EU Risk Management Plan for

VEVIZYE

(ciclosporin eye drops, solution)

RMP version to be assessed as part of this application:	
RMP Version number	1.0
Data lock point for this RMP	30-Apr-2023
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Summary of significant changes in this RMP	Not applicable, no significant changes were made in this RMP
Other RMPs versions under evaluation	Not applicable
Details of the currently approved RMP	Not applicable
QPPV name	Dr. Diana Witticke
QPPV oversight declaration	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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List of Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
DED	Dry Eye Disease
eCTD	electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
LLoQ	Lower Limit of Quantification
NEI	National Eye Institute
NOAEL	No Observed Adverse Effect Level
OSDI	Ocular Surface Disease Index
PSUR	Periodic Safety Update Report
QoL	Quality of Life
RMP	Risk Management Plan
RSI	Reference Safety Information
SCE	Sister Chromatid Exchange
SFA	Semifluorinated Alkane
SmPC	Summary of Product Characteristics
TEAEs	Treatment-Emergent Adverse Events
tCFS	total Corneal Fluorescein Staining
US	United States
VAS	Visual Analogue Scale

Part I: Product(s) Overview

Table Part I.1: Product(s) Overview

Active substance(s) (INN or common name)	**Ciclosporin eye drops, solution**
Pharmacotherapeutic group(s) (ATC Code)	Ophthalmologicals, other ophthalmologicals (ATC code: S01XA18)
Marketing Authorisation Holder	Novaliq GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	VEVIZYE The development name of the product is CyclASol
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Ciclosporin is a natural cyclic poly peptide and calcineurin inhibitor. The vehicle perfluorobutylpentane is a lipophilic organic solvent for ciclosporin and a novel excipient.
	Summary of mode of action Ciclosporin is a calcineurin inhibitor with anti-inflammatory and immunosuppressant properties. Calcineurin inhibition leads to various secondary effects (a) blockage of the opening of the mitochondrial permeability transition pore (MPTP) thereby inhibiting activation of caspases in the mitochondria, which in turn blocks apoptosis of inflamed conjunctival cells and restores goblet cell density (b) in activated T cells on the ocular surface, MPTP are opened, resulting in the activation of apoptosis (c) the nuclear factor kappa B (NFκB) translocation and the mitogen-activated protein kinase pathway is blocked, inhibiting the transcription and secretion of inflammatory cytokines and subsequent T cell recruitment.
	Important information about its composition VEVIZYE contains: • Active substance: ciclosporin 0.1 %

Active substance(s) (INN or common name)	**Ciclosporin eye drops, solution**
	• Excipients: perfluorobutylpentane, ethanol ([redacted])
Hyperlink to the Product Information	VEVIZYE SmPC
Indications in the EEA	**Current:** Treatment of moderate to severe dry eye disease (keratoconjuctivitis sicca) in adult patients, which has not improved despite treatment with tear substitutes
	Proposed (if applicable): Not applicable
Dosage in the EEA	**Current:** One drop twice daily to be applied to each eye approximately 12 hours apart.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	**Current:** VEVIZYE 1 mg/mL ciclosporin eye drops, solution. Clear, colourless and preservative-free solution. For ocular use only.
	Proposed (if applicable): Not applicable
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)

Indication:
Treatment of moderate to severe dry eye disease (keratoconjuctivitis sicca) in adult patients, which has not improved despite treatment with tear substitutes.

Incidence and prevalence:

Dry eye disease (DED), also known as keratoconjunctivitis sicca, is one of the most common ocular surface disorders. Over the past decades, the number of patients with DED has increased dramatically (Tsubota et al., 2020). The reported global prevalence of DED is highly variable, ranging from 5% to 50% given that studies used different criteria to define DED (Stapleton et al., 2017). For Europe, the estimated prevalence ranges from 10% to 30% (Malet et al., 2014, Vehof et al., 2014, Viso et al., 2009). It varies from country to country; Spain has the lowest rate of diagnosed DED cases (4.7 %) and France the highest rate (12.6%) among the 5 largest European countries. Approximately 50% of patients have mild DED which should be treated with artificial tears (Global Data DED Report, 2022).

Demographics of the population in the current indication – age and gender:

The prevalence is greater in females and the elderly. In a long-term epidemiological study in the United States (US) over a 12-year period an overall prevalence of about 5.3%, being in female patients 2 to 3 times higher than in male patients (Dana et al., 2019). Prevalence increases with age and up to 11.7% for ages over 50 years. Overall, DED prevalence and incidence were found to increase over time for all demographics.

