SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vevizye 1 mg/mL eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 1 mg of ciclosporin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe dry eye disease (keratoconjunctivitis sicca) in adult patients, which has not improved despite treatment with tear substitutes (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated and supervised by an ophthalmologist.

Posology

The recommended dose is one drop (corresponding to 0.01 mg ciclosporin) twice daily to be applied to each eye approximately 12 hours apart.

If a dose is missed, treatment should be continued with the next dose as normal. Patients should be advised not to instil more than one drop in each eye.

Elderly patients
No dose adjustment is required for elderly patients.

Paediatric population

There is no relevant use of ciclosporin in the paediatric population for the indication of dry eye disease.

Method of administration

For ocular use only.

Patients should be instructed to first wash their hands. Patients should be advised not to allow the dropper tip to touch the eye or any other surface, as this may contaminate the solution.

If more than one topical ophthalmic medicinal product is being used, the medicinal products should be administered at least 15 minutes apart (see section 4.4). For patients who wear contact lenses, please refer to section 4.4.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Ocular or peri-ocular malignancies or premalignant conditions.

Active or suspected ocular or periocular infections.

4.4 Special warnings and precautions for use

Monitoring

Regular examinations of the eye are recommended for topical ocular ciclosporin therapy, e.g. within 3 months after treatment initiation and thereafter approximately every 6 months.

Glaucoma

There is limited experience with ciclosporin in the treatment of patients with ocular hypertension or glaucoma. Regular clinical monitoring should be exercised when treating patients receiving glaucoma medication and ciclosporin eye drops.

Contact lenses

Vevizye should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of Vevizye.

Effects on the immune system

Ophthalmic medicinal products, which affect the immune system, including ciclosporin, may affect host defence against local infections and malignancies. In case of signs of an eye infection the patient should seek medical advice.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Vevizye.

No systemic interactions are expected, since ciclosporin does not become systemically available after use of Vevizye. Co-administration of eye drops containing corticosteroids could potentiate the effects of ciclosporin on the immune system (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Vevizye in pregnant women.

Animal studies have shown reproductive toxicity following systemic administration of ciclosporin at exposure considered sufficiently in excess of the maximum human exposure indicating little relevance to the clinical use of Vevizye.

Vevizye is not recommended during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to ciclosporin in Vevizye is negligible. As a precautionary measure, it is preferable to avoid the use of Vevizye during breast-feeding.

Fertility

There is no data on the effects of Vevizye on human fertility.
No effects on fertility are anticipated since the systemic exposure to ciclosporin is negligible.

4.7 Effects on ability to drive and use machines

Vevizye has mild influence on the ability to drive and use machines. If transient blurred vision occurs at instillation, the patient should wait until vision has cleared before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are instillation site reactions (8.1%) followed by blurred vision (0.8%). Instillation site reactions were more common in patients ≥ 65 years of age as compared to younger patients.

Tabulated list of adverse reactions

The following adverse reactions listed below were observed in clinical studies.

Adverse reactions are presented below according to MedDRA system organ classification (SOC and preferred term level). They are ranked according to frequency: 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), or not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System organ class	Frequency	Adverse reactions
General disorders and administration site conditions	Common	Instillation site pain (burning)
Eye disorders	Uncommon	Vision blurred, Eye irritation, Eye pain, Eye erythema, Visual acuity reduced, Eye pruritus

Description of selected adverse reactions:

Instillation site pain (reported as burning) (7.9%) was the most frequently reported adverse reaction associated with the use of Vevizye during clinical trials. Other instillation site reactions such as erythema or pruritus occurred at lower frequency (0.1%). All instillation site reactions are typically mild and transient.

Reporting of suspected adverse reactions

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

4.9 Overdose

A topical overdose is unlikely to occur after ocular administration. If overdose with Vevizye occurs, treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, other ophthalmologicals, ATC code: S01XA18.

Mechanism 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.

The spreading properties of the water-free vehicle reduce friction and thereby contribute to the efficacy.

