Orphan designation withdrawal assessment report

Elfabrio (pegunigalsidase alfa)
Treatment of Fabry disease
EU/3/17/1953

Sponsor: Chiesi Farmaceutici S.p.A.

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Pegunigalsidase alfa
Other name(s)	Alpha-galactosidase replacements Alpha-galactosidase; CHF 6657; Modified recombinant human alpha-GAL-A protein; Pegunigalsidase alfa; PRX-102; Recombinant human alpha galactosidase-A
International Non-Proprietary Name	Pegunigalsidase alfa
Tradename	Elfabrio
Orphan condition	Treatment of Fabry disease
Sponsor's details:	Chiesi Farmaceutici S.p.A. Via Palermo 26 A 43122 Parma PR Italy

Orphan medicinal product designation procedural history	
Sponsor/applicant	Protalix B.V.
COMP opinion	31 October 2017
EC decision	12 December 2017
EC registration number	EU/3/17/1953

Post-designation procedural history	
Transfer of sponsorship	Transfer from Protalix B.V. to Chiesi Farmaceutici S.p.A – EC decision of 8 May 2019

Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Beata Maria Jakline Ullrich
Applicant	Chiesi Farmaceutici S.p.A.
Application submission	25 January 2022
Procedure start	24 February 2022
Procedure number	EMA/H/C/005618
Invented name	Elfabrio
Proposed therapeutic indication	Elfabrio is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase). Further information on Elfabrio can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Elfabrio
CHMP opinion	23 February 2023

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Olimpia Neagu / Armando Magrelli
Sponsor's report submission	9 September 2022
COMP discussion and adoption of list of questions	14-16 February 2023
Oral explanation	21 March 2023
Sponsor's removal request	23 March 2023

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2017 designation was based on the following grounds:

"The sponsor Protalix B.V. submitted on 17 July 2017 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing pegunigalsidase alfa for treatment of Fabry disease (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

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 pegunigalsidase alfa was considered justified based on non-clinical data showing reduced accumulation of toxic metabolites in relevant tissues and on clinical data demonstrating the stabilisation of kidney function;

- the condition is chronically debilitating due to recurrent episodes of severe pain that do not respond to standard analgesics, and life-threatening due to renal failure, cardiovascular and cerebrovascular complications;

- the condition was estimated to be affecting approximately 2.2 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 pegunigalsidase alfa will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a model of the condition that demonstrate that the product reduced peripheral neuropathy, which is an improvement over the authorised products. Clinical data also demonstrate reduced immunogenicity of the product compared to other authorised treatments. In addition, the product can be used in a wider patient population than migalastat. 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 pegunigalsidase alfa, as an orphan medicinal product for the orphan indication: treatment of Fabry disease".

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

Fabry disease is an X-linked multisystem lysosomal storage disorder caused by the absence or reduction of α-galactosidase-A (α-Gal-A), which is a lysosomal enzyme that catalyses the hydrolysis of globotriaosylceramide (Gb3) from oligosaccharides, glycoproteins and glycolipids. The accumulation of glycosphingolipids (e.g. Gb3) leads to chronic pain, skin lesions, cardiac deficiencies and, in particular, renal involvement. End-stage renal failure and cardiomyopathy often lead to early death in Fabry disease patients.

Typical symptoms include neuropathic pain, angiokeratoma formation, abnormal sweating, hearing loss, and gastrointestinal symptoms. The major complications of Fabry disease include kidney disease, cardiac disease and cerebrovascular disease.

Fabry disease continues to be acceptable as an orphan condition.

The approved therapeutic indication "Elfabrio is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase)" falls within the scope of the designated orphan condition "Treatment of Fabry disease".

