17 February 2020
EMADOC-1700519818-273084
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Vyndaqel (tafamidis)
Sponsor: Pfizer Europe MA EEIG

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. Introductory comment

The approved therapeutic indication "Vyndaqel is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)" falls within the scope of the two designated orphan conditions familial amyloid polyneuropathy and senile systemic amyloidosis. The maintenance of the two respective orphan designations is covered in this one document.

2. Vyndaqel (N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate) for treatment of familial amyloid polyneuropathy EU/3/06/401

2.1. Product and administrative information

Product	
Active substances(s) at the time of orphan designation	N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate
Other name(s)	PF-06291826-83
International Non-Proprietary Name	Tafamidis
Tradename	Vyndaqel
Orphan condition	Treatment of familial amyloid polyneuropathy
Sponsor's details:	Pfizer Europe MA EEIG Boulevard De La Plaine 17 1050 Brussels Brussels-Capital Region Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	ICON Clinical Research Limited
COMP opinion date	12 July 2006
EC decision date	28 August 2006
EC registration number	EU/3/06/401
Post-designation procedural history	
Transfer of sponsorship Sponsor's name change	- Transfer from ICON Clinical Research Limited to FoldRx Pharmaceuticals Limited – EC decision of 14 September 2009 - Name change from FoldRx Pharmaceuticals Limited to Pfizer Specialty UK Limited – EC letter of 24 August 2011 - 2nd transfer from Pfizer Specialty UK Limited to Pfizer Limited – EC decision of 25 May 2012 - 3rd transfer from Pfizer Limited to Pfizer Europe MA EEIG – EC decision of 25 July 2018
COMP opinion on review of orphan designation at the time of marketing authorisation	16 September 2011
Type II variation procedural history	
Rapporteur / Co-rapporteur	J.M. Race / B. Sepodes
Applicant	Pfizer Europe MA EEIG
Application submission date	7 January 2019
Procedure start date	30 January 2019
Procedure number	EMEA/H/C/002294/X/0049/G
Invented name	Vyndaqel

Proposed therapeutic indication	Vyndaqel is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). Further information on Vyndaqel can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/vyndaqel
CHMP opinion date	12 December 2019
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	A. Magrelli / A. Lorence
Sponsor's report submission date	6 December 2019
COMP opinion date	19 December 2019

2.2. Grounds for the COMP opinion

2.1 Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2006 designation was based on the following grounds:

The sponsor, ICON Clinical Research Limited, submitted on 24 May 2006 an application for designation of a medicinal product containing N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate as an orphan medicinal product for treatment of familial amyloid polyneuropathy.

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- familial amyloid polyneuropathy (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.1 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and life threatening due to progressive sensitive and motor polineuropathy, and reduction of the life expectancy;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate may be of significant benefit to those affected by the condition.

The COMP recommends the designation of this medicinal product, containing N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate, as an orphan medicinal product for the orphan indication: treatment of familial amyloid polyneuropathy.

2.2 Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2011 was based on the following grounds:

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 familial amyloid polyneuropathy (hereinafter referred to as "the condition") was established to remain below 0.1 in 10,000 at the time of the review of the designation criteria;
- the condition is chronically debilitating and life threatening due to progressive sensory and motor polyneuropathy and reduction of the life expectancy;
- although liver transplantation has been considered by the COMP as a satisfactory method of treatment of the condition, the assumption that Vyndaqel may be of potential significant benefit to those affected by the orphan condition still holds. This is justified by the fact that this is the first medicinal product for this condition authorized in the EU which has activity over amyloid deposition and delays peripheral neurological impairment, providing an additional treatment option.

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 Vyndaqel, N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate, tafamidis, EU/3/06/401 for treatment of familial amyloid polyneuropathy is not removed from the Community Register of Orphan Medicinal Products.

2.3. Review of criteria for orphan designation at the time of type II variation

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 sponsor applied for an extension of indication for transthyretin amyloid cardiomyopathy (ATTR-CM). ATTR-CM is an infiltrative heart muscle disease caused by extracellular deposition of misfolded proteins which form insoluble amyloid fibrils. ATTR-CM exists as 1 of 2 subtypes, as part of hereditary or mutant ATTR (ATTRm) amyloidosis caused by TTR mutations, and as wild-type ATTR (ATTRwt) amyloidosis, which results from age-related changes in wild-type TTR stability.

Vyndaqel has 2 separate orphan designations in the EU, the first from 2006, the European for 'the treatment of familial amyloid polyneuropathy' (EU/3/06/401), and the second from 2012 for 'senile systemic amyloidosis' (EU/3/12/1066).

