

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VEVYE safely and effectively. See full prescribing information for VEVYE.

VEVYE (cyclosporine ophthalmic solution) 0.1%, for topical ophthalmic use

Initial U.S. Approval: 1983

-----**INDICATIONS AND USAGE**-----

VEVYE (cyclosporine ophthalmic solution) 0.1% is a calcineurin inhibitor immunosuppressant indicated for the treatment of the signs and symptoms of dry eye disease. (1)

-----**DOSAGE AND ADMINISTRATION**-----

Instill one drop of VEVYE twice a day in each eye approximately 12 hours apart. (2)

-----**DOSAGE FORMS AND STRENGTHS**-----

Ophthalmic solution containing cyclosporine 0.1%. (3)

-----**CONTRAINDICATIONS**-----

None. (4)

-----**WARNINGS AND PRECAUTIONS**-----

Care should be taken to not touch the eye or other surfaces with the bottle tip to avoid potential for eye injury and/or contamination. (5.1)

-----**ADVERSE REACTIONS**-----

The most common adverse reaction following the use of VEVYE were instillation site reactions (8%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novaliq at toll-free phone 1-888-298-4926 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

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U.S. Food and Drug Administration

Silver Spring, MD 20993

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VEVYE is indicated for the treatment of the signs and symptoms of dry eye disease.

2 DOSAGE AND ADMINISTRATION

Wash hands before using. Instill one drop of VEVYE twice a day in each eye approximately 12 hours apart. If used with other eye drops, a 15-minute interval between products should occur.

3 DOSAGE FORMS AND STRENGTHS

Clear, colorless, non-preserved ophthalmic solution containing cyclosporine 0.1% (1 mg/mL), delivering 0.01 mg of cyclosporine per one drop (0.01 mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Eye Injury and Contamination

To avoid the potential for eye injury and/or contamination, patients should not touch the bottle tip to the eye or other surfaces.

5.2 Use with Contact Lenses

VEVYE 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 VEVYE ophthalmic solution.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials with 738 subjects receiving at least 1 dose of VEVYE, the most common adverse reactions were instillation site reactions (8%) and temporary decreases in visual acuity (3%).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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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 approximately 4,700 times lower than recommended oral doses, with blood concentrations being undetectable after topical administration.

Data

Animal Data

Oral administration of cyclosporine oral solution to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body weight) were approximately 7,250 and 48,000 times higher than the daily maximum recommended human ophthalmic dose (MRHOD) of 0.67 mcg/kg/day, respectively.

No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 4,100 and 14,500 times higher than the MRHOD, respectively).

An oral dose of 45 mg/kg/day cyclosporine (approximately 10,900 times higher than MRHOD) 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 mothers or offspring were observed at oral doses of up to 15 mg/kg/day (3600 times greater than MRHOD).

8.2 Lactation

Risk Summary

Cyclosporine 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 approximately 4,700 times lower than recommended oral doses of cyclosporine, with blood concentrations being undetectable after topical administration. However, caution should be exercised when VEVYE is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

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

11 DESCRIPTION

VEVYE (cyclosporine ophthalmic solution) 0.1% contains the immunomodulatory agent cyclosporine. Cyclosporine's chemical name is Cyclo[[*(E)*-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-

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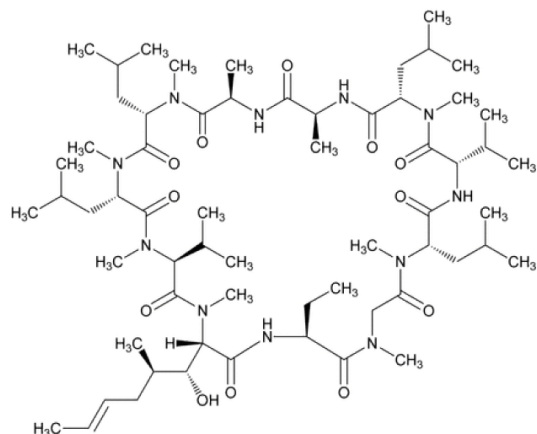
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methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]

and it has the following structure:

Structural Formula



Formula: $C_{62}H_{111}N_{11}O_{12}$, Molecular weight: 1202.6

Cyclosporine is a white powder that is soluble in perfluorobutylpentane. VEVYE is supplied as a 2 mL sterile, clear, colorless, non-aqueous ophthalmic solution for topical ophthalmic use.