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

Fabry disease is associated with the following characteristic signs and symptoms: neurological (pain), cutaneous (angiokeratoma), renal (proteinuria, kidney failure), cardiovascular (cardiomyopathy, arrhythmia), and cochleovestibular and cerebrovascular (transient ischemic attacks, strokes). Pain is a common early symptom of Fabry disease (chronic pain characterized by burning and tingling paresthesia and occasional episodic crises characterized by agonizing burning pain). With age, progressive damage to vital organ systems develops, possibly leading to organ failure, which is life threatening. Fabry disease is associated with an impaired quality of life and reduced life expectancy. Most common cause of death shifted from renal disease (pre-2001) to cardiovascular disease (post 2001, Mehta et al 2009). Data from the Fabry Outcome Survey (Beck et al. Orphanet Journal of Rare Diseases (2022) 17:238) suggest that the estimated median survival for male patients with Fabry Disease treated with ERT for 5 years was 77.5 years, compared with 60 years for untreated male patients. Women continue to live longer than men nearing normal life-expectancy.

The condition is therefore chronically debilitating and life threatening.

Number of people affected or at risk

The sponsor has conducted a literature search to establish the prevalence estimate. The publications used are summarised below in table 1.

Table 1. Fabry Disease: Prevalence in newborns

Country	Study details	Period	Reported birth prevalence (per newborn)	Reference
The Netherlands	All 963 enzymatically confirmed from laboratory records of clinical genetic centers	1970-1996	**0.21 per 100,000**	Poorthuis et al., 1999
Northern Portugal	Report from central laboratory for post- and prenatal diagnosis, enzymatic screening, followed by mutation analysis	1982-2001	**0.12 per 100,000**	Pinto et al., 2004
Italy (Piemonte area)	Blot spot analysis of 37,104 consecutive male neonates; enzymatic screening, followed by mutation analysis	2003-2005	1 per 3,100 (males) **32.3 per 100,000** (male newborns only)	Spada et al., 2006
Czech Republic	Report from central laboratory for post- and prenatal diagnosis, enzymatic screening, followed by mutation analysis	1975-2008	**0.52 per 100,000**	Poupětová et al., 2010
Austria	34,736 consecutive newborn blood samples, screened for α-glucosidase enzyme activity, followed by genetic mutation analysis	2010	1:3,859 birth **25.9 per 100,000**	Mechtler et al., 2012
North East Italy	173,342 consecutive newborn blood samples, screened for α-glucosidase enzyme activity, followed by genetic mutation analysis	2015-2021	1:7,879 newborns **12.7 per 100,000**	Gragnaniello et al., 2021
Hungary	40,024 consecutive newborn blood samples, screened by tandem mass	Not disclosed	3:40,024 newborns	Wittmann et al., 2012

	spectroscopy, followed by genetic mutation analysis		**7.5 per 100,000**	

The published prevalence varies significantly, ranging from 0.12/100,000 (Pinto et al., 2004) to 32.3 per 100,000 (Spada et al., 2006), although the latter only refers to male newborns; female newborns were excluded from this study. There is a trend towards higher prevalence in more recent studies, most likely due to raised awareness and improved screening strategies and analytical methods.

The sponsor proposes to use an incidence published by Spada et al 2006 which is 32.3/100,000 newborns (Spada et al., 2006) (the highest incidence number) which is believed to have remained stable up to 2020. The total number of births in the EU in 2020 was then used to establish the number of children who were born with the condition. A total of 1,334 newborns were estimated to have been born with Fabry Disease in this manner which translates into 1,334 new cases per the total EU population or an incidence of 0.029/10.000.

According to the 'Points to Consider' on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation (COMP/436/01, March 2002), the prevalence of a disease can be estimated on the basis of the incidence, using the following formula:

Prevalence = Incidence x Mean Disease Duration

Since Fabry disease is an incurable inherited disease, by taking the incidence rate derived from genetic screening of newborns, the assumed disease duration in this calculation must be lifelong.

Before enzyme replacement therapy with α-Galactosidase became available, a reduced life expectancy of Fabry patients was reported (MacDermot et al., 2001a,b). Since ERTs have become standard therapy Fabry patients' mean life expectancy was prolonged to 81 years (average for both women and men although men still live slightly less than the normal male population) to be in line with the general life expectancy in the EU 27 countries.

Using this figure, a **prevalence of 2.35 per 10,000** (0.029 per 10,000 x 81) can be estimated.

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 treatment guidelines include a very long list of adjunctive and preventive measures in Fabry disease patients for common Fabry related morbidities (Eng et al., 2006). Three medicinal products for the treatment of Fabry disease were approved via the centralised procedure in the EU: Replagal (agalsidase alfa), Fabrazyme (agalsidase beta) and Galafold (migalastat).

