ANNEX I

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 national reporting system listed in Appendix V.

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.

After opening the sachet

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)

EU/1/24/1840/001
EU/1/24/1840/002
EU/1/24/1840/003

9. DATE OF FIRST AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

SIFI S.p.A.
Via Ercole Patti, 36
95025 Aci Sant'Antonio (CT)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution contains 0.8 mg of polihexanide.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate dodecahydrate, sodium chloride, purified water.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution

20 × 0.3 mL single-dose containers
30 × 0.3 mL single-dose containers

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Ocular use.
Read the package leaflet before use.

[QR code] https://qr.sifigroup.com/akantior/

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After opening the sachet, use the single-dose containers within 28 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SIFI S.p.A.
Via Ercole Patti, 36
95025 Aci Sant'Antonio (CT)
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1840/001 20 × 0.3 mL single-dose containers
EU/1/24/1840/002 30 × 0.3 mL single-dose containers

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AKANTIOR

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution contains 0.8 mg of polihexanide.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate dodecahydrate, sodium chloride, purified water.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution

Multipack: 120 (4 packs of 30) × 0.3 mL single-dose containers

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Ocular use.

Read the package leaflet before use.

[QR code] https://qr.sifigroup.com/akantior/

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After opening the sachet, use the single-dose containers within 28 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SIFI S.p.A.
Via Ercole Patti, 36
95025 Aci Sant'Antonio (CT)
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1840/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AKANTIOR

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of solution contains 0.8 mg of polihexanide.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate dodecahydrate, sodium chloride, purified water.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution

30 × 0.3 mL single-dose containers. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Ocular use.

[QR code] https://qr.sifigroup.com/akantior/

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After opening the sachet, use the single-dose containers within 28 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SIFI S.p.A.
Via Ercole Patti 36
95025 Aci Sant'Antonio (CT)
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1840/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

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

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 × 0.3 mL single-dose containers

6. OTHER

[QR code] https://qr.sifigroup.com/akantior/

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SINGLE-DOSE CONTAINER LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

AKANTIOR 0.8 mg/mL eye drops
polihexanide
Ocular use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AKANTIOR is and what it is used for

AKANTIOR contains the active substance polihexanide.

AKANTIOR is used in adults and children from 12 years of age to treat *Acanthamoeba* keratitis, *Acanthamoeba* is a parasite (tiny organism that lives inside humans and can cause disease) which can cause an infection resulting in keratitis (inflammation of the cornea, the clear layer in front of the eye). *Acanthamoeba* keratitis can cause severe defects on the surface of the cornea, including ulcers (open sores).

AKANTIOR damages the membrane (outer skin) of the *Acanthamoeba* parasite resulting in leakage of the cellular contents which destroys the cell. AKANTIOR also prevents the *Acanthamoeba* parasite from making copies of its DNA by interfering with enzymes (proteins) responsible for the replication process, which stops the growth and reproduction of the parasite in humans.

2. What you need to know before you use AKANTIOR

Do not use AKANTIOR
If you are allergic to polihexanide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before using AKANTIOR.

Treatment with AKANTIOR may cause you mild to moderate eye discomfort (such as eye pain) and eye redness. In the case you are experiencing a severe eye reaction, contact your doctor.

Children and adolescents
AKANTIOR is not recommended in children under 12 years, as it has not been tested in this age group.

Other medicines and AKANTIOR
Tell your doctor or pharmacist if you are using, have recently used, or might use any other medicines.

If you are using other eye drops, wait at least 5 minutes between applying AKANTIOR and the other drops. AKANTIOR should be administered last.

Pregnancy and breast-feeding

There is no experience of using AKANTIOR in pregnant women. AKANTIOR is not recommended during pregnancy. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is unknown whether AKANTIOR passes into breast-milk. Ask your doctor or pharmacist for advice before AKANTIOR treatment.

Driving and using machines
Your sight may become temporarily blurred after using AKANTIOR. Avoid driving or using machines until your sight is clear again.

AKANTIOR contains phosphates
This medicine contains 0.37 mg phosphates in each drop which is equivalent to 10.66 mg/mL. If you suffer from severe damage to the clear layer at the front of the eye (the cornea), phosphates may cause in very rare cases cloudy patches on the cornea due to calcium build-up during treatment.