Clinical efficacy and safety

The efficacy of Vevizye for the treatment of dry eye disease was assessed by two randomised, multi-centre, double-masked, vehicle-controlled studies (ESSENCE-1 and ESSENCE-2). Both studies included moderate to severe dry eye disease (DED) patients as defined by a total corneal staining (tCFS) score of ≥ 10 on the National Eye Institute (NEI) scale, unanaesthetised Schirmer's test score between 1 and 10 mm, total lissamine green conjunctival score of ≥ 2 and the presence of symptoms.

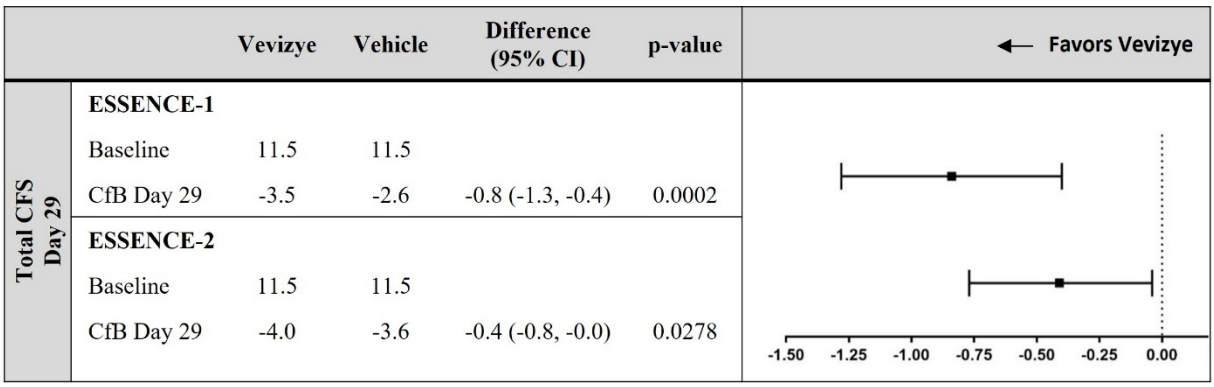
In the ESSENCE-1 study, 328 patients were randomised in a 1:1 ratio to Vevizye (N=162) or vehicle (N=166) twice daily for 3 months. In the ESSENCE-2 study, 834 patients were randomised in a 1:1 ratio to receive Vevizye (N=423) or vehicle (N=411) twice daily for 1 month.

The change from baseline in tCFS score at Day 29 was the primary endpoint in both trials. tCFS score was the sum score (range 0-15) of the 5 cornea subregions (inferior, superior, central, nasal, and temporal), each region was rated by the investigator using the National Eye Institute (NEI) scale from grade 0 (no staining) to grade 3 (heavy staining). Primary symptom endpoints were ocular surface disease index (OSDI, range 0-100) in ESSENCE-1 and dryness score (visual analogue scale, range 0-100) in ESSENCE-2. Key secondary endpoints included tCFS score at Day 15, tCFS responders defined as ≥ 3 grades improvement, conjunctival lissamine green staining score (Oxford sum of temporal and nasal; range 0-10) at Day 29, central corneal fluorescein staining score (cCFS [National Eye Institute scale; range 0-3]), and blurred vision score (visual analogue scale, range 0-100) and Schirmer responder at Day 85 in ESSENCE-1 and Day 29 in ESSENCE-2.

The majority of patients in this clinical program were female (73%), the mean (standard deviation [SD]) age was 58 (15.2) years and 38% were 65 years and older. The mean (SD) baseline tCFS score was 11.5 (1.35), the mean (SD) baseline cCFS score was 2.1 (0.60), the mean (SD) baseline conjunctival lissamine green staining score was 3.9 (1.71), the mean (SD) baseline unanaesthetised Schirmer's tear test score was 5.0 mm (2.83), the mean (SD) baseline OSDI was 47.1 (19.23), and the mean (SD) baseline dryness score was 69.9 (15.43).

At Day 29, a statistically significant reduction in tCFS favouring Vevizye was observed in both studies (see Figure 1).