- Replagal is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency).

- Fabrazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency). Fabrazyme is indicated in adults, children and adolescents aged 8 years and older.

- Galafold is indicated for long-term treatment of adults and adolescents aged 12 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation (see the tables in section 5.1).

Elfabrio is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).

As Galafold is only indicated for patients who have an amenable mutation this is a narrower indication than the one for Elfabrio, and therefore Galafold is not considered a satisfactory method to be discussed in the significant benefit section.

The therapeutic indication for Elfabrio completely overlaps with the two ERTs (Replagal and Fabrazyme) currently authorised for the treatment of Fabry's disease, and they will subsequently be discussed in the significant benefit section.

Significant benefit

The sponsor did not request protocol assistance for the justification of significant benefit.

The sponsor included a discussion on the significant benefit over Galafold (migalastat) but as this product is not considered a satisfactory treatment for the full patient population of Elfabrio, it will not be discussed in this report.

The justification for the significant benefit is based on claims of efficacy, safety and a major contribution to patient care (MCPC), discussed below.

Efficacy:

The sponsor states that both ERT products are efficacious in preventing morbidity outcomes, but a trend towards improved efficacy of agalsidase beta over agalsidase alfa has been described recently (El Dib et al., 2017). Therefore, they focus on the demonstration of significant benefit of pegunigalsidase alfa over agalsidase beta only as it is considered equally applicable to agalsidase alfa.

The efficacy of pegunigalsidase alfa was directly compared to agalsidase beta in the randomized, double-blind, active Control Study PB-102-F20. The two treatment arms were found to be comparable with regards to efficacy in the treatment of Fabry disease. There was a good overlap of the confidence intervals for the eGFR slopes of the two arms, with the lower bound of the confidence interval being well above the non-inferiority margin. The predefined primary efficacy testing for non-inferiority of Elfabrio compared to agalsidase beta on the measure of eGFR slope showed a margin of -2.444 mL/min/1.73 m2/year for the ITT and a similar difference between the slopes for the PP population. Considering a non-inferiority margin of -3 mL/min/1.73 m2/year, these results indicate non-inferiority of Elfabrio compared to agalsidase beta. As such, the current study is considered successful. The treatment difference was slightly in favour of Elfabrio when the clinically relevant stratification factor, urine protein-to-creatinine ratio (UPCR), was included as covariate in the primary analysis model.

Safety:

Safety data from pegunigalsidase alfa was directly compared to agalsidase beta in the randomized, double-blind, active Control Study PB-102-F20.

Cumulatively, 2574 infusions of PRX-102 and 1303 of agalsidase beta were administered in the study. Patients in the PRX-102 arm received a mean (SE) of 49.5 (1.6) infusions, while those in the agalsidase beta arm received a mean (SE) of 52.1 (0.6).

Table 2 below presents an overview of the categories of Treatment Emergent Adverse Event (TEAEs) reported in the study, showing the number of patients who experienced events in each category and the number of events. The majority of patients experienced at least one TEAE: 90.4% in the PRX-102 arm and 96.0% in the agalsidase beta arm.

Table 2.

	PRX-102; N=52		Agalsidase Beta; N=25	
	Patients with at least one event, n (%)	Number of events (rate) [1]	Patients with at least one event, n (%)	Number of events (rate) [1]
All adverse events				
Any TEAE	47 (90.4)	561 (572.36)	24 (96.0)	406 (816.85)
Mild or moderate TEAE	47 (90.4)	535 (545.83)	24 (96.0)	387 (778.63)
Severe TEAE [2]	15 (28.8)	26 (26.53)	7 (28.0)	19 (38.23)
Serious TEAE	8 (15.4)	14 (14.28)	6 (24.0)	11 (22.13)
TEAE leading to withdrawal	2 (3.8)	2 (2.04)	0	0
TEAE leading to death	0	0	0	0
Related adverse events only				
Any related TEAE [3]	21 (40.4)	42 (42.85)	11 (44.0)	76 (152.91)
Related mild or moderate TEAE	21 (40.4)	40 (40.81)	11 (44.0)	75 (150.90)
Related severe TEAE	2 (3.8)	2 (2.04)	1 (4.0)	1 (2.01)
Related serious TEAE	1 (1.9)	1 (1.02)	0	0
Related TEAE leading to withdrawal	1 (1.9)	1 (1.02)	0	0

[1] Rate is calculated as the adjusted number of events per 100 years of exposure.

