NEW ZEALAND DATASHEET

1 PRODUCT NAME

Vevye® (Cyclosporin) eye drops solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of Vevye® contains 1 mg (0.1%) of cyclosporin.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMCEUTICAL FORM

Vevye® is a clear colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Vevye® is indicated for the treatment of the signs and symptoms of moderate to severe dry eye disease in adult patients, which has not improved despite treatment with tear substitutes.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Instill one drop (0.01 mL) of Vevye® twice a day in each eye approximately 12 hours apart. Can be used concomitantly with other eye drops, allowing a 15-minute interval between products.

4.3 CONTRAINDICATIONS

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

Ocular or peri-ocular malignancies or premalignant conditions

Active or suspected ocular or peri-ocular infection. Treatment with Vevye® should not be initiated or continued until all signs of infection have cleared.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

A comprehensive eye examination should be performed to determine the aetiology of symptoms. Any reversible underlying conditions, not associated with dry eye disease, should be treated prior to initiating treatment with Vevye®.

Vevye® has not been studied in patients with a history of ocular herpes and should therefore be used with caution in such patients.

Potential for Eye Injury and Contamination

Be careful not to touch your eye or other surfaces with the bottle tip to avoid potential for eye injury and contamination.

Use with Contact Lenses

Vevye® 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 Vevye®.

Use in paediatrics

The safety and effectiveness of Vevye® have not been established in pediatric patients (below the age of 18 years).

Use in elderly

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed with Vevye®.

Combination with other medicinal products that affect the immune system

Co-administration of Vevye® with eye drops containing corticosteroids could potentiate the effects of ciclosporin on the immune system.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Oral administration of cyclosporin to rats for 12 weeks (male) and 2 weeks (female) prior to mating produced no adverse effects on fertility at doses up to 15 mg/kg/day (22,000 times higher than the maximum recommended human ophthalmic dose).

Use in pregnancy

Category C

There are no adequate and well-controlled studies of Vevye® administration in pregnant women to inform a drug-associated risk. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses. Vevye® doses are approx. 4,700 times lower than recommended oral doses, with blood concentrations being undetectable after topical administration.

Use in lactation

Cyclosporin is known to be excreted in human milk following systemic administration but excretion in human milk after topical treatment has not been investigated. Vevye® doses are approx. 4,700 times lower than recommended oral doses of cyclosporin, with blood concentrations being undetectable after topical administration. However, caution should be exercised when Vevye® is administered to a nursing woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since reduction of visual acuity has been reported in a small proportion (2.7%) of patients during clinical trials, patients should be cautious while driving or using machines till they know how Vevye® affects them.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The most common adverse reactions are instillation site reactions (8.1%) followed by blurred vision (0.8%).

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).

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 Vevye® 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.

Post-marketing experience

Vevye® has been launched in USA in January 2024. During the reviewed time, no serious event has been reported. None of the events was reported in >1% of the patients.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

A topical overdose is not likely to occur after ocular administration. If overdose with Vevye® occurs, treatment should be symptomatic and supportive.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Cyclosporin, a calcineurin inhibitor, is a potent anti-inflammatory and selective immunomodulatory drug. It blocks opening of the mitochondrial permeability transition pore (MPTP) thereby inhibiting activation of caspases in the mitochondria, which blocks apoptosis of inflamed conjunctival cells and restores goblet cell density. In activated T cells on the ocular surface, cyclosporin opens MPTP, resulting in the activation of apoptosis. Additionally, cyclosporin blocks nuclear factor kappa B (NFκB) translocation and the mitogen-activated protein kinase pathway, inhibiting the transcription and secretion of inflammatory cytokines and subsequent T cell recruitment. The novel vehicle perfluorobutylpentane enhances local distribution and bioavailability of cyclosporin.

Clinical trials

The efficacy of Vevye® for the treatment of dry eye disease was assessed by two randomised, multi-centre, double-masked, vehicle-controlled studies: CYS-003 (ESSENCE-1) and CYS-004 (ESSENCE-2). Both studies included moderate to severe DED patients as defined by 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 presence of symptoms.

In the ESSENCE-1 study, 328 patients were randomised in a 1:1 ratio to Vevye® (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 Vevye® (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 Vevye® was observed in both studies (see Figure 1).

