21 June 2022
EMA/OD/0000070235
EMADOC-1700519818-819883
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Filsuvez (Dry extract from birch bark (DER 5-10 : 1), extraction solvent n-heptane 95% (w/w))
Treatment of epidermolysis bullosa
EU/3/10/845
Sponsor: Amryt Pharmaceuticals Designated Activity Company

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Product and administrative information

Product	
Designated active substance	Dry extract from birch bark (DER 5-10 : 1), extraction solvent n-heptane 95% (w/w)
Other name	--
International Non-Proprietary Name	*Betulae cortex* dry extract (5-10 : 1); extraction solvent: n-heptane
Tradename	Filsuvez
Orphan condition	Treatment of epidermolysis bullosa
Sponsor's details:	Amryt Pharmaceuticals Designated Activity Company 45 Mespil Road Ballsbridge Dublin 4 D04 W2F1 Co. Dublin Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Birken GmbH
COMP opinion	8 December 2010
EC decision	23 February 2011
EC registration number	EU/3/10/845
Post-designation procedural history	
Sponsor's name change	Name change from Birken GmbH to Birken AG – EC letter of 1 July 2011
Transfer of sponsorship	Transfer from Birken AG to Amryt Research Limited – EC decision of 8 October 2019
Transfer of sponsorship	Transfer from Amryt Research Limited to Amryt Pharmaceuticals Designated Activity Company – EC decision of 5 March 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Kristina Dunder / Peter Kiely
Applicant	Amryt Pharmaceuticals Designated Activity Company
Application submission	8 March 2021
Procedure start	25 March 2021
Procedure number	EMA/H/C/005035/0000
Invented name	Filsuvez
Proposed therapeutic indication	Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older. Further information on Filsuvez can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/filsuvez
CHMP opinion	22 April 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Elisabeth Johanne Rook / Darius Matusevicius

Sponsor's report submission	7 September 2021
COMP discussion	11-13 April 2022
COMP opinion (adoption via written procedure)	26 April 2022

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2011 was based on the following grounds:

- epidermolysis bullosa (hereinafter referred to as "the condition") was estimated to be affecting less than 0.5 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating and life-threatening, in particular due to severe generalised blistering and wounds with a risk of skin cancer development, resulting in poor quality of life and shortened life expectancy;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

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

The designated orphan condition is treatment of epidermolysis bullosa (EB) and is still acceptable as an orphan condition. The therapeutic indication is t*reatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa in patients 6 months and older*. Dystrophic and junctional EB are two severe sub-forms of EB and are considered to be fully covered by the orphan condition.

EB is a heterogeneous group of genetic skin fragility disorders characterized by blistering of the skin in response to minor trauma or friction. EB is caused by mutations in one of at least 14 genes encoding anchoring proteins of the dermo-epidermal junction. EB is divided into four main categories: EB simplex, junctional EB, dystrophic EB, and Kindler syndrome, each comprising different subtypes. A common symptom for all EB subtypes is trauma-induced skin blistering and painful wounds.

EB simplex (EBS) is the most common subtype of EB causing mild to moderate disease. Junctional EB (JEB) is less frequent and has a broad spectrum of severity from the lethal form of JEB Herlitz type to very mild forms often diagnosed later in life. The majority of patients encountered in specialized centres suffer from dystrophic EB (DEB). Dominant and recessive DEB forms cause moderate to severe skin fragility and scarring. Severely affected patients suffer from widespread blistering and painful wounds causing multiple secondary medical problems which often lead to physical impairment.

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

One of the most significant problems in EB is the lifelong presence of skin blistering and partial-thickness wounds that result in pruritus, pain, scarring, deformity, loss of function, and immobility as well as a high risk of complications, such as infection. Patients with EB take care to minimize new wounds; however, this is particularly difficult for young children as minor trauma or friction results in partial-thickness wounds. In addition, there is an increased incidence of aggressive cutaneous SCC at a younger age than in the general population. In patients with generalized severe recessive DEB (RDEB), squamous cell carcinoma occurs in approximately 80% of patients by their mid-40s and can occur as early as adolescence.