In 2012, the sponsor submitted an EU orphan drug application for the 'treatment of symptomatic transthyretin amyloid cardiomyopathy' in order to have full coverage for all potential indications under ATTR-CM. During the procedure the COMP confirmed that the existing orphan designation for the 'treatment of familial amyloid polyneuropathy' was considered to include all phenotypes based on TTR mutations even in the absence of polyneuropathy symptoms (i.e. the existing orphan designation includes ATTR-CM due to a mutation). ATTRwt amyloidosis was not considered to be included under the existing orphan designation (EU/3/06/401). The COMP recommended that the sponsor apply for a separate orphan designation to cover the ATTRwt amyloidosis population. For this reason, the sponsor pursued and obtained an orphan designation for "senile systemic amyloidosis" which at that time was the wording used for wild-type ATTR. It can also be noted that today the COMP would designate the broader condition "ATTR-amyloidosis" covering collectively all the above aetiologies and phenotypes.

Based on the above, the approved therapeutic indication "treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy" is considered to fall within the scope of the designated orphan conditions "treatment of senile systemic amyloidosis" and "familial amyloid neuropathy", when both designations are considered together. These two designations will be discussed in two separate summary reports.

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

There have been no changes in the seriousness of the condition. Familial amyloid neuropathy remains a chronically debilitating and life-threatening condition, with median survival of 43.0 months (Ruburg et al 2012). Death in most patients with cardiac amyloidosis is from cardiac causes, including sudden death, heart failure, and myocardial infarction.

Number of people affected or at risk

The sponsor performed a literature review, retrieving a limited number of publications. In general, the prevalence estimates from publication on familial forms include patients with ATTRm amyloidosis with polyneuropathy (PN) only or those with ATTRm amyloidosis with PN and cardiomyopathy (CM). Two key publications from Schmidt et al (2018) and Parman et al (2016) were identified that provided the most current data on the prevalence or incidence of ATTR from familial forms globally including the EU. One other article from Ines et al (2019) was located that described the epidemiology of ATTR-PN in Portugal based on a nationwide survey of sources including reference centre registries and a centralized prescription database. Based on the available literature the sponsor proposed a prevalence of 0.11 in 10,000, which is acceptable.

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

Vyndaqel, the product of this application, is authorised for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Other medicinal products authorized for polyneuropathy in familial forms of amyloidosis are Onpattro (patisiran) and and Tegsedi (inotersen).

There are currently no medicinal products specifically authorized for the treatment of cardiomyopathy (ATTR-CM) in familial forms of transthyretin-related amyloidosis. The cardiac-specific treatment of all forms of amyloidosis largely involves volume management (diuretics/salt restriction) and arrhythmia management. Treatments to manage disease symptoms therefore include diuretics, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and second-generation calcium channel blockers. However, these treatments have not shown to improve the prognosis of the condition in ATTR-CM.

Except for these medications and pacemaker placement for cardiac arrhythmias, the only treatment option currently available for some ATTR-CM patients might be heart transplantation, or for some patients with variant type disease, orthotopic liver and/or heart transplant might be an option.

Significant benefit

The fact that the therapeutic indication will be for ATTR-CM, i.e. for the cardiac manifestations of TTR amyloidosis, is sufficient to confirm the significant benefit in the light of the positive benefit-risk from the CHMP, as no treatment is currently authorized specifically for the cardiac manifestations of ATTR amyloidosis, neither for the wild type transthyretin amyloid (designated in 2012 as senile amyloidosis) nor for the hereditary type.

From a quantitative point of view the pivotal Phase 3 Study B3461028 of Vyndaqel as a treatment for ATTR-CM met its primary and key secondary objectives demonstrating a significant reduction in all-cause mortality and CV-related hospitalisations, with better functional outcomes and quality of life, in the active group compared with placebo. Both doses of tafamidis studied were superior to placebo over 30 months on the primary analysis of all-cause mortality and frequency of CV-related hospitalisations: p=0.0048 with the 20mg and p=0.0030 with the 80mg group.

2.4. COMP position adopted on 19 December

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the two orphan designated orphan conditions "treatment of familial amyloid polyneuropathy" and "treatment of senile systemic amyloidosis". Familial amyloid polyneuropathy and senile systemic amyloidosis are currently classified together under the term 'ATTR-amyloidosis';
- the prevalence of familial amyloid neuropathy (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be 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 progressive sensitive and motor polyneuropathy and reduction of the life expectancy;
- although satisfactory methods for the condition have been authorised in the European Union, the assumption that Vyndaqel may be of potential significant benefit to those affected by the condition still holds. The available clinical data support reduction in all-cause mortality and CV-related hospitalisations in ATTR-cardiomyopathy patients. In contrast the already authorised products only target patients with polyneuropathy. The committee considered that this constitutes a clinically relevant advantage.

