6 July 2018
EMA/425827/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Tegsedi (phosphorothioate oligonucleotide targeted to transthyretin)

Treatment of ATTR amyloidosis

EU/3/14/1250 (EMA/OD/098/13)

Sponsor: Ionis USA Ltd

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 transthyretin
International Non-Proprietary Name	Inotersen
Orphan indication	Treatment of ATTR amyloidosis
Pharmaceutical form	Solution for injection
Route of administration	Subcutaneous use
Pharmaco-therapeutic group (ATC Code)	N07XX
Sponsor's details:	Ionis USA Ltd Tower 42, Level 30 International Finance Centre 25 Old Broad Street London EC2N 1HQ United Kingdom
Orphan medicinal product designation procedural history	
Sponsor/applicant	Isis USA Ltd
COMP opinion date	6 February 2014
EC decision date	26 March 2014
EC registration number	EU/3/14/1250
Post-designation procedural history	
Sponsor's name change	Name change from Isis USA Ltd to Ionis USA Ltd– EC letter of 07 April 2016
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	Martina Weise, Tuomo Lapveteläinen
Applicant	Ionis USA Ltd
Application submission date	3 November 2017
Procedure start date	23 November 2017
Procedure number	EMA/H/C/004782
Invented name	Tegsedi
Therapeutic indication	Treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR) Further information on Tegsedi 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	31 May 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	Kerstin Westermark /Frauke Naumann-Winter
Sponsor's report submission date	18 November 2017
COMP discussion	17-19 April 2018 and 22-24 May 2018
COMP opinion date	5 June 2018

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2014 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing phosphorothioate oligonucleotide targeted to transthyretin was considered justified based on preclinical data showing reduction of levels of circulating TTR protein after administration of the proposed product;
- the condition is life-threatening and chronically debilitating due to the development of polyneuropathy and cardiomyopathy;
- the condition was estimated to be affecting less than 3 in 10,000 persons in the European Union, at the time the application was made.

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 orphan condition “ATTR-amyloidosis” is a distinct medical entity and its articulation follows the recommendations of the Nomenclature Committee of the International Society of Amyloidosis (of Amyloid. 2012 Dec;19(4):167-70. doi: 10.3109/13506129.2012.734345. Epub 2012 Nov 1). As per these recommendations “the continued use of disease classifications such as familial amyloid neuropathy and familial amyloid cardiomyopathy generates confusion” and a classification based on the amyloid forming protein is advocated instead.

The therapeutic indication is: “Treatment of stage 1 or Stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)”

This falls entirely within the scope of the designated orphan indication which was worded in broader terms as “Treatment of ATTR amyloidosis”.

Also of note that it was explicitly considered at the time of designation that the orphan condition is inclusive of all ATTR forms and may be hereditary (producing two clinical phenotypes, namely polyneuropathy and cardiomyopathy depending on the predominant sites of deposition) or non-hereditary (also referred to as senile amyloidosis).

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any change in the seriousness of the condition since the designation of Inotersen as an orphan drug for the treatment of ATTR amyloidosis (March 2014).

The COMP acknowledged that ATTR amyloidosis is chronically debilitating and life-threatening in particular due to the development of polyneuropathy and cardiomyopathy.

Number of people affected or at risk

In their maintenance report, the sponsor provided an estimate of ATTR-amyloidosis including as discussed above both hereditary (mutated) and non-hereditary senile cases.

This was done in two steps: a) assuming an overall amyloidosis prevalence of 4.7 per 10,000 (Parman et al, Curr Opin Neurol. 2016 Feb; 29(Suppl 1): S3–S13.) and then b) by assuming that approximately 2/3 of cases correspond to ATTR-amyloidosis. This last assumption was based on a study by Magy-Bertnard et al, (Magy-Bertrand NM, Clinical and Experimental Rheumatology 2008: 26: 1074-1078).

This gives a conclusion of approximately 3 (3.1) per 10,000 which was considered acceptable the COMP for this maintenance procedure.

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

Tafamidis (Vyndaqel) is the only pharmaceutical product authorised in the EU for the treatment of ATTR amyloidosis. Tafamidis is a ligand at the T4 binding site of TTR and the therapeutic indication is: Treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.

Significant benefit

The therapeutic indication “treatment of stage 1 or Stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)” is broader than the authorised indication of tafamidis, in that it extends beyond stage 1 to include also stage 2 polyneuropathy.

With regards to polyneuropathy manifestations, Stage 1 patients present with weaknesses in the lower limbs and do not require assistance with ambulation, while in Stage 2 they show gait dysfunctions, distal amyotrophies and hand involvement. In Stage 3 they depend on assistance with ambulation, and are either wheel-chair bound or bedridden with generalised weakness and areflexia.

The pivotal study supports delays in neurological impairment in stage 2 patients with regards to both primary endpoints Norfolk QoL-DN and mNIS+7 at 60 weeks as shown in the stratification below.

Table 1. Subgroup analysis of CS2 results (sourced from the sponsor's maintenance report)

	Norfolk QoL-DN		**mNIS+7**	
Subgroup	**Month 15 Change from Baseline (Difference Inotersen – Placebo)**		**Month 15 Change from Baseline (Difference Inotersen – Placebo)**	
Val30Met	-12.25 (4.700)	p = 0.010	-18.86 (4.689)	p < 0.001
Non-Val30Met	-11.12 (4.918)	p = 0.025	-21.27 (4.950)	p < 0.001
Stage I Disease	-9.93 (4.169)	p = 0.019	-14.20 (4.195)	p < 0.001
Stage II Disease	-15.04 (5.623)	p = 0.008	-29.12 (5.610)	p < 0.001
Previous use of stabilisers	-9.05 (4.62)	p = 0.052	-20.02 (4.634)	p < 0.001
Treatment naïve	-14.70 (4.935)	p = 0.003	-20.84 (4.958)	p < 0.001
CM-Echo Set	-9.05 (4.266)	p = 0.036	-17.17 (4.268)	p < 0.001
Non-CM-Echo Set	-16.35 (5.530)	p = 0.004	-25.18 (5.497)	p < 0.001

Data are also available regarding patients that had previously been treated with tafamidis or diflunisal. The table above includes a stratification with regards to previous use of fibril stabilisers. The COMP considered that the extension of the therapeutic indication to stage 2, for which no authorised products exist, constitutes a clinically relevant advantage.

4. COMP position adopted on 5 June 2018

The COMP concluded that:

- the proposed therapeutic indication “treatment of stage 1 or Stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)” falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product which is broadly worded as “treatment of ATTR amyloidosis”;
- the prevalence of ATTR-amyloidosis (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be approximately 3 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 in particular due to the development of polyneuropathy and cardiomyopathy;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Tegsedi may be of potential significant benefit to those affected by the orphan condition still holds. This was considered in particular on the basis of clinical data supporting a delay in the progression of neurological impairment in stage 2 polyneuropathy patients.

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 Tegsedi, phosphorothioate oligonucleotide targeted to transthyretin, inotersen, EU/3/14/1250 for treatment of ATTR amyloidosis is not removed from the Community Register of Orphan Medicinal Products.