CEQUA™ (cyclosporine ophthalmic solution) 0.09%, for topical ophthalmic use

Initial U.S. Approval: 1983

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1 INDICATIONS AND USAGE

CEQUA ophthalmic solution is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye). (1)

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2 DOSAGE AND ADMINISTRATION

Instill one drop of CEQUA twice daily (approximately 12 hours apart) into each eye. Discard the vial immediately after using in both eyes. (2)

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3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing cyclosporine 0.9 mg/mL. (3)

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4 CONTRAINDICATIONS

None. (4)

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5 WARNINGS AND PRECAUTIONS

5.1 Potential for Eye Injury and Contamination

To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces (5.1).

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6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The most common adverse reactions following the use of CEQUA (cyclosporine ophthalmic solution) 0.09% was instillation site pain (22%) and conjunctival hyperemia (6%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

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1 INDICATIONS AND USAGE

CEQUA ophthalmic solution is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye). (1)

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2 DOSAGE AND ADMINISTRATION

Instill one drop of CEQUA twice daily (approximately 12 hours apart) into each eye. CEQUA can be used concomitantly with artificial tears, allowing a 15-minute interval between products. Discard the vial immediately after using in both eyes. (2)

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3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing cyclosporine 0.9 mg/mL. (3)
Cyclosporine is a white powder that is insoluble in water. CEQUA is supplied as a sterile, clear, colorless ophthalmic solution for topical ophthalmic use. It has an osmolality of 160 to 190 mOsmol/kg and a pH of 6.5-7.2. Each mL of CEQUA contains:

- Active: cyclosporine 0.09%
- Inactives: Polyoxyl 40 Hydrogenated Castor Oil, Octoxynol-40, polyvinylpyrrolidone, sodium phosphate monobasic dihydrate, sodium phosphate dibasic anhydrous, sodium chloride, water for injection, and sodium hydroxide or hydrochloric acid to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cyclosporine is a calcineurin inhibitor immunosuppressant agent when administered systemically. In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, topical administration of cyclosporine is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

12.3 Pharmacokinetics

Blood concentrations of cyclosporine after twice daily topical ocular administration of CEQUA into each eye of healthy subjects for up to 7 days, and once on Day 8, were either not detectable or were marginally above the lower limit of assay quantitation of 0.100 ng/mL (range 0.101 to 0.195 ng/mL) for up to 2 hours after a single dose, and up to 4 hours after multiple doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 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 the 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 55 times higher than the maximum recommended human ophthalmic dose (1.5 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 (1620 times higher than the maximum recommended human ophthalmic dose).

14 CLINICAL STUDIES

Two multicenter, randomized, adequate and well-controlled clinical studies treated 1,048 patients with keratoconjunctivitis sicca (NCT # 02254265 and NCT # 02688556). In both studies, compared to vehicle at Day 84, there was a statistically significant (p<0.01) higher percentage of eyes with increases of ≥ 10 mm from baseline in Schirmer wetting. This effect was seen in approximately 17% of CEQUA-treated patients versus approximately 9% of vehicle-treated patients.

<table>
<thead>
<tr>
<th>Tear Production</th>
<th>CEQUA N = 152</th>
<th>Vehicle N = 152</th>
<th>CEQUA N = 371</th>
<th>Vehicle N = 373</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 10-mm increase in tear production (% of eyes) at Day 84</td>
<td>16.8%</td>
<td>8.6%</td>
<td>16.6%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>8.2% (1.9%, 14.6%)</td>
<td>7.3% (3.3%, 11.3%)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING

CEQUA ophthalmic solution is packaged in sterile, preservative-free, single-use vials. Each vial contains 0.25 mL fill in a 0.9 mL LDPE vial; 10 vials (2 cards of 5 vials) are packaged in a polyfoil aluminum pouch; 6 pouches are packaged in a box. The entire contents of each box of 60 vials must be dispensed intact.

60 Single-Use Vials 0.25 mL each - NDC 47335-506-96
Storage: Store at 20°C to 25°C (68°F to 77°F). Store single-use vials in the original foil pouch.

17 PATIENT COUNSELING INFORMATION

Handling the Vial

Advise patients not to allow the tip of the vial to touch the eye or any surface, as this may contaminate the solution. Advise patients also not to touch the vial tip to their eye to avoid the potential for injury to the eye [see Warnings and Precautions (5.1)].

Use with Contact Lenses

CEQUA should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that 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 CEQUA ophthalmic solution [see Warnings and Precautions (5.2)].

Administration

Advise patients that the solution from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Rx Only

Manufactured for: Sun Pharma Global FZE
By: Laboratoire Unither
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France

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