CEQUA®: A Novel Formulation That Provides Clinical Benefits

Cequa® (cyclosporine ophthalmic solution) 0.09%

New phase 4 data show improvements for patients whose DED symptoms were inadequately controlled.

In the United States, topical anti-inflammatory eye drops are the mainstay treatment for dry eye disease (DED).[1] Yet, eye care practitioners know that historically, the adherence rate for topical prescription dry eye therapies is quite low. In 2019, White et al concluded that most patients who were prescribed commercially available Restasis® (cyclosporine ophthalmic emulsion) 0.05% (AbbVie/Allergan) and Xiidra® (lifitegrast ophthalmic solution) 5.0% (Bausch + Lomb) discontinued the drops within 12 months (70.8% and 64.4%, respectively).[2] In a related study published in 2020, White et al found that a significant proportion of patients using these two medications were dissatisfied with the onset of effect for their treatment, and they often experienced side effects upon instillation (a burning sensation being the most common).[3]

DED is best managed by continued and consistent treatment. In multiple studies, researchers have found that patients who suffer from DED want a therapy that is comfortable to use, relieves their symptoms quickly, and begins improving their underlying pathology in short order.[4-8]

CEQUA: A NOVEL FORMULATION OF CYCLOSPORINE

CEQUA (cyclosporine ophthalmic solution) 0.09% (Sun Ophthalmics) was developed to meet patients' needs for a comfortable, fast-acting, and efficacious topical treatment for DED. CEQUA is a calcineurin inhibitor immunosuppressant that gained FDA approval in 2018 and is indicated to increase tear production in patients with keratoconjunctivitis sicca.[9] It is the first and only treatment for DED where cyclosporine A is being delivered with nanomicellar technology (the novel NCELL® Technology), which allows the medication to penetrate the aqueous layer better than non-nanomicellar formulations. In a comparison study, researchers randomized 112 New Zealand white female rabbits to receive either commercially available Restasis or 0.05% CEQUA with NCELL Technology daily for 7 days (note the apples-to-apples comparison of the strength of cyclosporine). The eyes that received cyclosporine with NCELL showed up to three times the amount of drug penetration than the eyes treated with cyclosporine A without NCELL.[10]

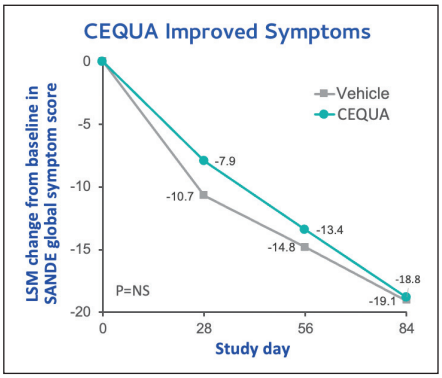

Figure 1. In the phase 3 clinical trial, both the group treated with CEQUA and the group treated with the vehicle demonstrated a mean decrease from baseline of approximately 30% in mSANDE scores. No difference in treatment effect was observed. (Note: Artificial tear use was not permitted during the phase 3 study). Data shown for the ITT population; missing data on day 84 were imputed by baseline values carried forward; *P*=NS.[11,12]

IMPROVED CORNEAL STAINING AND VISUAL ACUITY

The clearest demonstration of the efficacy of CEQUA occurred in its phase 2b/3, randomized, multicenter, double-masked, vehicle-controlled study. There, patients who received CEQUA experienced a statistically significant improvement in Schirmer's scoring (a primary endpoint) of $P < 0.01$. The researchers evaluated total and central corneal fluorescein staining (CFS) at baseline and on days 14, 28, 42, 56, and 84.[11,12] By day 84, CEQUA recipients showed an improvement from baseline of -1.4 (0.09) versus -0.9 (0.09) with the vehicle ($P = 0.0002$). Also by day 84, the researchers found a significantly high correlation ($P = 0.0117$) between CEQUA recipients' reduced central corneal staining and improved Snellen visual acuity.[12] Furthermore, Goldberg et al reported that both the CEQUA treatment group (n = 371) and the vehicle treatment group (n = 373) demonstrated a mean decrease from baseline in modified SANDE scores of approximately 30% by day 84 (Figure 1).[13]

INDICATIONS AND USAGE

CEQUA® (cyclosporine ophthalmic solution) 0.09% is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

Please see additional Important Safety Information and the enclosed Brief Summary.

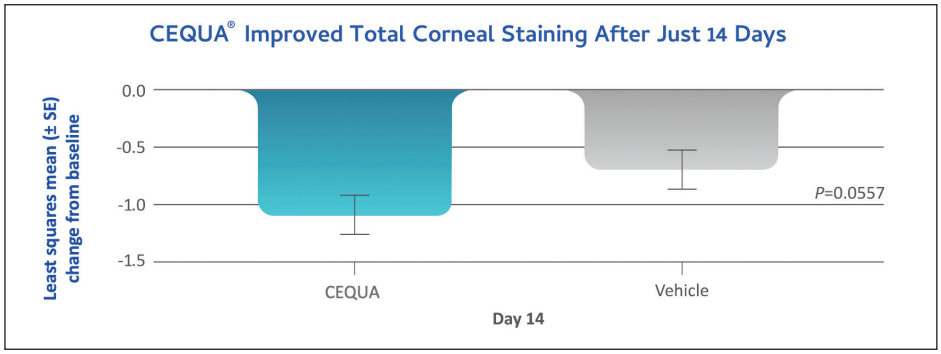

Figure 2. Outcomes shown from the phase 2b/3, randomized, multicenter, double-masked, vehicle-controlled, dose-ranging study. The co-primary efficacy endpoints were a mean reduction in the total conjunctival staining score and a mean reduction in the global symptom score at day 84. Conjunctival and corneal staining were assessed at baseline and days 14, 28, 42, 56, and 84/early discontinuation. Conjunctival staining was assessed in 6 conjunctival zones 1-4 minutes after instilling 1 drop of 1% lissamine green. Corneal staining was evaluated in 5 corneal regions 2-2.5 minutes after instilling 1 drop of 0.5% fluorescein.[12,14]

