB1102-101A (Study 101A), with its long-term extension study CAEB1102-102A (Study 102A), and a single pivotal randomised study CAEB1102-300A (Study 300A).

Study 300A was a multicentre, double-blind, placebo-controlled trial 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. The dose was individually titrated within a range of 0.05 mg to 0.2 mg/kg, guided by the target arginine plasma levels of the patient. All subjects were to continue on any previously prescribed dietary regimen and ammonia scavengers throughout the study period.

This study was designed to assess the effect of pegzilarginase in combination with patients' individualized disease management (IDM) plans, which included a prescribed diet with severe protein restriction and, typically, essential amino acid (EAA) supplementation, with or without the use of ammonia scavengers. Subjects were required to have a stable, consistent diet for the entire duration of the blinded period, which included the 24-week randomization period and the first 8 weeks of the open-label period of the study. Any prescribed changes of more than 15% from baseline protein intake were documented. Subjects receiving ammonia scavenger therapy must have been willing to remain on a stable dose during the double-blind phase and the investigator blinded follow-up phase of the study.

Overall, all 32 subjects (100%) received concomitant medications during the study. The most frequently used concomitant medications were the ammonia scavengers sodium benzoate and glycerol phenylbutyrate (Ravicti). 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. 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.

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, which assesses 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.

Based on the results of the study, pegzilarginase induced a 76.7% (95% CI 67.1%, 83.5%) reduction in geometric least squared (GLS) mean ratio for change of plasma arginine at week 24 from baseline relative to placebo ($p<0.0001$).

The mean GMFM-E scores overall improved from baseline to week 24 for the pegzilarginase treatment arm (4.2 points), whereas it declined in the placebo group (-0.4 points, LS mean difference 4.6 (95% CI -1.1, 10.2)).

At baseline, the mean (SD) distance walked over 2 minutes for subjects who received pegzilarginase was longer at 109.0 meters (55.76 meters) compared to subjects who received placebo at 99.9 meters (49.00 meters). In addition, the mean distance walked over 2 minutes in the pegzilarginase group increased by 7.4 meters (19/21 subjects) from baseline to Week 24, compared to an increase of 1.9 meters (10/11 subjects) in the placebo group, leading to an LS mean difference of 5.5 meters (95% CI -15.6, 26.7, p=0.5961).

Study CAEB1102-101A (Study 101A) was a Phase 1 /2 open-label uncontrolled study to investigate the safety, pharmacokinetics and pharmacodynamics of pegzilarginase. From this study, 14 subjects entered the open-label extension study CAEB1102-102A (Study 102A). Study 102A was a Phase 2

open-label, uncontrolled international, multicenter study to evaluate the long-term safety, tolerability, and efficacy of pegzilarginase in patients with Arg1-D. Study 102A is still ongoing (interim study report data cut-off date: 11 June 2021). Data are available for up to 120 weeks for individual patients. Clinical outcomes included (amongst others) the 6-minute walk text (6MWT), GMFM-E and GMFM-D (Gross Motor Function Measure Part D, on standing).

In the long-term extension study 102A, the motor function scores continued to improve from baseline. At Week 48, the mean change from baseline was 44.9 m (95% CI 18.6, 71.3) for the 6MWT, 5.8 (95% CI 2.5, 9.1) points for GMFM-E, and 2.8 (1.2, 4.3) for GMFM-D. Such changes can be considered clinically relevant. Plasma arginine levels also remained low and within the clinical target levels in the long term (48 weeks or longer).

The sponsor claimed that 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, showed a clinically meaningful and consistent benefit with pegzilarginase treatment compared to placebo for patients affected by this rare, progressive and debilitating disease.

COMP conclusion

The COMP considered the results from study 300A. Pegzilarginase showed a 76.7% (95% CI 67.1, 83.5%) reduction in geometric least squared (GLS) mean ratio for change of plasma arginine at week 24 from baseline relative to placebo. Also, in the open-label extension phase of two studies (300A and 102A), plasma arginine was maintained within target levels at continuous treatment (last observation 12-36 months). Importantly, the reduction in arginine levels due to pegzilarginase treatment was associated with clinically meaningful improvements of gross motor function scales (GMFM-D and -E) and 2- or 6-minutes walking test, whereas normally a deterioration of motor function would be expected in this chronic and progressive disorder. The COMP concluded that the significant reduction of hyperargininaemia to the level of normal ranges in patients with arginase-1 deficiency cannot be achieved with the standard of care of a protein-restricted diet with nitrogen scavengers including Ravicti. In addition, there are no other authorised medicinal products to reduce hyperargininaemia.

Furthermore, a similar mean reduction in plasma arginine at primary assessment at week 24 from baseline has been observed in patients who have been pre-treated with or without Ravicti. This is to be expected, as due to its mode of action, Ravicti and other nitrogen scavengers do not target hyperargininaemia. In general, it can be concluded that pegzilarginase is an effective add-on to the standard of care with nitrogen scavengers, and a protein restricted diet.

In conclusion, the COMP agreed that the significant benefit of pegzilarginase over the authorized Ravicti (glycerol phenylbutyrate) is considered to be established based on the significant reduction of hyperargininaemia to the level of normal ranges observed with pegzilarginase which cannot be achieved with Ravicti or a low-protein diet alone.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 13 October 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of hyperargininaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 0.02 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life threatening due to accumulation of arginine and its neurotoxic derivates, leading to progressive spastic diplegia, developmental delay, cognitive impairment, seizures, and liver function impairment;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Loargys, the assumption that Loargys may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical study data that demonstrated a significant reduction of hyperargininaemia to the level of normal ranges observed with pegzilarginase, which cannot be achieved with Ravicti or a protein restricted diet alone. The clinical relevance of this biomarker reduction was supported by improvement of gross motor function.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan medicinal products has recommended that Loargys, pegzilarginase, for treatment of hyperargininaemia (EU/3/16/1701) is not removed from the Community register of orphan medicinal products.