EU Risk Management Plan for AKANTIOR 0.8 mg/mL eye drops, solution in single-dose container (polihexanide)

RMP version to be assessed as part of this application:

RMP Version number: 0.3

Data lock point for this RMP: 18 June 2021

Date of final sign-off: 05 March 2024

Rationale for submitting an updated RMP: Updates made in response to Day 180 List of Outstanding Issues

Summary of significant changes in this RMP: Amendments made following deletion of "Use during pregnancy and lactation" as proposed safety concern and to align with the revised SmPC.

Other RMP versions under evaluation: Not applicable

QPPV name:

QPPV signature:

Table of content

Part I: Product(s) Overview

Table Part I.1: Product(s) Overview

Active substance(s) **(INN or common name)**	Polihexanide
Pharmacotherapeutic group(s) (ATC Code)	Ophthalmologicals, other antiinfectives (S01AX24)
Marketing Authorisation Applicant	SIFI S.p.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	AKANTIOR 0.8 mg/mL eye drops, solution in single-dose container (hereafter referred to as AKANTIOR)
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Biguanides
	Summary of mode of action Polihexanide is highly effective at eradicating *Acanthamoeba* in the active trophozoite and dormant cystal form with a dual targeted mechanism of action which involves: • Disruption of *Acanthamoeba* cell membranes. Polihexanide binds to the phospholipid bilayer of the trophozoites membrane 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. • DNA binding. Once it has passed through the cell membrane, polihexanide condenses and damages *Acanthamoeba* chromosomes. It interacts extensively with the DNA phosphate backbone to block *Acanthamoeba* DNA replication process. Polihexanide is positively charged. It interacts with negatively charged protozoan membrane. The neutral phospholipids in mammalian cell membrane are only marginally affected. Polihexanide is not able to penetrate the nucleus of mammalian cells. If polihexanide does enter the mammalian cell it becomes entrapped within endosomes which restrict its entry into the nucleus.

	Important information about its composition: not applicable
Hyperlink to the Product Information	AKANTIOR Product Information
Indication(s) in the EEA	Current: Treatment of acanthamoeba keratitis.
Dosage in the EEA	Current: The recommended dose is 1 drop 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., absence of corneal inflammation or no evidence of infection).
Pharmaceutical form(s) and strengths	Current Eye drops, solution in single-dose container. Each mL of solution contains 0.8 mg polihexanide.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Treatment of patients with acanthamoeba keratitis

Incidence and prevalence:

Acanthamoeba keratitis is a rare, painful, and sight-threatening infection caused by *Acanthamoeba* species, a family of free-living, ubiquitous protozoa commonly found in water, dust, and soil. This infection results from invasion of ocular tissue through a corneal lesion. Several different species and genotypes of *Acanthamoeba* have been recognized, but *Acanthamoeba castellani* and *Acanthamoeba polyphaga* most commonly cause acanthamoeba keratitis (*Dart et al 2009*). In Europe, the incidence of acanthamoeba keratitis varies between 1 and 4 cases per million persons in the general population (*Randag et al 2019; Nielsen et al 2019*). The Dutch retrospective study estimated for 2015 an incidence rate of 1 in 21,000 soft contact lens users (*Randag et al 2019*). In addition, data from several European Union (EU) countries (Denmark, the Netherlands and Austria) reported a 2- to 3-fold increase in incidence over the last years (*Randag et al 2019, Nielsen et al 2019, List et al 2021*). The incidence of acanthamoeba keratitis is also seasonal with most patients becoming infected during warmer months, starting in March or April (*Walkden et al 2018*) and reaching a peak in summer (*Walkden et al 2018; Randag et al 2019; List et al 2021*).