		Vevye	Vehicle	Difference (95% CI)	p-value	← Favors Vevye
Total CFS Day 29	**ESSENCE-1**					
	Baseline	11.5	11.5			
	CfB Day 29	-3.5	-2.6	-0.8 (-1.3, -0.4)	0.0002	
	ESSENCE-2					
	Baseline	11.5	11.5			
	CfB Day 29	-4.0	-3.6	-0.4 (-0.8, -0.0)	0.0278	

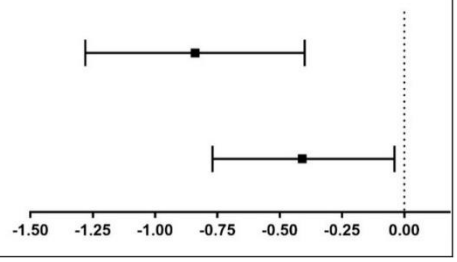


Figure 1: Mean change (SD) from baseline in tCFS at Day 29

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 Vevye in both studies at Day 29 (see Table 1).

Table 1: 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	

*post hoc analysis

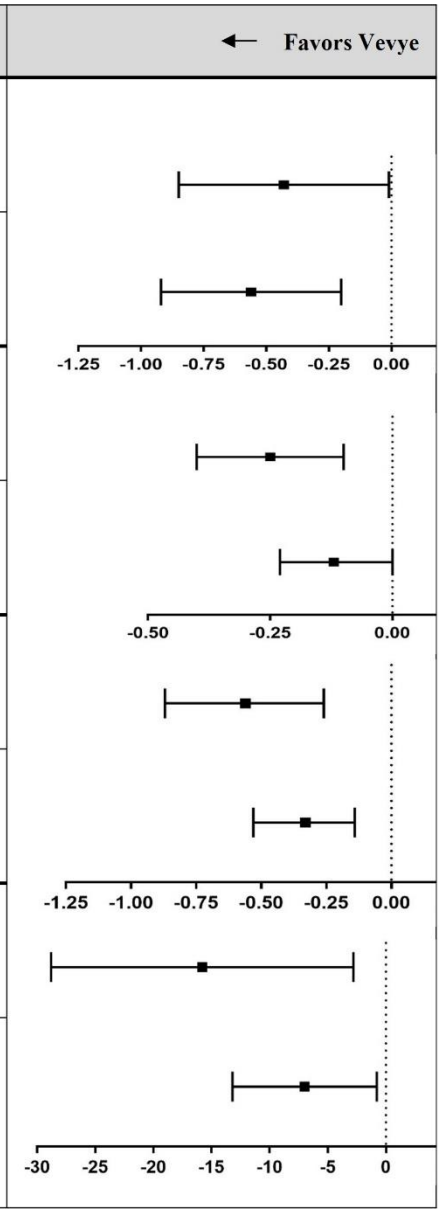
In ESSENCE-1, the second hierarchically tested primary symptom endpoint change from baseline in OSDI at Day 29 showed numerical improvement in the Vevye® group (least squares [LS] mean -8.8) but did not reach statistical significance when compared to vehicle (LS mean -6.8) (p=0.2634).

In ESSENCE-2, the second hierarchically tested primary symptom endpoint, dryness score, improved statistically significantly compared to baseline in both groups: Vevye® 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 Vevye® in ESSENCE-1 and ESSENCE-2 (see Figure 2).

In addition, patients with significant central staining scores at baseline treated with Vevye® 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).

		Vevye	Vehicle	Difference (95% CI)	p-value
Total CFS Day 15	**ESSENCE-1**				
	Baseline	11.5	11.5		
	CfB Day 15	-2.5	-2.0	-0.4 (-0.8, -0.0)	0.0434
	ESSENCE-2				
	Baseline	11.5	11.5		
	CfB Day 15	-3.5	-3.0	-0.6 (-0.9, -0.2)	0.0022
Central CFS Day 29	**ESSENCE-1**				
	Baseline	2.0	2.0		
	CfB Day 29	-0.8	-0.5	-0.2 (-0.4, -0.1)	0.0008
	ESSENCE-2				
	Baseline	2.1	2.1		
	CfB Day 29	-0.8	-0.7	-0.1 (-0.2, 0.00)	0.0410
Conjunctival Staining Day 29	**ESSENCE-1**				
	Baseline	4.2	4.4		
	CfB Day 29	-1.1	-0.5	-0.6 (-0.9, -0.3)	0.0003
	ESSENCE-2				
	Baseline	3.7	3.8		
	CfB Day 29	-1.2	-0.9	-0.3 (-0.5, -0.1)	0.0009
Blurred Vision Day 29*	**ESSENCE-1**				
	Baseline	51.6	52.7		
	CfB Day 29	-17.7	-2.0	-15.8 (-28.8; -2.8)	0.0183
	ESSENCE-2				
	Baseline	58.8	52.5		
	CfB Day 29	-11.7	-4.6	-7.0 (-13.2, -0.8)	0.0262



* Subgroup with high central staining

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

Statistically significantly higher proportions of responders to Schirmer's tear test (≥ 10 mm improvement) 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) in post-hoc analysis.