[2] Events classified as "Very Severe" per CTCAE severity in the eCRF are included in the category "Severe".

[3] A TEAE was defined as related if was reported as possibly, probably, or definitely related to study drug.

With respect to the subset of TEAEs that were considered related to study drug (either possibly, probably, or definitely), similar percentages of patients reported at least one related event of any type (40.4% vs. 44.0%), but the rate of related events was considerably higher in the agalsidase beta arm: 42.9 events per 100 patient-years of exposure in the PRX-102 arm vs. 152.9 in the agalsidase beta arm. Similar percentages of patients had at least one related event of severe intensity (3.8% vs. 4.0%) with corresponding similar rates (2.04 vs 2.01).

As patients in the agalsidase beta had already been on agalsidase beta stable treatment for at least one year at the start of the study, the almost 4-fold lower rate of related TEAE for the patients switched to PRX-102 is believed to offer a clinically relevant advantage. The COMP does not share this view as they noted that the number of patients in the dataset was quite small making interpretation of this safety claim difficult.

Serious AEs: There were no deaths in the study. Eight patients (15.4%) in the PRX-102 arm experienced a total of 14 SAEs, for an exposure-adjusted rate of 14.3 events per 100 patient-years of treatment, and 6 (24.0%) patients in the agalsidase beta arm experienced a total of 11 SAEs, for an adjusted rate of 22.1 events. The COMP did not consider there was any significant difference between the products again as the number of patients included in the dataset provided is quite small making comparative analysis difficult.

Infusion-Related Reactions (IRRs)

IRRs were defined as TEAEs that occurred during an infusion or within 2 hours after its completion, and whose causality was assessed as definitely, probably, or possibly related to study treatment. IRRs do not include injection site reactions (ISRs). In the PRX-102 arm, 11 patients (21.2%) experienced a total of 13 IRRs associated with 12 infusions, for an adjusted rate of 0.5 events per 100 infusions. The rate in the agalsidase beta arm was considerably higher, with 6 (24.0%) patients experiencing a total of 51 IRRs associated with 40 infusions, for an adjusted rate of 3.9 events per 100 infusions. The sponsor noted a reduced need for pre-infusion medication seen in the PRX-102 arm compared to the

agalsidase beta arm. In the PRX-102 arm, 44.2% (23/52) of patients had at least one premedication during the study, compared to 68.0% (17/25) in the agalsidase beta arm. Even though there was a reduction in use of pre-medication, IRRs were still less reported with PRX-102, both indicative for a significant safety benefit of PRX-102 over agalsidase beta.

Immunogenicity

In both treatment arms, most cases of seroconversion were transient in nature: i.e., the patients were positive at only one or two timepoints and reverted to being negative thereafter. At the end of the study, higher portion of patients who were positive to ADA at baseline became ADA negative in the PRX-102 arm: 5 (27.8% of the ADA positives) vs. 1 (12.5% of the ADA positives) from the agalsidase beta arm. The COMP concluded there was no difference between the treatments.

Integrated immunogenicity profile

The development of anti-pegunigalsidase alfa IgG and neutralising anti-pegunigalsidase alfa ADA over time in studies PB-102-F01/F02/F03, PB-102-F20, PB-102-F30 and PB-102-F50 was presented for Cohorts 1, 2 and 4. The immunogenicity assessments were performed following a multi-tiered approach, thus further ADA assessments (including tests for neutralising antibodies) were only performed in IgG-positive patients.

At Baseline, 25% of the patients with data in Cohort 1 and 33% of the patients in Cohort 2 tested positive for IgG and 89% and 100% of these patients, respectively, carried neutralising antibodies against pegunigalsidase alfa. The proportion of patients with IgG detected in Cohort 1 increased to 36% of patients with data in the first 6 months of treatment but decreased steadily in the further course of treatment (note that the sample size decreased also over time). In Cohort 2, the proportion of IgG-positive patients remained fairly constant over time.