Risk factors for the disease:

DED is multifactorial disease and several risk factors have been identified. Older age and female sex are known risk factors. Environmental triggers such as exposure to pollutants and allergies, nutritional deficiencies, contact lenses, Meibomian gland dysfunction, and frequent digital screen use can also trigger DED. Some underlying diseases or conditions such as thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus, and Sjögren syndrome may exacerbate or cause DED. In addition, glaucoma can be a risk factor for DED. Studies suggest that from 50 to 60% of people who are being treated for glaucoma also have dry eye disease. There are a two major reasons for this, (1) the conditions share risk factors such as age and having diabetes, (2) chronic use of glaucoma medications can be associated with toxicities to the ocular surface, most often due to the nature of the preservative included in the medication (Zhang et al., 2019). Also, a number of systemic medications such as betablockers or antihistamines have been described to increase the risk for DED (Donaldson et al., 2022).

Important co-morbidities:

The most common comorbidities in DED patients are hypertension, cataracts, thyroid disease, type 2 diabetes, and glaucoma (Dana et al., 2019).

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

DED is initially marked by ocular discomfort signs (e.g., reduction in tear production, mucus discharge, fast tear break-up time) and symptoms (e.g., eye dryness, burning, irritation, redness, fluctuating vision) of increasing frequency. If left untreated or undertreated, DED typically progressively damages the ocular surface and may lead to impairments in visual functions (Rouen and White, 2018). In DED patients, activities that require prolonged gazing

with involuntary suppression of blinking can lead to tear instability, ocular surface irregularities and corneal epithelium damage, both affecting visual function and eventually preventing patients from performing basic activities of daily life such as reading, driving, or working with screens. A compromised ocular surface secondary to DED may also compromise refractive measurements before keratorefractive and phacorefractive surgeries and adversely impact expected visual outcomes after surgeries (Starr et al., 2019, Stapleton et al., 2017, Goto et al., 2002, Donaldson et al., 2022).

The direct or indirect impact of the corneal surface damage secondary to DED on visual function is a largely underestimated aspect of the disease and multiple guidelines recommend treatment of the corneal surface damage prior to ocular procedures (Starr et al., 2019, Craig et al., 2017, Steinert et al.).

The impact of dry eye on quality of life (QoL) of patients is significant (Buchholz et al., 2006, Leonardi et al., 2021, Morthen et al., 2021). A large population-based study investigating the relationship with health-related quality of life and its determinants in 78,165 participants in the Netherlands showed that DED is associated with substantial reductions in both physical and mental QoL, also after correction for associated comorbidities (Morthen et al., 2021).

The main existing treatment options:

There is no gold standard for DED disease management. A staged management according to the severity of physician-measured findings and respective, often multifactorial, etiology is a common recommendation for DED management. Patient education and potential impact of the environment, work and lifestyle modifications form the basis for the disease management and are critical for treatment success. Artificial tears are the second pillar of this first line management of DED (Craig et al., 2017, Akpek et al., 2019).

The pathophysiology of chronic DED can include a cycle of inflammation involving both innate and adaptive immune responses (Baudouin et al., 2018). Based on the concept that inflammation plays an important role in the pathogenesis of dry eye (Calonge, 2001, Stevenson et al., 2012), several anti-inflammatory agents are used in more severe forms of DED. These include ciclosporin, corticosteroids and lifitegrast (lymphocyte function-associated antigen-1 antagonist).

Topical therapies using ciclosporin as active ingredient are commonly used to treat DED and are recommended by leading DED experts and the International Dry Eye Workshop (Messmer et al., 2023, Berufsverband der Augenärzte Deutschland e.V) when a patient does not improve with over-the-counter artificial tears, lid hygiene measures and modification of environmental factors.

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

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

- **Key issues identified from acute or repeat-dose toxicity studies**

Ciclosporin

VEVIZYE contains the well characterized active ingredient ciclosporin, which is also used in various systemic indications at doses ranging from 2.5 mg/kg/day to 15 mg/kg/day.

The daily dose of VEVIZYE of 10 µl twice daily in each eye results in 0.67 µg/kg/day ciclosporin (calculated on a 60 kg human). This provides a safety margin of > 3,700-fold compared to the daily ciclosporin dose of 2.5 mg/kg/day in the indication psoriasis.

