SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

AKANTIOR 0.8 mg/mL eye drops, solution in single-dose container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 0.8 mg polihexanide (0.08% w/w). One drop (about 0.032 g) contains on average 0.025 mg polihexanide.

Excipients with known effect

Each drop of the solution contains approximately 0.4 mg phosphates which is equivalent to 11 mg/mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution in single-dose container (eye drops)

Clear, colourless solution, practically free of visible particles.
pH: 5.6 – 6.0
Osmolality: 270 – 330 mOsmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AKANTIOR is indicated for the treatment of *Acanthamoeba* keratitis in adults and children from 12 years of age.

4.2 Posology and method of administration

AKANTIOR should be prescribed by physicians experienced in the diagnosis and treatment of *Acanthamoeba* keratitis.

Posology

AKANTIOR should be started as early as possible in the course of *Acanthamoeba* infection.

Adults and children from 12 years of age
The recommended dose is 1 drop of AKANTIOR in the affected eye according to the following regimen:

Intensive 19-day treatment phase:
- 16 times a day at 1-hour intervals, daytime only, for five days
- 8 times a day at 2-hour intervals, daytime only, for further seven days
- 6 times a day at 3-hour intervals, daytime only, for further seven days

Continuation treatment phase:
- 4 times a day at 4-hour intervals, until cure (i.e. corneal healing, absence of corneal inflammation or no evidence of infection) and for no longer than 12 months.

Reinitiation of intensive treatment.
The 19-day intensive regimen phase may be reinitiated if a deterioration (or exacerbation) of ocular inflammation occurs during the continuation treatment phase and *Acanthamoeba* culture is negative. Treatment with AKANTIOR should be stopped if deterioration is accompanied by a positive culture.

Discontinuation of treatment.
AKANTIOR should be discontinued in patients with failure to achieve cure within 12 months of treatment start.

Special populations

Paediatric population
The safety and efficacy of AKANTIOR in children younger than 12 years has not yet been established. No data are available.

Elderly
No dose adjustment is required in patients 65 years of age and older.

Method of administration

For ocular use.

For single use only.

The contents of the single-dose container must be used immediately after opening.

Patients should be instructed:

- To avoid contact between the single-dose container tip and the eye or eyelids.

- To use the solution immediately after opening the single-dose container and to discard it afterwards.
- To instil AKANTIOR at least 5 minutes after any other ophthalmic product.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Subjects with urgent need of ocular surgery due to advanced *Acanthamoeba* keratitis.

4.4 Special warnings and precautions for use

AKANTIOR may cause mild to moderate eye discomfort (such as eye pain) and eye redness.
The patient should be advised to contact the doctor in case of concern or a severe eye reaction.
No data are available on the use of AKANTIOR in subjects with immunodeficiency disorders or requiring systemic immunosuppressive therapy.

Excipients

AKANTIOR contains phosphates. Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Local interactions with other medicinal products cannot be excluded.

If more than one topical ophthalmic product is being used, AKANTIOR must be administered at least 5 minutes after the last administration.

As systemic absorption of polihexanide after use of AKANTIOR is negligible or not detectable, no interactions with systemic medicinal products are expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of polihexanide in pregnant women.
Animal studies using oral administration do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of AKANTIOR during pregnancy.

Breast-feeding

It is unknown whether polihexanide is excreted in human milk.

A decision must be made as to whether to discontinue breast-feeding or to discontinue/abstain from AKANTIOR therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of polihexanide on human fertility.

4.7 Effects on ability to drive and use machines

AKANTIOR has minor influence on the ability to drive and use machines, as it may cause temporary blurred vision or other visual disturbances, which is expected to last a few minutes after instillation. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Summary of safety profile

The most common adverse reactions are eye pain (13.0%) and ocular hyperaemia (11.6%).
The most serious are corneal perforation (1.4%), corneal transplant (1.4%) and visual impairment (1.4%), which are also part of the natural history of the disease.

Tabulated list of adverse reactions

The adverse reactions listed below were observed in clinical trials in patients treated with AKANTIOR with a reasonable possibility of causality to the medicinal product.
Adverse reactions are presented according to MedDRA system organ classification (SOC and Preferred Term Level).
They are classified according to the subsequent convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000) and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions observed in clinical trial 043/SI

System organ class	Frequency	Adverse reactions
Infections and infestations	Common	Conjunctivitis Eye infection
Eye disorders	Very common	Eye pain Ocular hyperaemia
	Common	Corneal perforation Visual impairment Ulcerative keratitis Corneal epithelium defects Corneal infiltrates Punctate keratitis Tearing Conjunctival hyperaemia Eye inflammation Eye irritation Photophobia Conjunctival papillae Eye pruritus Eye discharge Eye swelling Foreign body sensation Ocular discomfort Dry eye
General disorders and administration site conditions	Common	Condition aggravated Application site pain Application site discomfort Product intolerance Application site pruritus
Injury, poisoning and procedural complications	Common	Persistent epithelial defect Toxicity to various agents
Surgical and medical procedures	Common	Corneal transplant

Adverse reactions reported in phosphate containing eye drops

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No information is available on overdose in humans; overdose is unlikely to occur after ocular administration.