3. How to use AKANTIOR

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The treatment consists of two parts: intensive treatment that lasts for the first 19 days and continuation treatment that lasts from day 20.
The recommended dose is **1 drop** of AKANTIOR in the affected eye as follows:

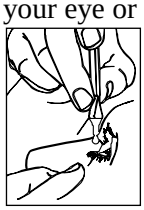
Starting intensive treatment (19 days)
- Apply one drop every hour (16 times a day), for the first five days (days 1 to 5)
- Apply one drop every 2 hours (8 times a day), for a further seven days (days 6 to 12)
- Apply one drop every 3 hours (6 times a day) , for a further seven days (days 13 to 19)

Continuation treatment
- Apply one drop every 4 hours (4 times a day), until there is no corneal inflammation or no evidence of infection (cured)
  Your doctor will advise you when to stop treatment.

Instructions for use
1) Wash your hands.
2) Open the aluminium sachet containing the single-dose containers.
3) Separate the single-dose container from the strip and put the unopened containers back into the sachet.

4) Open the single-dose container by twisting the upper part without pulling. Do not touch the tip after opening the container.

5) Tilt the head back. The single-dose container is now open. Keep the single dose container upright, and do not squeeze.
6) Use your finger to gently pull down the lower eyelid of your affected eye.
7) Invert the single-dose container and place the tip of the container close to your eye. Do not touch your eye or eyelid with the container tip.



8) Squeeze the single-dose container in order to administer only one drop, then release the lower eyelid.
9) Close your eye and press a finger against the corner of the affected eye by the side of your nose. Hold for 2 minutes.
10) Discard the single dose container after use.

If you use more AKANTIOR than you should
Put your next dose in at the usual time, as it is unlikely to cause you any serious harm.

If you forget to use AKANTIOR
Apply the next dose as usual. Do not use a double dose to make up for a forgotten dose.

If you stop using AKANTIOR
Use AKANTIOR as prescribed for best effect. Always tell your doctor if you are thinking about stopping the treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The majority of side effects generally occur at the treated eye.
Contact your doctor if you have a **severe eye reaction**.

The following side effects have been reported:
Very common (may affect more than 1 in 10 people)
- eye pain
- ocular hyperaemia (eye redness)

Common (may affect up to 1 in 10 people)
- corneal perforation (damage to the corneal surface)
- visual impairment
- ulcerative keratitis (inflammation or infection of the cornea)
- corneal epithelium defects (defects of outermost corneal layer)
- corneal infiltrates (immune response to corneal insult)
- punctuate keratitis (small breaks in the surface of the eye)
- tearing (watery eyes)
- conjunctival hyperaemia (redness of the conjunctiva)
- eye inflammation
- eye irritation
- photophobia (unpleasant eye sensitivity to light)
- conjunctival papillae (inside of eyelid gets red, swollen and irritated)
- eye pruritus (itchy eyes)
- eye discharge

- eye swelling
- foreign body sensation in the eye
- discomfort in the eye
- dry eye
- conjunctivitis (inflammation of the outermost layer of the eye)
- eye infection
- condition aggravated (disease worsening)
- product intolerance (hypersensitivity to the medicine)
- application site reactions such as pain
- application site reactions such as discomfort
- application site reactions such as pruritus (itching)
- persistent epithelial defect (persistent loss of outermost corneal layer after injury)
- toxicity to various agents
- corneal transplant required

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AKANTIOR

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month of the unopened product.

This medicine does not require any special storage conditions.

After opening the sachet, the single-dose containers have to be used within 28 days. After this period, the unused single-dose containers must be discarded.

The contents of the single dose container must be used immediately after opening and any remaining content should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away any medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AKANTIOR contains
- The active substance is polihexanide. Each mL of solution contains 0.8 mg of polihexanide.
- The other ingredients are sodium dihydrogen phosphate monohydrate, disodium phosphate dodecahydrate, sodium chloride and purified water.

AKANTIOR contains phosphates (see section 2).

What AKANTIOR looks like and contents of the pack
AKANTIOR eye drops, solution in single-dose container (eye drops) is a clear and colourless solution in a single-dose container.

The single-dose containers are moulded in 5 sealed units strip, 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.

Marketing Authorisation Holder and Manufacturer
SIFI S.p.A.
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95025 Aci Sant'Antonio (CT)
Italy

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Detailed and updated information on this product is available by scanning the QR code included in the package leaflet and outer carton with a smartphone/device. The same information is also available on the following URL: https://qr.sifigroup.com/akantior/

[QR code]