Topical administration of CyclASol (VEVIZYE as an investigational medicinal product, containing 0.5 mg/mL and 1 mg/mL ciclosporin in perfluorobutylpentane [F4H5]) to healthy volunteers or dry eye patients did not lead to any quantifiable blood concentration (LLoQ = 0.1 ng/mL) at any of the tested time points in the Phase 1 and Phase 2 studies. Therefore, no systemic ciclosporin toxicity is expected.

To assess local toxicity, studies in rabbits were conducted with topical ocular administration of the novel formulation for 1-month and 6-months. The highest dose was 0.15% ciclosporin in perfluorobutylpentane 40 µL/eye/day 3 times daily. The formulation was safe, and the no observed adverse effect level (NOAEL) was the highest dose tested. Therefore, the ocular safety margin for ciclosporin is 9 times higher than the proposed daily dose for humans.

Ocular tissue concentrations of ciclosporin after CyclASol administration were in the same range as those seen with the approved products (Restasis and Ikervis).

Excipient perfluorobutylpentane

The novel excipient perfluorobutylpentane has been characterised in a range of genotoxicity studies, special toxicity studies and repeat-dose toxicity studies up to 6 months duration using oral and topical ocular dose routes. Examinations in the studies included local (ocular) tolerance as well as full systemic assessments. Perfluorobutylpentane, as an eye drop, was well tolerated with no significant ocular irritation or toxicity at doses of 200 µL to both eyes, three times a day for as long as six months. NOAEL for both the 28-day and 6-months studies was 200 µL three times a day.

Administration of perfluorobutylpentane to rats by oral gavage at dose levels of up to 1,000 mg/kg/day for 6 months resulted in no significant toxicologic findings. Repeat-dose oral toxicity studies in rats demonstrated a low order of toxicity, with NOAELs from the 28-day and 6-months studies determined to be 2,000 mg/kg/day and 1,000 mg/kg/day, respectively.

- **Reproductive/ developmental toxicity**

Ciclosporin

No reproductive and developmental toxicity studies of CyclASol were conducted by the sponsor. Reproductive and developmental toxicity studies are described in literature with ciclosporin using the oral route (Ryffel et al., 1983). No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of ciclosporin up to 15 mg/kg/day for 12 weeks (male) and 2 weeks (female) prior to mating (Ryffel et al., 1983).

The no-effect doses for embryofetal toxicity observed in rats or rabbits receiving ciclosporin during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively. An oral dose of 45 mg/kg/day ciclosporin administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (Ryffel et al., 1983).

Systemic exposure in oral carcinogenicity studies is considerably higher compared with ocular dosing. Therefore, the reproductive and developmental toxicity findings are not considered to be relevant for ocular use of ciclosporin.

Excipient perfluorobutylpentane

Since repeat-dose oral and topical ocular toxicity studies up to 6-months in rats and rabbits, respectively, did not reveal any effect on male or female reproductive organs and the drug product will be used by the topical ocular route in small amounts with low systemic exposure, no fertility and early embryonic development, embryofetal development, or pre- and postnatal development studies on reproductive toxicity of perfluorobutylpentane have been conducted.

- **Genotoxicity**

Ciclosporin

No genotoxicity studies of CyclASol were conducted by the sponsor. Ciclosporin was not found to be mutagenic/genotoxic in the Ames Test (Matter et al., 1982), the V79-HGPRT Test (Zwanenburg et al., 1988), the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice (Matter et al., 1982).

A study analysing sister chromatid exchange (SCE) induction by ciclosporin using human lymphocytes in vitro showed increased SCE frequencies in ciclosporin treated lymphocytes, that was dependent on ciclosporin concentration (Yuzawa et al., 1987, Yuzawa et al., 1986).

Excipient perfluorobutylpentane

Genotoxicity studies did not reveal any mutagenic, aneugenic or clastogenic potential of perfluorobutylpentane.

Safety pharmacology

Ciclosporin

Following bilateral topical ocular dosing of CyclASol twice daily in humans, the blood concentrations of ciclosporin were below the limit of quantification (0.1 ng/mL) at all timepoints. Due to the negligible systemic exposure of animals and humans to ciclosporin following topical ocular instillation of CyclASol at the intended clinical dose, safety pharmacology of ciclosporin was not examined.