Therefore, the condition is considered to be chronically debilitating and life-threatening due to blister formation in response to minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma.

Number of people affected or at risk

To evaluate the epidemiology of EB in the Community a detailed Medline search was performed using the search terms "epidermolysis bullosa" and "prevalence OR incidence OR epidemiology". In addition, references cited in the publications identified above were hand searched and evaluated. An overview of studies evaluating the prevalence of EB in the EU is presented in Table 1. The prevalence in these studies is in the range of 0.04 to 0.61 per 10,000. Most studies report a prevalence in the range of 0.1-0.2 per 10,000.

Table 1. Prevalence of EB in EU member states.

Country	Population size (million)	Cases/patient numbers	Prevalence (per 10,000)	Reference
Austria	8.2	500	0.61	Pohla-Gubo & Hintner, 2010
Croatia	4.6	58	0.09	Pavicic et al., 1990
Germany	82.3*	2000 (est.)	0.24	Volz et al., 2007
Hungary	10	150	0.15	Medvecz & Karpati, 2010
Italy	57.7	697	0.10	Tadini, 2005
	59.2*	897	0.15	Castiglia & Zambruno, 2010
Netherlands	16.5	335	0.20	Duipmans & Jonkman, 2010
Romania	20.1	89	0.04	Danescu et al., 2014

* Country population number was not published, and this value was taken from Eurostat (https://ec.europa.eu/eurostat)

In one study from Spain only DEB was evaluated [Hernandez-Martin et al., 2013], the subform of EB that represented the vast majority in the study population of BEB-13. Based on 152 patients a prevalence of DEB of 0.06 per 10,000 was reported. Since it has been reported that approximately 40% of all EB patients belong to this form [Bruckner-Trudermann, 2010] it can be estimated that the prevalence of EB in Spain is 0.15 per 10,000 which is well in alignment with the information

presented in the table above.

The figures in Table 1 do not indicate any temporal trend in the epidemiology which is plausible in the light of the genetic nature of the disease. Hence, it appears safe to conclude that these figures are relevant for a current estimate of the prevalence of EB. In a conservative approach the highest figure reported (0.61 per 10,000) is used for this prevalence estimation even though the median figure of 0.15 per 10,000 appears more realistic. This approach most likely results in an overestimation of the actual prevalence of EB in the EU.

Based on the information presented above, the prevalence of EB is not more than 0.6 per 10,000 in the Community which is well below the orphan threshold of 5 in 10,000. It is therefore concluded that EB fulfils the epidemiological criterion of an orphan disease in the EU.

It is noted that the latest agreed (initial) orphan designation for this condition from October 2020 (EMA/OD/0000035451) states a slightly higher prevalence estimate of approximately 0.8 in 10,000 persons in the European Union. This estimate was based on the then highest prevalence reported in the article by Mellerio (Mellerio, 2010). However, this estimate is based on a study from the UK and as the UK is no longer a member of the EU, the sponsor has not included this reference in their prevalence calculation.

Considering the above, the sponsor's proposed estimate of approximately 0.6 in 10,000 persons in the European Union is considered to be acceptable and sufficiently conservative.

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

No curative treatment for any sub-type of EB exists and no medicinal product is approved in the EU for this indication.

Supportive symptomatic treatment consists mainly of minimizing risk of blister formation, wound management, pain management and occasionally surgical interventions to treat severe symptoms or disease-associated complications.

Significant benefit

Not applicable.

4. COMP position adopted on 26 April 2022

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 epidermolysis bullosa (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.6 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 blister formation following minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma;
- there is, at present, no satisfactory method for the treatment of epidermolysis bullosa that has been authorised in the European Union for patients affected by the condition.

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 Filsuvez, dry extract from birch bark (DER 5-10 : 1), extraction solvent n-heptane 95% (w/w), for treatment of epidermolysis bullosa (EU/3/10/845) is not removed from the Community Register of Orphan Medicinal Products.