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; 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 Vyndaqel, N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate, tafamidis, for treatment of familial amyloid neuropathy (EU/3/06/401) is not removed from the Community Register of Orphan Medicinal Products.

3. Vyndaqel (tafamidis) for treatment of senile systemic amyloidosis EU/3/12/1066

3.1. Product and administrative information

Product	
Active substances(s) at the time of orphan designation	Tafamidis
Other name(s)	PF-06291826-83
International Non-Proprietary Name	Tafamidis

Tradename	Vyndaqel
Orphan condition	Treatment of senile systemic amyloidosis
Sponsor's details:	Pfizer Europe MA EEIG Boulevard De La Plaine 17 1050 Brussels Brussels-Capital Region Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pfizer Limited
COMP opinion date	5 October 2012
EC decision date	8 November 2012
EC registration number	EU/3/12/1066
Post-designation procedural history	
Transfer of sponsorship	Transfer from Pfizer Limited to Pfizer Europe MA EEIG - EC decision of 25 July 2018
Type II variation procedural history	
Rapporteur / Co-rapporteur	J.M. Race / B. Sepodes
Applicant	Pfizer Europe MA EEIG
Application submission date	7 January 2019
Procedure start date	30 January 2019
Procedure number	EMEA/H/C/002294/X/0049/G
Invented name	Vyndaqel
Proposed therapeutic indication	Vyndaqel is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) Further information on Vyndaqel can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/vyndaqel
CHMP opinion date	12 December 2019
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	A. Magrelli / A. Lorence
Sponsor's report submission date	16 January 2019
COMP opinion date	19 December 2019

3.2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2012 designation was based on the following grounds:

The sponsor Pfizer Limited – UK, submitted on 19 July 2012 an application for designation as an orphan medicinal product to the European Medicines Agency for tafamidis for treatment of senile systemic amyloidosis.

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- senile systemic amyloidosis (hereinafter referred to as "the condition") was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made; The sponsor has based their evaluation of the prevalence in Europe on a literature search.
- the condition is life-threatening. Actual median survival rates from diagnosis for patients with the condition are approximately 60 months. Most patients (42-71%) die from cardiac causes, including sudden death, congestive heart failure and myocardial infarction.
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP recommends the designation of this medicinal product, containing tafamidis, as an orphan medicinal product for the orphan indication: treatment of senile systemic amyloidosis.

3.3. Review of criteria for orphan designation at the time of type II variation

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

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an infiltrative heart muscle disease caused by extracellular deposition of misfolded proteins which form insoluble amyloid fibrils. ATTR-CM exists as 1 of 2 subtypes, as part of hereditary or mutant ATTR (ATTRm) amyloidosis caused by TTR mutations, and as wild-type ATTR (ATTRwt) amyloidosis, which results from age-related changes in wild-type TTR stability.

Vyndaqel has 2 separate orphan designations in the EU, the first from 2006, the European for 'the treatment of familial amyloid polyneuropathy' (EU/3/06/401), and the second from 2012 for 'senile systemic amyloidosis' (EU/3/12/1066).

In 2012, the sponsor submitted an EU orphan drug application for the 'treatment of symptomatic transthyretin amyloid cardiomyopathy' in order to have full coverage for all potential indications under ATTR-CM. During the procedure the COMP confirmed that the existing orphan designation for the 'treatment of familial amyloid polyneuropathy' was considered to include all phenotypes based on TTR mutations even in the absence of polyneuropathy symptoms (i.e. the existing orphan designation includes ATTR-CM due to a mutation). ATTRwt amyloidosis was not considered to be included under the existing orphan designation (EU/3/06/401). The COMP recommended that the sponsor apply for a separate orphan designation to cover the ATTRwt amyloidosis population. For this reason, the sponsor pursued and obtained an orphan designation for "senile systemic amyloidosis" which at that time was the wording used for wild-type ATTR. It can also be noted that today the COMP would designate the broader condition "ATTR-amyloidosis" covering collectively all the above aetiologies and phenotypes.

Based on the above, the approved therapeutic indication "treatment of transthyretin amyloidosis in adult patients with wild type or hereditary cardiomyopathy" is considered to fall within the scope of the

designated orphan conditions "treatment of senile systemic amyloidosis" and "familial amyloid neuropathy" , when both designations are considered together.

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

There have been no changes in the seriousness of the condition. Senile amyloidosis remains a chronically debilitating and life-threatening condition, with median survival of 43.0 months (Ruburg et al 2012). Death in most patients with cardiac amyloidosis is from cardiac causes, including sudden death, heart failure, and myocardial infarction.