Excipient perfluorobutylpentane

Stand-alone safety pharmacology studies have not been conducted with the novel excipient perfluorobutylpentane. Safety pharmacology assessments were incorporated into the 28-day repeated dose oral toxicity study of perfluorobutylpentane in rats (central nervous system and respiration) and the 28-day repeated dose ocular toxicity study of perfluorobutylpentane in rabbits (cardiovascular). No relevant effects on safety pharmacology parameters were observed, at any of the tested dose levels of perfluorobutylpentane and at significantly higher exposures than observed in patients.

There were no findings in safety pharmacology assessments of the novel excipient perfluorobutylpentane that would preclude its use in humans at the intended dose and route of administration.

Part II: Module SIII - Clinical trial exposure

The clinical program with CyclASol (development name for VEVIZYE) conducted by Novaliq comprises five clinical studies, one study in healthy subjects (CYS-001) and four studies in the target population of DED (CYS-002, CYS-003, CYS-004, CYS-005). In CYS-005, all subjects rolled over from CYS-004 (98 patients received CyclASol in CYS-004 and 102 received vehicle in CYS-004). All Novaliq studies were conducted in the US, except for the healthy subject study which was conducted in Germany. All studies are completed. The overview of the subject's exposure per study is presented in the Table SIII. 1.

The size of the study population exposed to CyclASol for the indication of DED (studies CYS-002, CYS-003, CYS-004, and CYS-005) is summarised below with details of duration of exposure (Table SIII. 2), age group (Table SIII. 3), gender (Table SIII. 4), and racial group (Table SIII. 5) of the subjects.

Table SIII. 1: Overview of exposure per study

Treatment	Phase 1 CYS-001	Phase 2 CYS-002	Phase 2b/3 CYS-003	Phase 3 CYS-004	Phase 3 CYS-005	Total
CyclASol	18[d]	102[d]	162	423	200[a]	**807[b]**
Vehicle	18	52	166	411	0	**647**
Restasis	0	53	0	0	0	**53**
Total	**18**	**207**	**328**	**834**	**200[a]**	**1,387[c]**

a: 200 CYS-005 subjects rolled over from CYS-004 (98 patients received CyclASol and 102 received the vehicle in CYS-004).
b: For the total number, only 102 subjects for the study CYS-005 were counted, which received previously vehicle in the study CYS-004.
c: 200 subjects from CYS-005 were not counted since they rolled over from CYS-004.
d: 18 subjects from CYS-001 and 51 subjects from CYS-002 were treated with CyclASol 0.05%

For the following tables the 102 subjects who participated in CYS-005 and who received vehicle in CYS-004 are counted in both the CyclASol 0.1% and Vehicle treatment arms.

Table SIII. 2: Duration of exposure (subjects from CYS-002, CYS-003, CYS-004, and CYS-005)

Cumulative for indication DED	
Duration of exposure to CyclASol 0.1%	**Total subjects**
< 6 months	417
> 6 months	182
≥ 12 months	139
Total	**738**

Source: ISS Tables Combined; Section 14.1.2

Table SIII. 3: Age group (subjects from CYS-002, CYS-003, CYS-004, and CYS-005)

Cumulative for indication DED				
Age group	**CyclASol 0.05%**	**CyclASol 0.1%**	**Restasis**	**Vehicle**
Paediatric (< 18 years)	0	0	0	0
Adult (18 - 65 years)	26	455	35	383
Elderly (> 65 years)	25	283	18	246
Total	**51**	**738**	**53**	**629**

Source: ISS Tables Combined; Section 14.1.2

Table SIII. 4: Gender (subjects from CYS-002, CYS-003, CYS-004, and CYS-005)

Cumulative for indication DED				
Gender	**CyclASol 0.05%**	**CyclASol 0.1%**	**Restasis**	**Vehicle**
Male	13	204	13	168
Female	38	534	40	461
Total	**51**	**738**	**53**	**629**

Source: ISS Tables Combined; Section 14.1.2

Table SIII. 5: Racial group (subjects from CYS-002, CYS-003, CYS-004, and CYS-005)

Cumulative for indication DED	
Racial group	**Total subjects**
Asian	122
Black	160
Caucasian	1,113
Other	23
Total	**1,418***

*subjects from CYS-002 treated with Restasis were not counted.

