3 May 2019
EMA/202821/2019
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Waylivra (volanesorsen)
Treatment of familial chylomicronemia syndrome
EU/3/14/1249 (EMA/OD/180/13)
Sponsor: Akcea Therapeutics Ireland Limited

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	
Active substance	Phosphorothioate oligonucleotide targeted to apolipoprotein C-III
International Non-Proprietary Name	Volanesorsen
Orphan condition	Treatment of familial chylomicronemia syndrome
Pharmaceutical form	Solution for injection
Route of administration	Subcutaneous use
Pharmaco-therapeutic group (ATC Code)	C10AX
Sponsor's details:	Akcea Therapeutics Ireland Limited Regus House Harcourt Centre Harcourt Road Dublin 2 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Isis USA Ltd
COMP opinion date	9 January 2014
EC decision date	19 February 2014
EC registration number	EU/3/14/1249
Post-designation procedural history	
Sponsor's name change	Name change from Isis USA Ltd to Ionis USA Ltd – EC letter of 7 April 2016
Transfer of sponsorship	Transfer from Ionis USA Ltd to Akcea Therapeutics UK Ltd – EC decision of 6 July 2017
	Transfer from Akcea Therapeutics UK Ltd to Akcea Therapeutics Ireland Limited – EC decision of 13 March 2019
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	J. L. Hillege, B. Van der Schueren
Applicant	Akcea Therapeutics Ireland Limited
Application submission date	26 July 2017
Procedure start date	17 August 2017
Procedure number	EMA/H/C/004538/0000
Invented name	Waylivra
Therapeutic indication	Waylivra is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. Further information on Waylivra can be found in the European public assessment report (EPAR) on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/waylivra
CHMP opinion date	28 February 2019

COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	V. Stoyanova, T. Leest
Sponsor's report submission date	22 February 2018
COMP opinion date	8 March 2019

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2. Grounds for the COMP opinion

The COMP opinion on the orphan medicinal product designation was based on the following grounds:

For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered that the active substance should be renamed as "phosphorothioate oligonucleotide targeted to apolipoprotein C-III".

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 phosphorothioate oligonucleotide targeted to apolipoprotein C-III was considered justified based on preclinical and preliminary clinical data in treated patients affected by the condition who responded to treatment with reduction of triglyceride levels;
- the condition is life threatening and chronically debilitating due to recurrent episodes of acute pancreatitis which may lead to pancreatic insufficiency resulting in malabsorption, failure to thrive and diabetes mellitus;
- the condition was estimated to be affecting less than 0.1 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 a satisfactory method of treatment of the condition has been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing phosphorothioate oligonucleotide targeted to apolipoprotein C-III may be of significant benefit to those affected by the condition. This was based on preclinical and preliminary clinical data showing that the product has an alternative mechanism of action, which is expected to be effective in a broader population affected by the condition than the authorised product. 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 phosphorothioate oligonucleotide targeted to apolipoprotein C-III, as an orphan medicinal product for the orphan indication: treatment of familial chylomicronemia syndrome.

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

Familial chylomicronemia syndrome is an autosomal recessive disorder with loss of function mutations of lipoprotein lipase resulting in hypertriglyceridemia and accumulation of chylomicrons in plasma, often leading to acute pancreatitis (Williams et al, J Clin Lipidol. 2018 Apr 27).

The proposed therapeutic indication:

"Waylivra is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate"

falls entirely within the scope of the designated orphan indication:

"Treatment of familial chylomicronemia syndrome".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition is considered justified.

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any changes in seriousness since designation.

It is acknowledged that the condition is life threatening and chronically debilitating due to recurrent episodes of acute pancreatitis which may lead to pancreatic insufficiency resulting in malabsorption, failure to thrive and diabetes mellitus (Williams et al, J Clin Lipidol. 2018 Apr 27).

Number of people affected or at risk

The applicant refers to the initial designation and to the Orphanet Rare Disease collection (Orphanet Prevalence and incidence of rare diseases: Bibliographic data. June 2017. http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf [Accessed October 2017) which currently estimates a prevalence for FCS of 1 per 100,000 of the European population.

Based on that data, an approximately 0.1 per 10,000 figure was considered acceptable for this maintenance procedure. The COMP endorsed the proposal.

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

Currently, there are no approved products specifically indicated for the treatment of FCS. Dietary management is of paramount importance, with limitation of fat to less than 15 to 20 g per day, focus on complex carbohydrate foods, and supplementation with fat-soluble vitamins, minerals, and medium-chain triglyceride oil, as needed. (Williams et al, J Clin Lipidol. 2018 Apr 27).

Also of note, that alipogene tiparvovec (Glybera) was an LPL gene therapy that has in the past been granted orphan designation for the treatment of homozygous LPL deficiency encompassing also a subset of FCS patients. However, the marketing authorisation expired in October 2017.

It was therefore considered by the COMP that no satisfactory treatments are authorised in the EU at the time of the review.

Significant benefit

Not applicable.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 8 March 2019

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 familial chylomicronemia syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life threatening and chronically debilitating due to recurrent episodes of pancreatitis which may lead to pancreatic insufficiency resulting in malabsorption, failure to thrive and diabetes mellitus;
- 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 Waylivra, phosphorothioate oligonucleotide targeted to apolipoprotein C-III, volanesorsen, EU/3/14/1249 for treatment of familial chylomicronemia syndrome is not removed from the Community Register of Orphan Medicinal Products.