31 May 2024
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Akantior (polihexanide)
Treatment of Acanthamoeba keratitis
EU/3/07/498

Sponsor: SIFI S.p.A.

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	
Designated active substance	Polihexanide
Other names	SF101; PHMB; Poliesanide; Polyhexamethylene biguanide hydrochloride - SIFI; Polyhexamethylene biguanide ophthalmic solution - SIFI
International Non-Proprietary Name	Polihexanide
Tradename	Akantior
Orphan condition	Treatment of Acanthamoeba keratitis
Sponsor's details:	SIFI S.p.A. Via Ercole Patti 36 95025 Aci Sant'Antonio CT Italy
Orphan medicinal product designation procedural history	
Sponsor/applicant	SIFI S.p.A.
COMP opinion	12 September 2007
EC decision	14 November 2007
EC registration number	EU/3/07/498
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Daniela Philadelphy / Jayne Crowe
Applicant	SIFI S.p.A.
Application submission	2 May 2022
Procedure start	19 May 2022
Procedure number	EMEA/H/C/005858/0000
Invented name	Akantior
Proposed therapeutic indication	Akantior is indicated for the treatment of acanthamoeba keratitis in adults and children from 12 years of age. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Akantior
CHMP opinion	30 May 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Armando Magrelli / Tim Leest
Sponsor's report submission	11 September 2023
COMP opinion (adoption via written procedure)	31 May 2024

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2007 designation was based on the following grounds:

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

- *Acanthamoeba* keratitis (hereinafter referred to as "the condition") was estimated to be affecting less than 0.1 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating due to the risk of loss of sight, resulting from the disease or from enucleation;
- there is, at present, no satisfactory treatment that has been authorised in the Community for patients affected by the condition;

The COMP recommends the designation of this medicinal product, containing polihexanide, as an orphan medicinal product for the orphan indication: treatment of *Acanthamoeba* keratitis".

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

Acanthamoeba keratitis is a rare parasitic infection of the cornea that can lead to permanent blindness if not diagnosed and treated promptly. This infection results from invasion of ocular tissue through a corneal lesion.

Several different species and genotypes of acanthamoeba have been recognized, all exist in two forms: an active form (trophozoite) and a dormant form (cyst). The trophozoite is the active form of acanthamoeba; it can reproduce by binary fission in optimal growth conditions and cause human infections. In unfavourable conditions, acanthamoeba trophozoites can transform into cysts; this is the dominant state of acanthamoeba characterised by a very low metabolic rate but resistance to environmental challenges. The cystic form of acanthamoeba is responsible for persistent disease.

Damage starts at the moment acanthamoeba enters the eye, proliferates and starts feeding from the cornea. This combined with a natural inflammatory response causes corneal vascularisation, scarring and corneal perforation. Extra-corneal complications such as scleritis, retinal necrosis, cataract, glaucoma, and iris atrophy can also occur.

The approved therapeutic indication "Akantior is indicated for the treatment of acanthamoeba keratitis in adults and children from 12 years of age" falls within the scope of the designated orphan condition "treatment of acanthamoeba keratitis".

Intention to diagnose, prevent or treat

The medical plausibility is confirmed by the benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The early symptoms of the infection are photophobia, tearing and ocular pain. The pain mostly is particularly severe, often disproportionate to the initial clinical signs. At the beginning of the infection epithelial micro erosions, irregularities, opacities and microcystic oedemas, often with patchy anterior stromal infiltrates can be observed (Clarke and Niederkorn 2006). In many cases the clinical picture of a dendriform keratitis makes this infection hard to discriminate from keratitis caused by herpes virus. The progressed infection is characterised by diffuse cellular inflammation in the cornea. Other characteristic symptoms (which appear in the early phases of infection) include eyelid ptosis, conjunctival hyperaemia, epithelial ulcers, and lack of discharge. These symptoms are often followed by the appearance of a ring-like stromal infiltrate in the later stages of disease (Niederkorn, Alizadeh et al. 1999; Sharma, Garg et al. 2000). A radial keratoneuritis seems to be pathognomonic for the infection, although it is only seen in about 50% of the cases. The disease usually progresses slowly, however, in most cases it ends up in a fulminant infection very often leading to severe loss of vision and sometimes even to the enucleation of the afflicted eye (Armstrong 2000; Moshari, McLean et al. 2001).

Due to the complicated diagnostics, the elaborate treatment, and the usually bad compliance of the patients, Acanthamoeba keratitis unfortunately very often takes a serious progression, which may lead to serious visual loss, pain and perforating keratoplasty.

The COMP agreed that the condition is chronically debilitating due to the risk of loss of sight, resulting from the disease or from enucleation.

Number of people affected or at risk

The sponsor proposes a prevalence estimate ranging from 0.03 to 0.14 per 10,000 persons for the condition acanthamoeba keratitis.

This estimate is the same as the one accepted by the COMP during the initial orphan designation in 2007. The sponsor has conducted a comprehensive literature search for any updates on the prevalence of acanthamoeba keratitis in the European Union (EU), considering publications from 2007 onward.

The sponsor has used incidence multiplied by the average duration of the disease to calculate prevalence; however, as the disease has an average duration of less than one year, incidence was directly used as an estimate of prevalence.

Studies providing information on the incidence of acanthamoeba keratitis in countries in the EU are summarised in Table 1. Three new publications were identified, reporting incidences in the range of 0.01 to 0.03 cases per 10,000 inhabitants per year. The provided estimates from European studies since 2007 agree with a recent systematic literature search, which estimated a global incidence of Acanthamoeba keratitis of 2.9 cases per million people or 0.029 cases per 10,000 inhabitants per year (Zhang et al. 2023).