Integrated Infusion Related Reactions profile

Infusion Related Reactions (IRRs) were defined as those related TEAEs which occurred during the infusion or within 2 hours after the completion of the infusion and were related to study treatment rather than to procedures.

The reporting frequencies for any IRR and serious IRRs are provided in Table 9 for all analysis cohorts. Both proportions of patients with TEAEs and event rates (events per 100 infusions) are presented. The proportions of patients with events were generally similar across the cohorts. Event rates were low in all cohorts and ranged from 0.7 to 3.8 IRRs per 100 infusions. Rates for any IRR were highest in Cohort 2, but no serious IRRs were observed in this cohort. Serious IRRs were rare in all cohorts with 0 or 0.1 serious IRRs being reported per 100 infusions in all cohorts.

IRRs were mostly mild or moderate in intensity and resolved under continued treatment In addition, 4 patients showed serious IRRs, all indicative of hypersensitivity reactions.

In summary, the sponsor concluded that PRX-102 showed a more favourable trend regarding safety, tolerability, and immunogenicity profile compared to agalsidase beta especially when exposure adjusted reporting rates for TEAEs, ADRs, SAE, and IRRs as well as ADA are assessed. As the efficacy of PRX-102 has been shown to be comparable to agalsidase beta, the improved safety profile of PRX-102 seems to be the main claim of significant benefit over existing ERT for Fabry disease patients. In line with the CHMP assessment (day 180 report) where it is stated that there is no difference in safety between Elfabrio and Replagal (agalsidase alfa) and Fabrazyme (agalsidase beta), the COMP does not consider the safety difference to be of such magnitude and relevance to that could be qualified as a clinically relevant advantage.

<u>Major contribution to patient care</u>:

To support the argumentation of major contribution to patient care the sponsor has submitted simulated PK data.

PK samples from studies PB-102-F01, PB-102-F02, PB-102-F20, and PB-102-F50 were used in a Modelling and Simulation Analysis to explore the exposure to PRX-102 with both treatment regimes, 1 mg/kg E2W and 2 mg/kg E4W.

PRX-102 plasma concentrations were simulated for the 2-dosing scenario following 24 months of dosing:

1. 1 mg/kg administered every 2 weeks (E2W) and infused over 3-hours for the first 3 months of dosing and over 1.5-hours thereafter
2. 2 mg/kg administered every 4 weeks (E4W) and infused over 5-hours for the first 3 months of dosing and over 2.5-hours thereafter

The results support that AUC and C_{ave} following dose regimens of 1 mg/kg E2W and 2 mg/kg E4W are similar, and as expected C_{max} is up to 86% higher for 2 mg/kg E4W dosing scheme as compared to 1 mg/kg E2W. C_{trough} is estimated to be detectable for both doses and is expected to be approximately 53% lower at steady state for 2 mg/kg dosing 4 weeks after dosing as compared to 1 mg/kg 2 or 4 weeks after dosing.

The sponsor reports that by changing from a twice a month to a once-a-month dosing schedule they will improve the quality of life of patients. They have not, however, provided any data to support this claim. The only data they have submitted is pharmacokinetic data to show that similar efficacy can be achieved with the once-a-month dosage and that this could offer an alternative to twice a month dosing. The sponsor should provide further data to support the basis of major contribution to patient care showing a reduction in healthcare professional use for example as well as improvement in the quality of life of patients. The benefit of home use if made should be contextualised with home use of the other Enzyme Replacement Therapies authorised for this condition.

The sponsor has not provided any significant data to support major contribution to patient care. The COMP therefore has requested that the sponsor further elaborate, with data from their clinical trials programme, the basis of a major contributions to patient care.

4. COMP list of issues

Significant Benefit

The sponsor has not established a clinically relevant advantage to the other authorised enzyme replacement therapies in the condition. They should therefore elaborate on the basis of a major contribution to patient care using clinical data in patients with the condition from their clinical development programme to support the basis of significant benefit.