Number of people affected or at risk

Given that the proposed therapeutic indication encompasses two different designations, and ATTR-CM can occur in both mutated and wild-type ATTR amyloidosis, the calculation of prevalence is difficult. The difficulties come from the changes in classification in the past years, as well as the fact that ATTR-CM is hardly ever reported per se but usually as relative to other causes of heart failure. ATTR-CM may also be underestimated due to the need for endomyocardial biopsy to establish a definitive diagnosis.

For providing a prevalence of senile amyloidosis some assumptions were performed by the sponsor, including that ATTR-CM from wild type occurs in patients 60 years or older, with male:female ratio of 20:1.

The sponsor initially performed a literature search on heart failure, spanning the last 25 years (1993 to date). The table reported by the sponsor contains five studies, the most recent of which is from 2013 (another one is from 2012) while others are quite old (two are from 2001 and 2005, respectively). However, it appears that the sponsor chose the most-relevant articles reporting population-based data, in which case the sources may be acceptable.

From here, the sponsor described ten steps leading to the estimate of ATTRwt among over 60-years old with heart failure (HF), taking into account potential 50% underdiagnoses and extrapolating the number of females from a 20:1 male:female ratio. With these calculations the sponsor obtained an estimated prevalence of 2.8 in 10,000 for ATTRwt. Further the sponsor performed a sensitivity analysis that resulted in the upper limit of 3.9 in 10,000 in the EU.

The calculations of the sponsor appear reasonably substantiated, albeit based on a number of assumptions, and allowed concluding that the average prevalence of ATTRwt is 2.8 in 10,000.

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

Vyndaqel, the product of this application, is authorised for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.

Other medicinal products authorized for polyneuropathy in familial forms of amyloidosis are Onpattro (patisiran) and Tegsedi (inotersen).

There are currently no medicinal products specifically authorized for ATTR-CM in the context of senile amyloidosis.

The cardiac-specific treatment of all forms of amyloidosis largely involves volume management (diuretics/salt restriction) and arrhythmia management. Treatments to manage disease symptoms therefore include diuretics, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and second-generation calcium channel blockers. However, these treatments have not shown to improve the prognosis of the condition in ATTR-CM.

Except for these medications and pacemaker placement for cardiac arrhythmias, the only treatment option currently available for some ATTR-CM patients might be cardiac transplantation, or for some patients with variant type disease, orthotopic liver and/or heart transplant might be an option.

Significant benefit

The fact that the therapeutic indication will be for ATTR-CM, i.e. for the cardiac manifestations of TTR amyloidosis, is sufficient to confirm the significant benefit in the light of the positive benefit-risk from the CHMP, because no treatment is currently authorized specifically for the cardiac manifestations of ATTR amyloidosis, neither for the wild-type transthyretin amyloid (designated in 2012 as senile amyloidosis) nor for the hereditary type.

From a quantitative point of view the pivotal Phase 3 Study B3461028 of Vyndaqel as a treatment for ATTR-CM met its primary and key secondary objectives demonstrating a significant reduction in all-cause mortality and CV-related hospitalisations, with better functional outcomes and quality of life, in the active group compared with placebo. Both doses of tafamidis studied were superior to placebo over 30 months on the primary analysis of all-cause mortality and frequency of CV-related hospitalisations: p=0.0048 with the 20mg and p=0.0030 with the 80mg group.

3.4. COMP position adopted on 19 December 2019

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the two orphan designated orphan conditions "treatment of familial amyloid polyneuropathy" and "treatment of senile systemic amyloidosis". Familial amyloid polyneuropathy and senile systemic amyloidosis are currently classified together under the term 'ATTR-amyloidosis';
- senile systemic amyloidosis was estimated to be affecting approximately 2.8 in 10,000 persons in the European Union, at the time the review of criteria;
- senile systemic amyloidosis is life-threatening and chronically debilitating due to the development of progressive heart failure which can lead to myocardial infarction and sudden death. The median progression to death is 43 months;
- although satisfactory methods for the treatment of senile systemic amyloidosis the condition have been authorised in the European Union, the assumption that Vyndaqel may be of potential significant benefit to those affected by the condition still holds. The available clinical data support reduction in all-cause mortality and CV-related hospitalisations in ATTR-cardiomyopathy patients. In contrast the already authorised products only target patients with polyneuropathy. The committee considered that this constitutes a clinically relevant advantage.

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 Vyndaqel, tafamidis for treatment of senile systemic amyloidosis (EU/3/12/1066) is not removed from the Community Register of Orphan Medicinal Products.