Table 1. Studies Published since January 2007 Reporting the Incidence of Acanthamoeba Keratitis in the European Economic Area

Study	Country	Description	Incidence

Walochnik et al. 2015	Austria	Cases presented to Austrian reference laboratory for Acanthamoeba diagnostics between 1993 to 2013	0.01 cases per 10,000 inhabitants per year[a] (equal to: 1 case per million inhabitants per year)
Randag et al. 2019	The Netherlands	Review of all patients diagnosed with Acanthamoeba keratitis in the Netherlands in 2015	0.03 cases per 10,000 inhabitants per year[b] (equal to: 3 cases per million inhabitants per year)
Nielsen et al. 2020	Western part of Denmark	Medical record search at sole highly specialized corneal unit in western part of Denmark for 2013-2018	0.03 cases per 10,000 inhabitants per year[c] (equal to: 3 cases per million inhabitants per year)
Zhang et al. 2023	Global	Complete clinical literature database search 1975-2021	0.029 cases per 10,000 inhabitants per year (equal to 2.9 per million inhabitants per year)

[a] The authors reported that in the past years, they saw around 10 Acanthamoeba keratitis cases per year, which would correspond to 0.125 cases/100,000 inhabitants. They also noted, however, that Acanthamoeba diagnostics is also established in several other laboratories in Austria, so this could be an under-estimate.
[b] Reported as 49 cases per 16,900,726 persons per year in 2015.
[c] Reported as 2.7 cases per 1,000,000 persons per year from 2013 to 2018.

It is recognised that AK is strongly associated with contact lens use (around 95% wear contact lenses). Randag et al. 2019 also calculated the incidence of acanthamoeba keratitis per contact lens users aged 15 to 65 years of age per year at 1 person per 21,000 or 0.5 per 10,000 contact lens users. When considering the country with the highest reported use of contact lenses in the EU (30% of persons in Sweden in 2020; Statista 2020), this would amount to an incidence of 0.14 per 10,000 persons a year (14 per million). However, even this low incidence is very much an overestimate, as other larger EU countries have much lower contact lens use (Table 2).

Table 2. Estimated incidence based on the percentage of contact lens users in selected EU member states

Country	**Population (million)[1]**	**Estimated number of contact lens wearers (percentage total population[2])**	**Estimated total number of persons affected by Acanthamoeba keratitis per year[3]**	**Estimated incidence in the total population**
Germany (2020)	83.17	5.16 million (6.2%)	246	0.03 per 10,000 persons per year (equal to: 3 cases per million inhabitants per year)
France (2018)	67.49	3.32 million (4.92%)	158	0.02 per 10,000 persons per year (equal to: 2 cases per million inhabitants per year)
Italy (2020)	59.64	3.58 million (6%)	170	0.03 per 10,000 persons per year (equal to: 3 cases per million inhabitants per year)

Spain (2020)	47.33	4.73 million (10%)	225	0.05 per 10,000 persons per year (equal to: 5 cases per million inhabitants per year)
Poland (2020)	37.96	1.67 million (4.4%)	80	0.02 per 10,000 persons per year (equal to: 2 cases per million inhabitants per year)
Sweden (2020)	10.33	3.10 million (30%)	148	0.14 per 10,000 persons per year (equal to: 14 cases per million inhabitants per year)

1. Source: Eurostat 2020. Displayed are the 5 most populous countries in the European Union and Sweden, as the country with the highest reported percentage of contact lens users.
2. Source: for persons aged 15-64 years in France Statista 2018; Statista 2020;
3. Calculated using an estimated yearly incidence of 1 in 21,000 contact lens users (Randag et al. 2019).

The COMP agreed with the sponsors prevalence calculation and considered that the final estimate should be less than 0.1 per 10,000 persons.

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

There are currently no medicinal products authorised for use in acanthamoeba keratitis and no standard treatment is established across the European Union (EU).

The usual multi-agent management comprises of several agents including polihexanide, propamidine, chlorhexidine, and hexamidine. In most cases additional concomitant therapy is applied (i.e. especially antibiotics, antifungals, corticosteroids, and pain killers) and in many cases (25%) corneal transplant(s) is/are required (Randag et al. 2019, Papa et al. 2020). Ophthalmologists have to rely on off-label/compounded locally available options, which significantly differ between countries and between expert centres within countries or they have to activate the importation of off-label products from foreign countries, which causes delay in the initiation of the treatment.

According to literature, in most cases additional concomitant therapy is applied (i.e. especially antibiotics, antifungals, corticosteroids and pain killers). In cases of medical failure, a surgical intervention (as amniotic membrane transplantation, deep anterior lamellar keratoplasty or penetrating keratoplasty) may be required in approximately one third of patients (Varacalli et al 2021; Robaei et al 2015; Randag et al 2019; List et al 2021).

Early diagnosis and immediate medical care are required to alleviate acute symptoms of infection and reduce the infection load (i.e. density of acanthamoeba) as soon as possible to prevent major damage to the patient’s cornea and ultimately to maintain patients' vision or prevent vision loss.

Significant benefit

Not applicable.

4. COMP position adopted on 31 May 2024

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 acanthamoeba keratitis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 0.1 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 the risk of loss of sight, resulting from the disease or from enucleation;
- at present, no satisfactory method for the treatment of the condition 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 Akantior, polihexanide for treatment of acanthamoeba keratitis (EU/3/07/498) is not removed from the Community Register of Orphan Medicinal Products.