Demographics of the population in the proposed indication and risk factors for the disease:

Acanthamoeba keratitis was first described in the early 1970s, with a dramatic increase in cases occurring in the early to mid-1980s associated with the increasing use of contact lenses (*US CDC 1986*). Contact lens use remains the most common risk factor for development of acanthamoeba keratitis. Accordingly, in Western countries approximately 93% of all cases of acanthamoeba keratitis are reported to occur in contact lens wearers (*Butler et al 2005*; *Radford et al 2002*; *Ross et al 2014*). Extended wear soft contact lenses carry a higher risk of infection than daily disposable lenses that are not worn or stored overnight (*Butler et al 2005*). The incidence of acanthamoeba keratitis in rigid contact lens wearers is 9.5 times lower than in soft contact lens wearers. In addition, contact lens storage cases may become colonized with *Acanthamoeba* and contaminated contact lens disinfection solution has been directly linked to outbreaks of *Acanthamoeba* infection (*Joslin et al 2007*; *Carnt et al 2018*). Additional risk factors include corneal trauma, particularly for those in a rural environment (*Sharma et al 2000*).

The main existing treatment options:

Currently no drugs are approved for the treatment of acanthamoeba keratitis in any country. Biguanides (polihexanide and chlorhexidine) and diamidines (propamidine and desomedine) are successful compounds used for the treatment of patients with acanthamoeba keratitis (*Dart et al 2009*; *Oldenburg et al 2011*; *Carrijo-Carvalho et al 2017*). Biguanides are effective against the *Acanthamoeba* cystic form, while diamidines have cystostatic but not cysticidal activity and thus should only be used in combination

with biguanides. There is a consensus for considering biguanides (and especially polihexanide), alone or in combination with diamidines, as best supportive care for patients with acanthamoeba keratitis (*Dart et al 2009*; *Oldenburg et al 2011*; *Lorenzo-Morales et al 2015*; *Varacalli et al 2021*). The actual unmet need for an effective treatment was highlighted in a recently published observational case series (n=227) (*Papa et al 2020a*). In this large cohort of patients, a medical cure with currently available unlicensed compounds was achieved within 1 year in approximately 60% patients, whereas the remaining cases failed to resolve within this time frame (23%) or required surgery (16%). In addition, a poor outcome (defined as visual acuity of <6/24 and/or need of surgery) was observed in roughly 50% patients (*Papa et al 2020a*).

The use of topical corticosteroids remains controversial in acanthamoeba keratitis. They are usually required in cases of significant anterior segment inflammation to facilitate rapid resolution of symptoms (*Dart et al 2009*; *Maycock et al 2016*). In cases of poorly responsive acanthamoeba keratitis, surgical intervention (as amniotic membrane transplantation, deep anterior lamellar keratoplasty or penetrating keratoplasty) may be required. Full-thickness penetrating keratoplasty is the most useful and definitive surgical treatment in cases of severe and progressive acanthamoeba keratitis (*Varacalli et al 2021*).

Natural history of the indicated condition in the untreated population, including morbidity:

Generally, patients have a unilateral acanthamoeba keratitis presentation but in approximately 10% of cases the disease may affect both eyes (*Dart et al 2009*).

Most patients with acanthamoeba keratitis complain of severe ocular pain, photophobia, blurred vision, and tearing associated with ocular redness, epithelial or subepithelial infiltrates and punctate keratopathy (*Dart et al 2009*; *Ross et al 2014*; *Maycock et al 2016*). These clinical features are similar to those with fungal or herpes simplex infection.

Diagnosis and treatment of *Acanthamoeba* infection are difficult. Early diagnosis and prompt delivery of appropriate medical therapy is essential to secure a good prognosis. If effective therapy is delayed for three weeks or more, the prognosis deteriorates (*Varacalli et al 2021*). A delayed diagnosis may cause deeper corneal involvement with severe sequelae requiring more intensive treatment, including surgery.

Important co-morbidities:

None known.

Part II: Module SII - Non-clinical part of the safety specification

The safety profile of polihexanide 0.8 mg/mL eye drops, solution in single-dose container has been established based on toxicological investigations reported in the literature and studies carried out by SIFI S.p.A.