VEVYE contains:

- Active: cyclosporine 0.1%
- Inactives: perfluorobutylpentane, ethanol (anhydrous).

The solution does not contain water or anti-microbial preservatives. As a water free product, there is no associated pH and no osmolarity.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cyclosporine, a calcineurin inhibitor, is a relatively selective immunomodulatory drug.

12.3 Pharmacokinetics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Evaluation of the potential carcinogenicity of cyclosporine 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 were approximately 120 times higher than the maximum recommended human ophthalmic dose (0.67 mcg/kg/day), normalized to body surface area.

Mutagenesis

In genetic toxicity tests, cyclosporine 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. Cyclosporine was positive in an in vitro sister chromatid exchange (SCE) assay using human lymphocytes.

Impairment of Fertility

Oral administration of cyclosporine 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 (approximately 3,600 times higher than the maximum recommended human ophthalmic dose).

14 CLINICAL STUDIES

The safety and efficacy of VEVYE were assessed in a total of 1369 patients with dry eye disease, of which 738 received VEVYE.

In two multicenter, randomized, adequate and well-controlled clinical studies, patients with dry eye disease (CYS-002: NCT02617667 and CYS-004: NCT04523129), treated with VEVYE were compared to patients treated with vehicle. At Day 29, there was a statistically significant higher percentage of eyes with increases of ≥ 10 mm from baseline in Schirmer's wetting. This effect was seen in approximately 10% of VEVYE-treated patients versus approximately 6% of vehicle-treated patients.

Percent of Patients Achieving ≥ 10 mm Improvement from Baseline in Schirmer's Tear Test Score in Study Eyes in Patients with Dry Eye Disease

	CYS-002 Day 29		CYS-004 Day 29	
	VEVYE N=51	Vehicle N=51	VEVYE N=409	Vehicle N=395
≥ 10 mm increase in tear production (% patients)	8%	0%	11%	7%
Difference (95% CI)	7.8% (0.5%, 15%)		3.9% (0.02%, 7.8%)	
p-value versus vehicle	0.04		0.05	

16 HOW SUPPLIED/STORAGE AND HANDLING

VEVYE is a sterile, clear, colorless, non-aqueous, non-preserved ophthalmic solution packaged in multiple-dose eye drop bottles delivering single drops of approximately 0.01 mL volume. Each unit contains 2 mL of VEVYE in a 5 mL transparent squeezable polypropylene bottle with a transparent polyethylene tip and a white polyethylene cap with tamper-evident ring.

NDC 83339-002-01

Storage and Handling

Do not use if tamper-evident ring attached to the white cap is not intact. After first opening the tamper-evident ring of the cap remains on the bottle neck. Retain the cap and keep the bottle tightly closed when not in use.

Store at 15°C to 25°C (59°F to 77°F). Do not freeze or refrigerate. After opening, VEVYE can be used until the expiration date on the bottle.

17 PATIENT COUNSELING INFORMATION

Risk of Contamination

Advise patients to wash their hands well before each use. Advise patients not to allow the dropper tip to touch the eye or any other surface, as this may contaminate the solution [*see Warning and Precautions (5.1)*].

Contact Lens Wear

Contact lenses should be removed prior to instillation of VEVYE and may be reinserted 15 minutes following administration [*see Warning and Precautions (5.2)*].

Manufactured for Novaliq GmbH by:

Alliance Medical Products, Inc. (DBA Siegfried Irvine), 9342 Jeronimo Road, Irvine, CA 92618 (USA)

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