Source: ISS Tables Combined; Section 14.1.2

A sixth study in the target population of DED (SHR8028-301) was recently conducted and completed by Novaliq's partner Jiangsu Hengrui Pharmaceutical Co. in China. The study design was comparable to CYS-004. A total of 206 subjects were randomized, 103 in the CyclASol group and 103 in the vehicle group. The majority of the patients was female (>89%), the mean age of subjects was 47.8 years (range: 19-79) and slightly younger than the population in the US studies. Han Chinese accounted for 98.1% of the subjects.

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

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

Patients with ocular or periocular malignancy

Reason for exclusion:

This is a standard exclusion criterion in DED studies. The assessment of treatment success and incidence/severity of adverse events (AEs) and therefore determination of both efficacy and safety endpoints might be influenced by underlying disease. Therefore, such patients were excluded.

Is it considered to be included as missing information? No

Rationale (if not included as missing information):

Ophthalmic formulation of ciclosporin has already been used for decades in the US and in the EU without any evidence of ciclosporin causing or aggravating malignant conditions. No effect on the treatment of patients with ocular or periocular malignancy is expected. Nevertheless, a contraindication “ocular or peri-ocular malignancies or premalignant conditions” has been included in Section 4.3 of the current SmPC.

Patients with a history of herpetic keratitis

Reason for exclusion:

Ciclosporin as immunosuppressive agent might reactivate herpetic keratitis. The assessment of treatment success and incidence/severity of AEs and therefore determination of both efficacy and safety endpoints might be influenced by underlying herpetic keratitis. Therefore, such patients were excluded.

Is it considered to be included as missing information? No

Rationale (if not included as missing information):

There is no evidence published in the literature that marketed ophthalmic formulations of ciclosporin reactivated herpetic keratitis. It was shown that prophylactic adjunctive treatments with topical administration of ciclosporin in patients with simultaneous stromal herpes simplex keratitis and dry eye disease provide significant benefit by minimising herpes simplex keratitis frequency and duration of recurrences for at least 1 year compared with the 1-year period prior to treatment (Sheppard et al., 2009).

Patients with an ongoing ocular infection

Reason for exclusion:

The assessment of treatment success and incidence/severity of AEs and therefore determination of both efficacy and safety endpoints might be influenced by underlying ocular diseases such as infections. Also, ciclosporin as immunosuppressive agent might aggravate the ongoing ocular infection or contribute to the development of new infections.

Is it considered to be included as missing information? No

Rationale (if not included as missing information):

Clinical studies involving various topical ocular ciclosporin formulation did not suggest a higher risk for ocular infections compared to control groups. No effect on the treatment of patients is expected. Nevertheless, a contraindication “active or suspected ocular or periocular infections” has been included in Section 4.3 of the current SmPC.

Patients who have worn contact lenses within 90 days before Visit 0 or anticipate using contact lenses during the trial

Reason for exclusion:

Contact lens wearing can cause symptoms similar to DED symptoms and has been associated with signs. This phenomenon is called contact lens discomfort. The assessment of treatment success and incidence/severity of AEs and therefore determination of both efficacy and safety endpoints might be influenced by concomitant contact lens wear (Markoulli and Kolanu, 2017).

Is it considered to be included as missing information? No

Rationale (if not included as missing information):

The standard warning regarding wearing contact lenses similar to other eye drops has been included to the Section 4.4 of the current SmPC. It is stated that patients wearing contact lenses have not been studied. VEVIZYE should not be administered while wearing contact lenses. Patients with dry eye disease typically should not wear contact lenses. If contact lenses

are worn, they should be removed prior to the administration of the solution. Lenses may be reinserted 15 minutes following administration of VEVIZYE.

Patients with known allergy or sensitivity to the IMP or its components: Ciclosporin or semifluorinated alkanes (SFA)

Reason for exclusion:

General safety criterion. Hypersensitivity may lead to local and systemic adverse reactions. Avoiding exposure effectively prevents adverse reactions. Use of an alternative treatment is recommended.

Is it considered to be included as missing information? No

Rationale (if not included as missing information):

Hypersensitivity to the active substance or to any of the excipients is considered as contraindication (Section 4.3 of current SmPC).

Woman who is pregnant, nursing, or planning a pregnancy

Reason for exclusion:

General safety criterion. Studies in animals have shown reproductive toxicity following systemic administration of ciclosporin at exposure considered sufficiently exceeding the maximum human exposure. Also, following oral administration, ciclosporin is excreted in breast milk.