In the pivotal 26-week toxicity and local tolerance study in rabbits, polihexanide eye drops at 0.08% (corresponding to 0.8 mg/mL) were well tolerated systemically and locally following topical application several times a day (16 times/day from Day 1 to 5, 8 times/day from Day 6 to Week 3, 4 times/day from Week 4 to Week 26) (*RTC Study No. A2018*). Importantly, in this study the animals initially received 16 topical instillations of one drop of 0.08% polihexanide (approximately 28 µg in 35 µL) per day on Days 1 to 5, yielding a total daily polihexanide dose of 448 µg/animal or 149 µg/kg (for rabbits weighing 3 kg). The results of the 26-week toxicity study in rabbits confirmed that topical administration of polihexanide 0.8 mg/mL is not associated with systemic toxicity. Indeed, *post mortem* macroscopic and histopathological examinations performed at the end of the study did not reveal any treatment-related changes. This is supported by published oral data showing that 3.1 mg/kg/day (after correction for bioavailability of 8.5%) was the no observed adverse effect level (NOAEL) in rats after daily dosing for 104 weeks (*SCCS 2015*).

Polihexanide is not genotoxic as supported by *in vitro* and *in vivo* studies (*ECHA 2011*; *SCCS 2015*; *Johnson et al 2020*).

Literature data provide evidence of a weak carcinogenic potential of polihexanide after systemic administration (*ECHA 2011*), which is not considered relevant for a topical eye product.

No evidence of reproductive and developmental toxicity was observed in studies in the rat and the rabbit (*ECHA 2011*). Whereas neat polihexanide was corrosive to the eye, 20% solutions of polihexanide were found to be moderately irritating to the eye (*ECHA 2011; SCCS 2015; Johnson et al 2020*). However, considering that the eye drop formulation is based on 0.8 mg/mL polihexanide that is approximately 250-fold lower than the limit of 20%, it is possible to state that the topical administration of 0.8 mg/mL polihexanide is not associated with eye irritation. This was confirmed by the 26-week toxicity and local tolerance study in rabbits.

Finally, polihexanide can be considered as a moderate to strong skin sensitiser in animals. The threshold for eliciting sensitisations in guinea pigs is approximately 1% (*ECHA 2011; SCCS 2015; Johnson et al 2020*). Considering that the eye drop formulation is based on 0.8 mg/mL polihexanide, that is approximately 12-fold lower than the limit of 1%, it is possible to state that the topical administration of 0.8 mg/mL polihexanide is not associated with sensitization.

Table SII.1 summarizes key safety findings from non-clinical studies and any relevance to human usage. Overall, these non-clinical data demonstrated that no potential toxicity concerns are related to polihexanide 0.8 mg/mL, solution in single-dose container when used as intended.

Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings from non-clinical studies	Relevance to human usage
Toxicity Key issues identified from repeat-dose toxicity studies: No issues were identified at the clinically-relevant dose in studies conducted by SIFI S.p.A. Local tolerance: No issues were identified at the clinically-relevant dose in studies conducted by SIFI S.p.A.	None
Genotoxicity: No issues were identified in analysis of the literature.	None
Carcinogenicity: The carcinogenic potential of polihexanide is not considered relevant for the topical route at the clinically-relevant dose.	None
Reproductive/developmental toxicity: No issues were identified in analysis of the literature.	None
Safety pharmacology: Due to local administration of polihexanide and the anticipated minimal systemic exposure, safety pharmacology studies are not considered required.	Not applicable
Other toxicity-related information or data: Sensitization: The sensitization potential of polihexanide is not considered relevant for the clinically-relevant dose.	None

Part II: Module SIII - Clinical trial exposure

The clinical development program includes 3 studies:

- a retrospective study, to evaluate the efficacy of current unlicensed supportive care for acanthamoeba keratitis. The study was recognized as an important part of the clinical development program to inform on the design of the pivotal clinical trial (Clinical Study Report [CSR] 038/SI);
- a phase 1 study, to evaluate the highest tolerated dose of polihexanide in healthy volunteers to subsequently be used in the pivotal clinical trial (CSR 042/SI; *Papa et al 2020b*); and
- a phase 3 pivotal trial to evaluate the efficacy and safety of 0.8 mg/mL polihexanide, as monotherapy in patients with acanthamoeba keratitis, compared with best available supportive care (CSR 043/SI).