Figure 1: Mean change (SD) from baseline in tCFS at Day 29



CFS = corneal fluorescein staining; CfB= change from baseline

Responder analyses showed that the proportion of patients with a clinically meaningful tCFS improvement of ≥ 3 grades at Day 29 was statistically significantly different and favouring Vevizye in both studies at Day 29 (see Table 2).

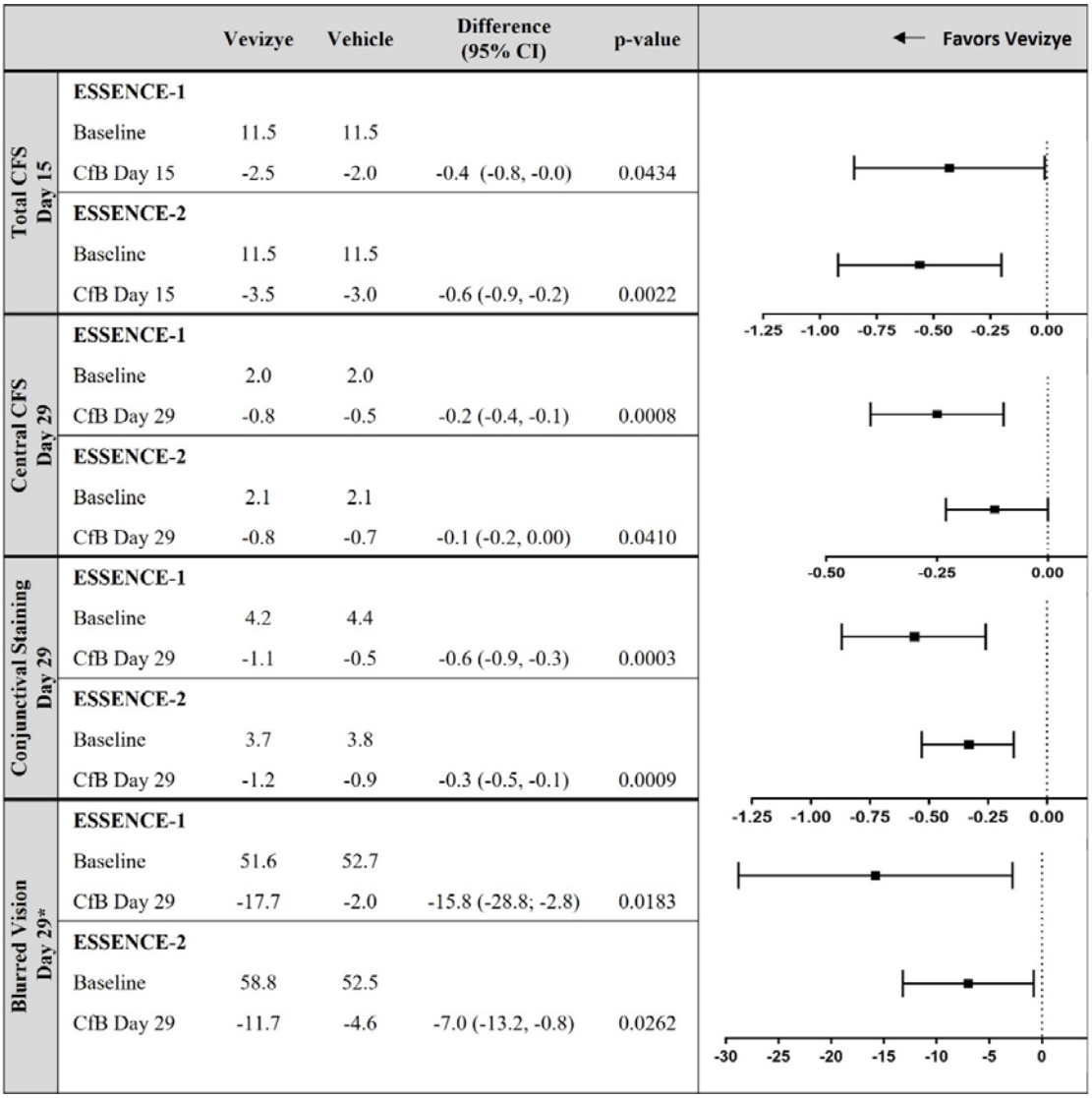
Table 2: Percent of patients achieving ≥ 3 Grades improvement in total corneal fluorescein staining score (tCFS) at Day 29 in studies in patients with dry eye disease