A total of 202 patients who completed ESSENCE-2 entered an open label extension study for 12 months (ESSENCE-2-OLE). ESSENCE-2-OLE was a prospective, open-label, clinical study including patients, who completed the ESSENCE-2 study. Eligible patients from both treatments were enrolled to receive Vevye® bilaterally twice-daily for 1 additional year.

The study population showed statistically significant improvements in most pre-specified efficacy endpoints compared to baseline (defined as the baseline of ESSENCE-2) and to Visit 1 (the first Visit in ESSENCE-2-OLE corresponding to Day 29 of ESSENCE-2) at each follow up visits, including corneal fluorescein staining and conjunctival staining scores, Schirmer's tear test scores as well as symptom scores.

More than 80% of all subjects responded with an improvement of ≥ 3 grades in tCFS after 4 weeks in ESSENCE-2-OLE, and this response level was maintained throughout observation period.

Notably, all symptom scores (dryness score, blurred vision score, OSDI etc.) reached a minimum at the last visit after 1 year of treatment with Vevye®, indicating continuous symptom improvement over 1 year of treatment.

5.2 PHARMACOKINETIC PROPERTIES

Following bilateral topical ocular dosing of one drop of Vevye® twice daily, the blood concentrations of cyclosporin were below the limit of quantification (0.1 ng/mL) at all timepoints.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In genetic toxicity tests, cyclosporin has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, 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. Cyclosporin was positive in an in vitro sister chromatid exchange (SCE) assay using human lymphocytes.

Carcinogenicity

Evaluation of the potential carcinogenicity of cyclosporin was conducted in male and female mice and rats. In a 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In a 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 740 times higher than the maximum recommended human ophthalmic dose (0.67 mcg/kg/day), normalized to body surface area.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Perfluorobutylpentane

Ethanol

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 °C. Discard after four weeks of opening.

6.5 NATURE AND CONTENTS OF CONTAINER

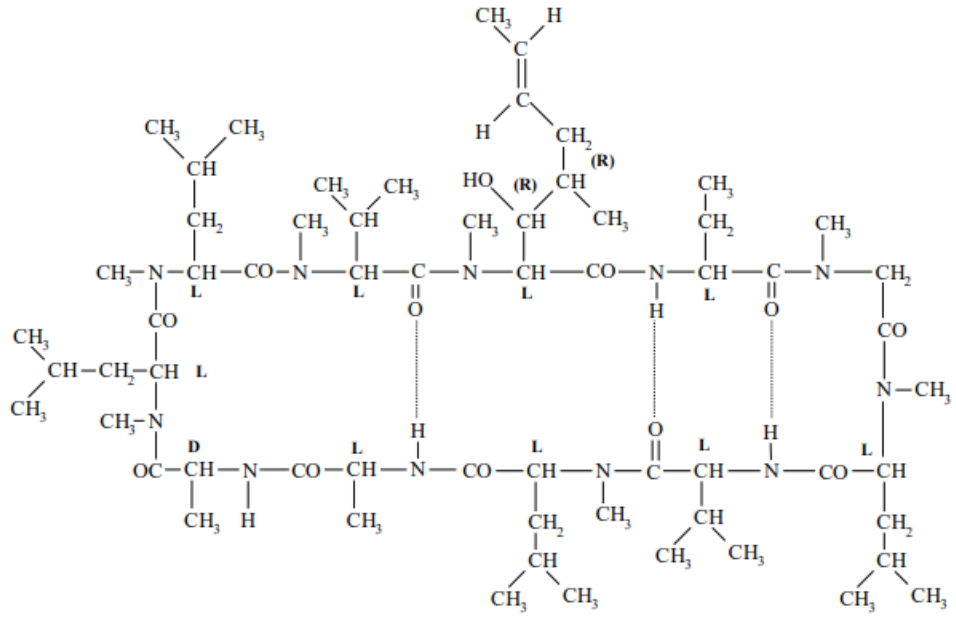
Vevye® is available in polypropylene bottle fitted with a dropper and screw cap. One bottle is packed in a carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOSHEMICAL PROPERTIES

Chemical structure



CAS number

59865-13-3

7 MEDICINE SCHEDULE

Prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

30 January 2025