Overall exposure and exposure by treatment group (dose) in Study 042/SI in healthy volunteers is provided in Table SIII.1 and broken down by gender in Table SIII.2. Note all participants in Study 042/SI were between the ages of 18 and 54 years. Overall exposure and exposure by treatment group

in Study 043/SI in patients with acanthamoeba keratitis is provided in Table SIII.3 and broken down by age/gender in Table SIII.4.

Table SIII.1: Overall exposure to polihexanide in healthy volunteers for up to 14 days (safety analysis set, Study 042/SI)

Treatment group	Number of subjects
0.4 mg/mL polihexanide	26
0.6 mg/mL polihexanide	28
0.8 mg/mL polihexanide	27
Total	81

Source: Table 12, CSR Study 042/SI

Table SIII.2: Exposure to polihexanide in healthy volunteers for up to 14 days by gender (safety analysis set, Study 042/SI)

Treatment group	Number of subjects	
	Male	Female
0.4 mg/mL polihexanide	12	14
0.6 mg/mL polihexanide	13	15
0.8 mg/mL polihexanide	17	10
Total	42	39

Source: Table 12, CSR Study 042/SI

Table SIII.3: Overall exposure to polihexanide in patients with acanthamoeba keratitis (safety analysis set; Study 043/SI)

Treatment group	Number of patients	Person time (days)
0.8 mg/mL polihexanide (+ placebo)	69	9542.7
0.2 mg/mL polihexanide (+ 1.0 mg/mL propamidine)	65	7403.5
Total	134	16937.6

Source: Table 14.3.1.1, CSR Study 043/SI

Person time = mean exposure x number of patients treated. If a patient had a missing end of treatment date, the end of study date was used to calculate duration.

Table SIII.4: Exposure to polihexanide by age group and gender (safety analysis set; Study 043/SI)

Treatment group **Age group**	**Number of patients**	
	Male	**Female**
0.8 mg/mL polihexanide (+ placebo)	**28**	**41**
Adolescents (12 to 17 years)	3	-
Adults (18 to 64 years)	25	39
Elderly persons (65 to 74 years)	-	2
0.2 mg/mL polihexanide (+ 1.0 mg/mL propamidine)	**28**	**37**
Adolescents (12 to 17)	-	1
Adults (18 to 64)	27	34
Elderly persons (65 to 74)	1	2
Total	**56**	**78**

Source: Listing 16.2.4.1, CSR Study 043/SI

Ethnic origin was not reported in either of the clinical studies.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Important exclusion criteria for the pivotal study (043/SI) in patients with acanthamoeba keratitis are discussed below:

1. Subject with documented history and/or clinical signs of concomitant presence of an ocular infection caused by viruses (herpes simplex virus [HSV]) or fungi.

Reason for exclusion: A history and/or current concomitant presence of a concomitant infection may have confounded safety and efficacy assessments.

Is it considered to be included as missing information?: No

Rationale: This exclusion criterion was to avoid confounding factors affecting assessments of efficacy and safety and not because of a particular safety concern.

2. Subject treated with drugs having effects on *Acanthamoeba* cysts prior to study entry, including biguanides (polihexanide (PHMB), chlorhexidine) and diamidines (propamidine, hexamidine).

Reason for exclusion: Diamidines and biguanides are currently the most effective cysticidal anti-amoebic agents.