Is it considered to be included as missing information? No

Rationale (if not included as missing information):

Reproductive toxicity was detectable only after systemic administration of high doses of ciclosporin in animals, indicating little relevance to the clinical use of VEVIZYE. The novel vehicle, perfluorobutylpentane (F4H5), is an inert coumpound, with minimal systemic exposure after topical administration as eye drop and, therefore, is not expected to have a risk for reproductive toxicity. A structural related compound (perfluorohexyloctane) also did not show any reproductive effects in rats and rabbits. However, the current SmPC, Section 4.6, does not recommend VEVIZYE during pregnancy, unless the potential benefit to the mother outweighs the potential risk to the foetus. Regarding breast-feeding during treatment, the current SmPC, Section 4.6, states: No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to ciclosporin in VEVIZYE is negligible and as a precautionary measure, it is preferable to avoid the use of VEVIZYE during breast-feeding.

Paediatric population under 18 years of age

Reason for exclusion:

General safety criterion.

Is it considered to be included as missing information? No

Rationale (if not included as missing information):

There is no relevant use of ciclosporin in the paediatric population for the indication of dry eye disease. The European Medicines Agency has waived the obligation to submit the results of studies with VEVIZYE in all subsets of the paediatric population in dry eye disease.

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

The population in the clinical development program represents the target population.

Table SIV.3: 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	Not included in the clinical development program.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients	These populations were not specifically excluded from the trials. Since the product is given topically and does not reach systemic circulation no specific risks for patients with these comorbidities are expected.
Patients with a disease severity different from inclusion criteria in clinical trials	Patients with mild DED defined as Dryness Score < 40 (VAS), with a total corneal fluorescein staining (tCFS) score of < 6 (i.e., sum of inferior, superior, central, nasal, and temporal regions) according to the NEI scale or with Ocular Surface Disease Index (OSDI) score < 20 were not included in the clinical development program.
Population with relevant different ethnic origin	Patients with different ethnic origin were included in the clinical development program. No difference in safety and efficacy between these groups were detected.
Subpopulations carrying relevant genetic polymorphisms	Not applicable, since no genetic testing of the patients included in the clinical development program was performed. Due to topical application of the product no difference in safety and efficacy in between subpopulations carrying different genetic polymorphisms is expected.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

VEVIZYE is not launched for sale in any country worldwide until data lock point of this report.

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

VEVIZYE will be a prescription medicine. The active substance ciclosporin has no risk of addiction. Thus, VEVIZYE has no potential for misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

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

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

The pooled analysis of the Novaliq studies in the target population (1,418 subjects) showed low frequency of treatment-related treatment-emergent AEs (TEAEs). A total of 9.4% of subjects reported 172 ocular treatment-related TEAEs. The most commonly reported ocular treatment-related TEAEs were general disorders and administration site conditions followed by eye disorders at System Organ Class level and instillation site pain at Preferred Term level. (Details, see ISS Tables Combined Section 14.3.1.6.1)

The following **known** adverse reactions reported in the clinical development program were non-serious and transient with mild severity. These adverse reactions are associated with most eye drops and are considered acceptable in the indication. They are included in the Section 4.8 “Undesirable effects” in the current SmPC:

System Organ Class	Frequency	Adverse reactions
General disorders and administration site conditions	Common (≥1/100 to <1/10)	Instillation site pain (reported as burning)
Eye disorders	Uncommon (≥1/1,000 to <1/100)	Vision blurred

Source: ISS Tables Combined, Section 14.3.1.6.1

The following **potential** adverse reactions reported by > 1 patient receiving active treatment in the clinical development program were non-serious and transient with mild severity and occurred at a low frequency. According to sponsors assessment a causal relationship is not confirmed, since reactions are signs/symptoms of the underlying disease. Their clinical impact is minimal and considering the low frequency and being mild and transient these events are acceptable in the indication. They are included in the Section 4.8 “Undesirable effects” in the current SmPC:

System Organ Class	Frequency	Adverse reactions
Eye disorders	Uncommon (≥1/1,000 to <1/100)	Eye irritation Eye pain Visual acuity reduced (temporarily) Eye pruritus Eye erythema

Source: ISS Tables Combined, Section 14.3.1.6.1

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

Instillation site reactions (eye pain, pruritus, and erythema) and blurred vision are associated with any eye drop and are generally acceptable in the indication.

