8 January 2018
EMA/1001/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Jorveza (budesonide)
Treatment of eosinophilic oesophagitis
EU/3/13/1181 (EMA/OD/078/13)
Sponsor: Dr Falk Pharma GmbH

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Product and administrative information

Product	
Active substance	Budesonide
International Non-Proprietary Name	Budesonide
Orphan indication	Treatment of eosinophilic oesophagitis
Pharmaceutical form	Orodispersible tablet
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	A07EA06
Sponsor's details:	Dr Falk Pharma GmbH Leinenweberstrasse 5 79108 Freiburg i.Br. Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Dr Falk Pharma GmbH
COMP opinion date	11 July 2013
EC decision date	5 August 2013
EC registration number	EU/3/13/1181
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	H. Enzmann, T. Boran
Applicant	Dr Falk Pharma GmbH
Application submission date	11 May 2017
Procedure start date	15 June 2017
Procedure number	EMA/H/C/004655
Invented name	Jorveza
Therapeutic indication	Treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age). Further information on Jorveza can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	9 November 2017
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	G. O'Dea, F. Naumann-Winter
Expert	An expert was appointed by the COMP for this application
Sponsor's report submission date	22 May 2017
COMP discussion and adoption of list of questions	30-31 October 2017
Oral explanation	5 December 2017
COMP opinion date	7 December 2017

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2013 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing budesonide was considered justified based on clinical trials from the literature showing histologic response and reduction of symptoms in adult and paediatric patients treated with budesonide;
- the condition is chronically debilitating due to chronic oesophageal inflammation, with development of dysphagia that affects dietary intake, and with oesophageal stenosis that can be treated only with invasive procedures. The increased fragility of the oesophageal wall due to the chronic inflammation can lead to oesophageal perforation, particularly during the endoscopic procedures needed for treating the stenosis;
- the condition was estimated to be affecting less than 5 in 10,000 persons in the European Union, at the time the application was made. The prevalence was estimated by the sponsor based on literature search;
- the sponsor has also established that there exists no satisfactory method of 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 approved therapeutic indication "the treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age)" falls within the scope of the designated orphan indication "treatment of eosinophilic esophagitis".

The recent 'Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults' (2017) from a Working Committee of the United European Gastroenterology (UEG), The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the European Academy of Allergy and Clinical Immunology (EAACI), and the European Society of Eosinophilic Oesophagitis (EUREOS) have revised the definition of EoE to include proton-pump inhibitor responsive esophageal esophagitis (PPI-REE) that was previously considered a separate entity.

Since 2011 there has been increasing evidence, mostly from adult patients, that PPI-REE and EoE are virtually indistinguishable from one another, even at the genetic level. Therefore, the new guidelines acknowledged the evidence that lack of response to PPI therapy is not a diagnostic criterion for EoE. Consequently, the 2017 guidelines consider that clinical and histological features suggestive of EoE may merit treatment with PPI therapy in addition to topical steroids or elimination diet.

While the proposed therapeutic indication still falls within the existing designation, the change of classification implies that now PPI-REE is included in the orphan condition, therefore the final estimate of the prevalence of the condition also took this population into account.

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat, prevent or diagnose the condition has been justified, based on placebo-controlled randomized clinical trials. Please refer to the EPAR of Jorveza.

Chronically debilitating and/or life-threatening nature

There have been no changes in the chronically debilitating nature of the disease since the time of orphan designation. Eosinophilic oesophagitis is a severe, chronically debilitating disease due to chronic oesophageal inflammation with development of dysphagia that affects dietary intake. The inflammation also leads to the development of oesophageal stenosis and to fragility of the oesophageal wall, with increased risk of oesophageal perforation during the endoscopic procedures needed for treating the stenosis. The most common clinical manifestation, both in adults and children is food impaction. Other common symptoms in children include feeding difficulties (usually before 2 years of age), dysphagia, vomiting, and abdominal pain. In adults chest pain and heartburn also frequently occur.

Number of people affected or at risk

The sponsor calculated the prevalence of EoE based on a literature search updated to November 2017, retrieving articles on the incidence and prevalence of EoE from single centre studies, national/population-based studies, and one meta-analysis (Arias 2016).

In recent years several articles have highlighted a significant increase in the prevalence of EoE, also due to better knowledge of the disease and the increasing use of endoscopy. The recent change in classification, including also patients responsive to proton pump inhibitors (PPI-REE) adds uncertainty to the current prevalence estimates of EoE since many of the publications of the past years did not include the PPI-REE population.