If overdose occurs, treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, other antiinfectives, ATC code: S01AX24

Acanthamoeba keratitis is a severe, progressive corneal infection characterized by intense pain, photophobia, and is sight threatening. *Acanthamoeba* keratitis is an ultra-rare disease primarily affecting contact lens wearers with an incidence of 1-4 per million. Results from a cohort of 227 patients in a retrospective study indicated substantial variations in the way patients are treated; a combination of polihexanide 0.2 mg/ml and propamidine 1.0 mg/ml was used in 45 patients and 57.8% of patients were cured within one year.

Mechanism of action

Pharmacodynamics were not tested in the scope of clinical trials.

Polihexanide acts on both the active trophozoite and dormant cystal forms of *Acanthamoeba*. Polihexanide is a polycationic polymer composed of hexamethylene biguanide units and has a dual-targeted mechanism of action that involves:

- Disruption of Acanthamoeba cell membranes. Polihexanide, positively charged, binds to the phospholipid bilayer of the trophozoites membrane, negatively charged, causing membrane damage, cell lysis and death due to leakage of essential cell components. Polihexanide is also able to penetrate the ostiole of the encysted Acanthamoeba to exert the same effect. This action only marginally affects the neutral phospholipids in mammalian cell membrane.

- DNA binding. Once polihexanide has passed through the cell membrane, it condenses and damages Acanthamoeba chromosomes. Polihexanide interacts extensively with the DNA phosphate backbone to block the Acanthamoeba DNA replication process. This mechanism is restricted to Acanthamoeba cells as polihexanide is unable to penetrate the nucleus of mammalian cells.

Clinical efficacy

The absolute efficacy of AKANTIOR was determined by comparing results observed in a randomised, double-blind, active-controlled phase III clinical trial with historical control data on subjects who received no treatment. These subjects were identified through a systematic literature review (n=56); the clinical resolution rate with no surgery in this historical control was 19.6% (95%CI: 10.2%, 32.4%). The remaining 80.4% of patients required surgery (keratoplasty 38/56: 67.9% [48.0%, 83.0%]), enucleation 4/56: 7.1% [3.0%, 18.0%]) or minor surgery 4/56: 7.1% [1.0%, 29.0%])).

The treatment effect (percentage of patients cured without surgery) of AKANTIOR versus absence of treatment (historical control) is shown in Table 2. A study effect of 30.7% (95%CI: 14.2%; 47.2%) was also estimated based on results observed for the chosen comparator in study 043 and the expanded retrospective study published by Papa et al. 2020. By performing a crude adjustment method of adding this estimated value of 30.7%, the estimated placebo effect would reach a hypothetical clinical resolution of 50.3% (95%CI: 36.6%; 64.1%).

Table 2. Absolute efficacy of AKANTIOR

Treatment	AKANTIOR + placebo	No treatment
Source	Phase III clinical trial	Historical control
N.	66	56
Cured	56	11
Clinical resolution rate (binomial exact 95% CI)	84.8% (73.9%, 92.5%)	19.6% (10.2%, 32.4%)
Clinical resolution rate including 30.7% study effect (binomial exact 95%CI)	84.8% (73.9%, 92.5%)	50.3 % (36.6%, 64.1%)
Treatment effect-mean difference (binomial exact 95%CI) unadjusted	65.2% (49.3%, 77.5%)	
Treatment effect-mean difference (binomial exact 95%CI) adjusting for a study effect	34.5% (16.8%,49.8%)	

CI=confidence interval

The phase III clinical trial was conducted using, as active control, 0.2 mg/ml polihexanide plus 1 mg/ml propamidine . In total, 135 patients with *Acanthamoeba* keratitis and no history of previous anti-amoebic treatment were enrolled in this trial. Subjects requiring urgent surgical intervention for advanced *Acanthamoeba* keratitis in either eye (e.g., for advanced corneal thinning/melting etc.) were excluded. The overall mean age was 36.5 years; 58.2% patients were female. Four patients were aged 15-17 years and two patients were aged > 65 years.