Is it considered to be included as missing information?: No

Rationale: This exclusion criterion was to avoid that the efficacy assessment of the therapy was affected by previous treatment with diamidines and biguanides.

3. Subjects requiring systemic immunosuppression for *Acanthamoeba* associated scleritis.

Reason for exclusion: Subjects with immunosuppressive treatment were not included in the clinical trial as the immunocompromised condition may have affected the response to treatment.

Is it considered to be included as missing information?: No

Rationale: This exclusion criterion was to avoid compromising the interpretation of study results.

4. Subjects requiring urgent surgical intervention for advanced acanthamoeba keratitis in either eye (e.g., for advanced corneal thinning/melting etc.).

Reason for exclusion: Subjects requiring urgent surgical intervention were not included in the clinical trial as their condition was considered too advanced for an investigational drug.

Is it considered to be included as missing information?: No

Rationale: In the case of subjects requiring urgent surgery, their condition was considered to have been too advanced for an investigational drug. The decision to treat with AKANTIOR is to be taken by

the healthcare professional taking the product information into consideration. This is considered sufficient.

5. Subject with known or suspected allergy to biguanides, diamidines or intolerance to any other ingredient of the investigational treatments.

Reason for exclusion: Hypersensitivity to the active substance or to any of the excipients is a contraindication for use.

Is it considered to be included as missing information?: No

Rationale: Hypersensitivity is addressed in the contraindication section of the summary of product characteristics (Akantior SmPC). This is considered sufficient.

6. Subject affected by immunodeficiency diseases or taking systemic immunosuppressive therapy.

Reason for exclusion: Subjects with immunodeficiency diseases or with immunosuppressive therapy were not included in the trial as the immunocompromised condition may have affected the response to treatment.

Is it considered to be included as missing information?: No

Rationale: This exclusion criterion was to avoid compromising the interpretation of study results.

7. Subject with a major systemic disease or other illness that would, in the opinion of the investigator, compromise subject's safety or interfere with the collection or interpretation of study results.

Reason for exclusion: This broad exclusion criterion was to protect subject safety and to avoid interference with the collection or interpretation of the study results.

Is it considered to be included as missing information?: No

Rationale: This exclusion criterion was to avoid compromising the interpretation of study results.

8. If female, pregnancy, planned pregnancy, or breast-feeding.

Reason for exclusion: Pregnant and breast-feeding women are routinely excluded from clinical trials.

Is it considered to be included as missing information?: No

Rationale: There are no data from the use of polihexanide in pregnant women. Systemic exposure to polihexanide after ophthalmic use is expected to be negligible or not to occur. Animal studies using oral administration do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, however, it is preferable to avoid the use of Akantior during pregnancy (see Akantior SmPC, Section 4.6).

Further, as stated in the SmPC, Section 4.6, it is unknown whether polihexanide is excreted in human milk. Systemic exposure to polihexanide after ophthalmic use is expected to be negligible or not to occur.

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.

9. Subject is participating in another interventional clinical study with an experimental or unapproved/unlicensed therapy or has participated in another interventional clinical study within 4 weeks prior to this study.

Reason for exclusion: Molecules for which the clinical significance of predictable drug interactions had not been confirmed, and were therefore still undergoing clinical evaluation, were not allowed in concomitant therapies for a wash-out period of 4 weeks (period to ensure the removal of the concomitant molecule from the body).