The meta-analysis from Arias et al (2016) presents prevalence estimates above 5 in 10,000 for the US (up to 5.5 in 10,000). In Europe, according to the studies identified in the meta-analysis the prevalence of EoE is in a range between 1.38 (Dellon et al, 2015) and 4.3 in 10,000 (Hruz et al. 2011). The prevalence conclusions from the meta-analysis appear quite heterogeneous, highlighting the limitations of the current meta-analysis methodology not only for EoE but rare diseases in general. The study from Hruz et al was based on data from a single Swiss canton (Olten). A more recent Swiss study (Giriens 2015) measured a prevalence of 2.4 in 10,000 in another part of the Swiss population.

Among the studies presented by the sponsor and included in the meta-analysis from Aries et al (2016), the one conducted by Dellon et al (2015) in the Danish population appears particularly robust because the case definition was based on a nation-wide, population-based, medical registry, the pathology registry, and the prescription registry, and included also patients responding to PPI. This study concluded with prevalence values of 1.38 in 10,000 in Denmark.

At present there are only three recent population-based studies that have been performed on the prevalence of EoE in Europe. Besides the Swiss study from Giriens et al, 2015 and the Danish study from Dellon et al, 2015, a recent population-based study from Warners et al. 2017 in the Netherlands calculated a 20-year prevalence of 1.3 in 10,000. Both the Danish and the Dutch study included also PPI-REE. It was also noted that no publications exist from the eastern European countries. The sponsor hypothesized that the incidence in Eastern Europe may be significantly lower than in Western Europe but since so far no data have been published there is also the possibility of underestimation due to low

referral rates. A number of studies from single specialized reference centres, some of which propose higher prevalence rates, were considered as additional information particularly relevant to flag the increasing incidence and prevalence of EoE, but were not taken into account for the final estimate of prevalence in the EU as they do not represent the population-level prevalence of the condition and they may be influenced by referral bias.

From the recent population-based studies, the COMP accepted that the Danish study from Dellon et al may be considered as the lower range of prevalence in the EU (1.38 in 10,000, approximated to 1.4), including also PPI-REE. The Swiss study from Giriens et al (2015), reporting the highest prevalence amongst all recent studies, i.e. 2.4 in 10,000 excluding PPI-REE, was used by the sponsor to calculate the worst-case scenario. This calculation assumed the same prevalence of PPI –REE as the reported prevalence of EoE reported in this study, therefore doubling the initial value of 2.4 in 10,000 and concluding with 4.8 in10,000. This was considered by the COMP as the current worst case scenario in Europe, and the upper limit of prevalence for EoE at this point in time. Due to the heterogeneity of the exact prevalence reported in the few population-based studies across Europe the COMP decided to adopt a range of prevalence between 1.4 and 4.8 in 10,000 persons in the EU for the grounds of this designation.

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

As reported by the applicant, there are no medicinal products registered for the treatment of eosinophilic oesophagitis (EoE) in the European Union.

There are three general approaches to the treatment of EoE: Avoidance of the allergen by dietary restriction, endoscopic oesophageal dilation, and off-label pharmacological treatment.

Dilation must be performed gradually over multiple sessions and successfully address the luminal narrowing that can complicate EoE (Moawad 2013). However, dilatation is frequently accompanied by chest pain. Although oesophageal dilation is now considered a safe and effective measure to alleviate dysphagia, it does not affect the underlying inflammatory process and repeated and multiple dilations are required in many patients (Straumann 2016).

In relation to off-label use, treatment with corticosteroids has shown to be effective.

Initially, systemic corticosteroids were used, with good clinical results. Due to the known side effects, including increased risk of infections, hyperglycaemia, cataract, and osteoporosis, long term treatment with systemic corticosteroids is however not considered a practicable option.

Treatment with locally acting corticosteroids licensed for the treatment of asthma, fluticasone and budesonide, was shown to be efficacious and safe in clinical trials, for induction of response (i.e. in the acute phases) and for the maintenance of clinical, endoscopic and histological responses or remission. However, since the formulations used were off-label liquid formulations generated for inhalation use, or hospital preparations from powder formulations, dose-responses were not established and the exposure of the oesophageal mucosa to corticosteroids was not optimal.

Significant benefit

At the time of designation it was agreed that there was no need of demonstration of significant benefit as no medicinal products were authorized for the treatment of the condition. It is assumed that in some cases pharmaceutical compounding may be used for preparing corticosteroid formulations adapted to the disease and patient population. However since there is no certainty about the extent of compounding for this disease across Europe, and the current clinical use of swallowed topical steroids is considered off-label, the COMP did not see the need of a discussion on significant benefit.

4. COMP position adopted on 7 December 2017

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of eosinophilic oesophagitis (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be between 1.4 and 4.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to oesophageal inflammation with development of dysphagia that affects dietary intake, oesophageal stenosis and fragility of the oesophageal wall;
- there is, at present, no satisfactory treatment 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 Jorveza, budesonide, EU/3/13/1181 for treatment of eosinophilic oesophagitis is not removed from the Community Register of Orphan Medicinal Products.