	ESSENCE-1		ESSENCE-2	
	Vevizye	**Vehicle**	**Vevizye**	**Vehicle**
Number of subjects at Day 29	157	165	409	395
≥ 3 grades improvement in tCFS at Day 29 (% of subjects)	52.9%	40.6%	71.6%	59.7%
Difference (95% CI)	12.3% (1.3%, 23.0%)		12.6% (6.0%, 19.3%)	
p-value	0.0337		0.0002	

In ESSENCE-1, the second hierarchically tested primary symptom endpoint change from baseline in OSDI at Day 29 showed numerical improvement in the Vevizye group (least squares [LS] mean -8.8) but did not reach statistical significance when compared to vehicle (LS mean -6.8) (p=0.2634).
In ESSENCE-2, the second hierarchically tested primary symptom endpoint, dryness score, improved statistically significantly compared to baseline in both groups: Vevizye LS mean -12.2 and vehicle LS mean -13.6 the between group difference was not significant (p=0.3842).

All other key secondary ocular surface sign endpoints (tCFS at Day 15, conjunctival staining at Day 29 and central corneal staining at Day 29) showed statistically significant effects favouring Vevizye in both studies (see Figure 2).
In addition, patients with significant central staining scores at baseline treated with Vevizye showed statistically significantly larger reductions in the blurred vision score at Day 29 compared to this group of patients treated with vehicle in both studies (see Figure 2).

Figure 2: Mean change (SD) from baseline in key secondary endpoints in both pivotal studies



* Subgroup with high central staining; CFS = corneal fluorescein staining; CfB= change from baseline

Statistically significantly higher proportions of responders to Schirmer`s tear test in the active arm compared to vehicle were demonstrated in ESSENCE-1 at Day 85 (Δ 6.74% [95% CI 0.50-12.98%] p=0.0344) and in ESSENCE-2 at Day 29 (Δ 3.92% [95% CI 0.02%-7.82%] p=0.0487).

A total of 202 patients who completed ESSENCE 2 entered an open label extension study for 12 months (ESSENCE-2-OLE). Eligible patients receive Vevizye bilaterally twice-daily for 1 additional year. More than 80% of the patients were responder (≥ 3 grades in tCFS) after 4 weeks and this response was maintained throughout the observation period.

<u>Paediatric population</u>

The MHRA has waived the obligation to submit the results of studies with Vevizye in all subsets of the paediatric population in dry eye disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetics of ciclosporin was investigated in 47 volunteers from two clinical studies. Blood concentrations of ciclosporin after single or multiple dose administration of Vevizye could not be measured as all analysed samples had values below the lower limit of quantification (0.100 ng/mL).

The physiochemical properties of the vehicle enhance local distribution and bioavailability of ciclosporin.

5.3 Preclinical safety data

Non-clinical data carried out with Vevizye formulation and ciclosporin scientific literature reveal no special hazard for humans based on conventional safety pharmacology, repeated dose toxicity studies, genotoxicity, carcinogenic potential, toxicity to reproduction and development as no systemic exposure for ciclosporin has been shown.

Non-clinical data for the excipient perfluorobutylpentane reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Environmental risk assessment studies have shown that the excipient perfluorobutylpentane has the potential to be persistent.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Perfluorobutylpentane
Ethanol, anhydrous

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

Vevizye can be used 4 weeks after first opening of the bottle. The bottle should be kept tightly closed when not in use.

6.4 Special precautions for storage

Do not store above 25 °C.
Do not freeze or refrigerate.

6.5 Nature and contents of container

Vevizye 1 mg/mL eye drops, solution are supplied in a multidose translucent polypropylene bottle with a translucent polyethylene tip and a white polyethylene cap with tamper-evident ring.

Carton containing a 5 mL bottle with 2 mL fill.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Pharmaceutical waste should not be disposed of via the toilet or sink. Unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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