Is it considered to be included as missing information?: No

Rationale: This exclusion criterion avoids the possibility of incurring in efficacy as well as safety bias, due to any possible synergistic, antagonistic, or inert effects by the concomitant investigational drugs. Moreover, the assessment of the relatedness of any possible adverse event either to one or the other investigation drug could be difficult to be established.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	

Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Ethnic origin was not reported in the clinical trials. As AKANTIOR is intended for the topical treatment of acanthamoeba keratitis, no relevant differences due to ethic origin are expected
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Polihexanide does not have intrinsic properties which could exercise effects on the central nervous system or contribute to addiction. Moreover, the topical, ocular route of administration does not lend itself to this type of use.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The identification of the safety concerns for AKANTIOR was based on the clinical trials 042/SI and 043/SI as well as on the available published literature. No serious adverse events were observed in clinical

studies 042/SI and 043/SI and no adverse events assessed as certainly related to the medicinal product were recorded in the pivotal clinical study 043/SI in patients. No safety concerns were detected in the medical literature. Consequently, no important identified or potential risks have been identified for AKANTIOR.

No important missing information was identified. Consequently, no further safety concern should be considered.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Conjunctivitis
- Eye infection
- Eye pain
- Ocular hyperaemia
- Corneal infiltrates
- Tearing
- Conjunctival hyperaemia
- Eye inflammation
- Eye irritation
- Photophobia
- Conjunctival papillae
- Eye pruritus
- Eye discharge
- Eye swelling
- Foreign body sensation
- Ocular discomfort
- Dry eye
- Application site pain
- Application site discomfort
- Product intolerance
- Application site pruritus
- Toxicity to various agents

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Corneal perforation
- Corneal epithelium defects
- Persistent epithelial defect
- Ulcerative keratitis
- Punctate keratitis
- Condition aggravated
- Corneal transplant
- Visual Impairment

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable. No risks are considered important for inclusion in the list of safety concerns in the RMP.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable, since the present RMP version is part of an initial marketing authorisation application.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable. No important identified or important potential risks have been identified for AKANTIOR.

SVII.3.2. Presentation of the missing information

Missing information: Not applicable. No missing information have been identified for AKANTIOR.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities are considered adequate and sufficient to monitor and analyse relevant safety data from post-marketing experience to fully assess the safety of the product as well as change and/or plan further actions other than those detailed below.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for <safety concerns>:

None proposed

Other forms of routine pharmacovigilance activities for <safety concerns>:

None proposed

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are deemed necessary for AKANTIOR.

III.3 Summary Table of additional Pharmacovigilance activities

The are no on-going or planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan for AKANTIOR.

Part IV: Plans for post-authorisation efficacy studies

To date, there are no factors that might affect the efficacy and the safety of the product in its proposed indication and in the target population. There are no studies that are conditions of the marketing authorization or specific obligation of polihexanide.

Based on the current knowledge, the Applicant considers that there are no gaps in knowledge about efficacy of AKANTIOR; thus, there is no need for post-authorization efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Not applicable. No safety concerns have been identified for AKANTIOR.

V.2. Additional Risk Minimisation Measures

There are no additional risk minimization measures proposed for AKANTIOR.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Not applicable. No safety concerns have been identified for AKANTIOR.

Part VI: Summary of the risk management plan

Summary of risk management plan for AKANTIOR 0.8 mg/mL eye drops, solution in single-dose container (polihexanide)

This is a summary of the risk management plan (RMP) for AKANTIOR 0.8 mg/mL eye drops, solution in single-dose container (AKANTIOR). The RMP details important risks of AKANTIOR and how more information will be obtained about AKANTIOR's risks and uncertainties (missing information).

AKANTIOR's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how AKANTIOR should be used.

This summary of the RMP for AKANTIOR should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of AKANTIOR's RMP.

I. The medicine and what it is used for

AKANTIOR is authorised for treatment of acanthamoeba keratitis (see SmPC for the full indication). It contains polihexanide as the active substance and it is given as eye drops.

Further information about the evaluation of AKANTIOR’s benefits can be found in AKANTIOR’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of AKANTIOR, together with measures to minimise such risks and the proposed studies for learning more about AKANTIOR's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

II.A List of important risks and missing information

Important risks of AKANTIOR are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of AKANTIOR. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not applicable. No safety concerns have been identified for AKANTIOR.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of AKANTIOR.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for AKANTIOR.