The other eye disorders reported in the program occurred at a low frequency and are signs/symptoms of the underlying disease, therefore it is difficult to distinguish if they are caused by the product or the disease itself. Due to the low frequency and being mild and transient these adverse reactions are acceptable in the indication.

In particular, visual acuity changes are known to occur in patients with DED (Szczotka-Flynn et al., 2019). In DED studies visual acuity is evaluated as a safety measurement and the methodology used for this purpose is not optimized for correction and thus may present variability in visual acuity.

No effect on the treatment of patients with ocular or periocular malignancy is expected, given that ophthalmic formulations of ciclosporin have been used for decades in the US and in the EU without any evidence of ciclosporin causing or aggravating malignant conditions. Based on the immunosuppressive mode of action these conditions are a potential risk thus ocular or peri-ocular malignancies or premalignant conditions are contraindicated for the use of VEVIZYE and will be further characterised in the periodic safety update reports.

Clinical studies involving various topical ocular ciclosporin formulation did not suggest a higher risk for ocular infections compared to control groups. No effect on the treatment of patients is expected, but there is a potential risk that ciclosporin as immunosuppressive agent might aggravate the ongoing ocular infection or contribute to the development of new infections active or suspected ocular or periocular infections. These are contraindicated for the use of VEVIZYE.

To minimize the known risk that ciclosporin affects the immune system and may affect host defence against local infections and malignancies a recommendation for regular examinations of the eye(s) for e.g. at least every 6 months is added to the SmPC. Any potential risk will be further characterised in the periodic safety update reports.

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

The safety profile for VEVIZYE is favourable based on the low incidence of ocular AEs and the low severity of AEs, and on the assessment of ocular parameters in subjects participating in the clinical development program.

Adverse effects resulting from systemic absorption of ciclosporin are unlikely, as systemic exposure is low after ocular administration. No systemic exposure of ciclosporin could be detected after application of 1 or 2 drops of VEVIZYE twice daily in neither of the two clinical trials CYS-001 and CYS-002, since all plasma concentrations were below the detection limit (i.e., < 0.100 ng/mL).

The safety of VEVIZYE was demonstrated in the Phase 1 study CYS-001 in healthy subjects and in studies in the target population DED (CYS-002, CYS-003, CYS-004, CYS-005, and SHR8028-301), and the analysis of pooled study data in the target population of Novaliq studies. The results demonstrate the safety and tolerability of VEVIZYE in the target population DED.

Thus, the Marketing Authorisation Holder did not identify any risks considered important for inclusion in the list of safety concerns in the RMP and considers the safety profile described in the current product information adequate.

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

Not applicable, this is the first RMP for VEVIZYE.

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

No important identified or important potential risks are included in the list of safety concerns in the RMP.

SVII.3.2 Presentation of the missing information

No missing information is included in the list of safety concerns in the RMP.

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

No other forms of routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are planned.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are planned.

III.3 Summary table of additional pharmacovigilance activities

No additional pharmacovigilance activities are planned.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned.

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

Risk Minimisation Plan

The safety information in the current product information is considered sufficient. No Risk Minimisation Plan is in place.

V.1 Routine risk minimisation measures

Not applicable, no risks or missing information were considered important for inclusion in the list of safety concerns in the RMP.

V.2 Additional risk minimisation measures

Not applicable

V.3 Summary of risk minimisation measures

Not applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for VEVIZYE (ciclosporin)

This is a summary of the risk management plan (RMP) for VEVIZYE. The RMP details important risks of VEVIZYE, how these risks can be minimised, and how more information will be obtained about VEVIZYE's risks and uncertainties (missing information).

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

This summary of the RMP for VEVIZYE 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 VEVIZYE's RMP.

I. The medicine and what it is used for

VEVIZYE is authorised for treatment of moderate to severe dry eye disease (keratoconjuctivitis sicca) in adult patients, which has not improved despite treatment with tear substitutes (see SmPC for the full indication). It contains ciclosporin as the active substance and it is given by ocular route of administration.

Further information about the evaluation of VEVIZYE's benefits can be found in VEVIZYE's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines.

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

Important risks of VEVIZYE, together with measures to minimise such risks and the proposed studies for learning more about VEVIZYE'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 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*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of VEVIZYE 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 VEVIZYE. 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

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 VEVIZYE.

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

There are no studies required for VEVIZYE.

Part VII: Annexes

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Annex 4 Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable

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