Patients were randomised 1:1 to receive AKANTIOR plus placebo (n = 69) or a combination of polihexanide 0.2 mg/mL plus propamidine 1 mg/mL (n = 66). Both treatment arms followed the same dosing regimen with an intensive 19-day treatment (16 times daily for 5 days, 8 times daily for 7 days, 6 times daily for a further 7 days) during the daytime only, followed by 4 times daily treatment until resolution of corneal inflammation. The investigators also received instructions when to stop or reinitiate treatment (see section 4.2). Treatment was allowed for a maximum of one year.

Of the 135 patients enrolled, 127 (66 AKANTIOR and 61 comparator-arm) had a confirmed diagnosis of *Acanthamoeba* keratitis by *in vivo* confocal microscopy, PCR, or culture. The intention-to-treat (ITT) population included 127 patients, and the per protocol (PP) population included 119 subjects (62 AKANTIOR and 57 comparator-arm).

The primary efficacy endpoint was the clinical resolution rate within 12 months from randomisation. Patients requiring an increase of the dose due to worsening of the condition (n=4), all of them in the monotherapy treatment group, were counted as treatment failure in the primary analysis. Analyses were performed on the ITT population.

Clinical resolution was defined as no corneal inflammation requiring treatment, no or mild conjunctival inflammation, no limbitis, scleritis or anterior chamber

inflammation, and no relapse within 30 days of discontinuing all topical therapy given for *Acanthamoeba* keratitis.
The clinical resolution rate obtained in the study is shown in **Table 3**.

Table 3. Primary efficacy analysis: cure rate within 12 months

Treatment	**n**	**Cured**	**% cured (95%CI)**	**Difference in proportion rate (95%CI)**
AKANTIOR + placebo	66	56	84.8% (73.9%, 92.5%)	-0.04 (-0.15, 0.08)
0.2 mg/ml polihexanide + 1 mg/ml propamidine	61	54	88.5% (77.8%, 95.3%)	

CI=confidence interval

The median time-to-cure was 140 days (95%CI=117,150) for 0.8 mg/ml polihexanide and 114 days (91,127) for the control arm (p=0.0442, log rank test).

Overall, 2 subjects had corneal transplantation, both in the 0.8 mg/ml polihexanide + placebo treatment group (1 was coded as “Corneal infiltrates” and therefore, it was not included in the respective table as “Corneal transplant”). There were small differences in the proportion of treatment failures (prematurely withdrawn subjects) between treatments: 10/66 (15.2%) in the group treated with 0.8 mg/ml polihexanide and 7/61 (11.5%) in the group treated with 0.2 mg/ml polihexanide plus 1 mg/ml propamidine.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with AKANTIOR in all subsets of the paediatric population with *Acanthamoeba* keratitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetics were not studied.

AKANTIOR is intended for topical ophthalmic application. The systemic absorption of polihexanide is expected to be negligible after topical administration to the eye.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

A 26-week toxicity study using daily administration (16 times/day at approximately 1-hour intervals from day 1 to day 5, 8 times/day at approximately 2-hour intervals from day 6 to week 3 and 4 times/day at approximately 4-hour intervals from week 4 to week 26) of polihexanide 0.8 mg/mL eye drops was conducted in rabbits. The study did not indicate any local or systemic effects of the treatment. No indications of a systemic effect of polihexanide 0.8 mg/mL eye drops were observed during 26 weeks of treatment period. *Post mortem* macroscopic and histopathological examinations performed at the end of the study did not reveal treatment-related changes.

There was no evidence of genotoxicity in *in vitro* and *in vivo* studies.

There was no evidence of embryo-foetal toxicity in oral studies in the rat and the rabbit.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate monohydrate
Disodium phosphate dodecahydrate
Sodium chloride
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

<u>After opening the sachet</u>

Once the outer sachet has been opened, the single-dose containers must be used within 28 days (after this period, any unused single-dose containers must be discarded).

After opening the single-dose container

The contents of the single dose container must be used immediately after opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

AKANTIOR is contained in low density polyethylene (LDPE) single-dose containers filled with 0.3 mL solution.

The single-dose containers are moulded in 5-unit sealed strips which in turn are wrapped in a polyester/aluminium/polyethylene sachet and packaged inside a carton box.

Pack sizes:

- 20 single-dose containers
- 30 single-dose containers
- multipack containing 120 (4 packs of 30) single-dose containers

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

SIFI S.p.A.
Via Ercole Patti, 36

95025 Aci Sant'Antonio (CT)
Italy

8 MARKETING AUTHORISATION NUMBER(S)

PL36078/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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