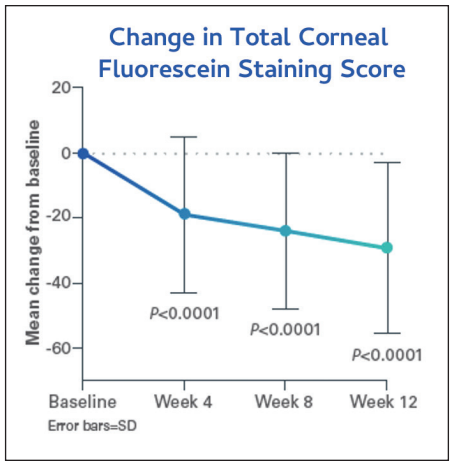

Figure 3. Most patients reported that their eyes felt more comfortabel after using CEQUA for 4 weeks than they did using Restasis.[16]

FAST ACTION

An important finding in the phase 2b/3 clinical trials was that CEQUA began working within 2 weeks of treatment initiation. In a separate evaluation of patients' ocular surface endpoints in the clinical trial phase 2b/3 at day 14, those randomized to CEQUA (n = 152) showed least squares mean (SE) change from baseline[14] in the following:

- in **conjunctival staining**, a score of -1.3 (0.1) (vehicle: -1.0 [0.1])[14]
- in **corneal staining**, a score of -1.1 (0.17) (vehicle: -0.7 [0.17]) (Figure 2)[14]
- in **tear break-up time**, a score of 0.52 (0.15) (vehicle: 0.36 [0.15])[14]
- in **modified SANDE total global symptoms**, a score of -4.93 (1.54) (vehicle: -9.1 [1.54])[14]
- CEQUA 0.09% demonstrated a numerically greater treatment effect compared with vehicle in conjunctival staining, corneal staining, and tear break-up time after **14 days**.[14]

Additionally, by 3 months, 65% of the corneas in the CEQUA group were completely clear, compared to 56.9% in the vehicle group (P = 0.02).[13]

SAFETY AND TOLERABILITY

In the CEQUA clinical trials, nearly 95% of those who received CEQUA 0.05% reported experiencing either no or mild instillation site pain after 10 minutes.[15] CEQUA is a clear, nonpreserved drop that has a neutral pH. The NCELL Technology of CEQUA is designed to provide comfort and help patients better tolerate cyclosporine.

CEQUA was generally well tolerated in its clinical trials, with most patient-reported adverse events classified as mild or moderate. The most common adverse reactions for CEQUA reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.[13]

Notably, CEQUA has no reported taste alterations or contraindications, making it an appropriate option for virtually all adults with DED.[12]

PHASE 4 DATA: SUSTAINED IMPROVEMENT IN DED SIGNS AND SYMPTOMS IN PATIENTS NOT ADEQUATELY CONTROLLED WITH RESTASIS

At the American Academy of Optometry (AAOpt) annual meeting in October 2023, researchers presented data from the 12-week phase 4 multicenter study of the CEQUA clinical trial.[16] Most notably, CEQUA provided sustained amelioration of the signs and symptoms of DED in patients for whom Restasis therapy had failed to control their disease.

The study included 124 adults who had a clinical diagnosis of DED and had been using Restasis for at least 3 months (the average length of Restasis therapy was 38 months), yet who were still symptomatic and/or were exhibiting signs of DED. They received one drop of CEQUA® in each eye, twice

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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.

Please see additional Important Safety Information and the enclosed Brief Summary.

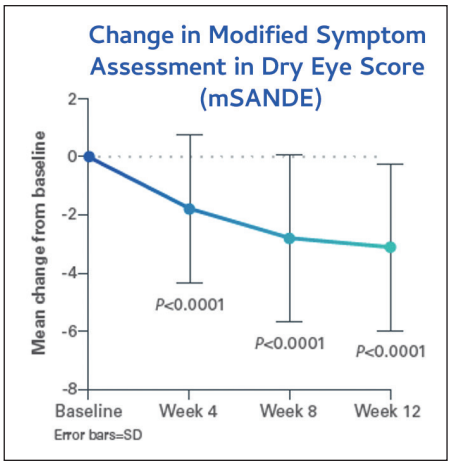

Figure 4. Most patients showed statistically significant improvements in total corneal staining as early as week 4, continued to week 12.[16]

per day for 12 weeks. Significantly, the study allowed patients to use artificial tears as needed, thereby replicating real-world circumstances in this modified intent-to-treat population.[16]

The investigators evaluated patients' CFS and mSANDE scores at baseline and at weeks 4, 8, and 12. Patients showed statistically significant improvements in CFS (Figure 3) and mSANDE scores (Figure 4) in as early as 4 weeks of treatment, and they maintained these improvements through week 12. At baseline, the mean (SD) total CFS score was 5.7 (3.37), which improved significantly (P <0.0001) to 4.0 (3.12) at week 4, 2.9 (2.54) at week 8, and 2.7 (2.36) at week 12. The mean (SD) mSANDE score at baseline was 67.1 (21.05), which also improved significantly (P <0.0001) to 48.4 (23.31) at week 4, 44.2 (24.28) at week 8, and 38.3 (25.99) at week 12. Notably, patients' artificial tear use dropped from 3x to 1x per day after switching from Restasis to CEQUA for 12 weeks.

As in its phase 2b/3 clinical trial, CEQUA was generally well tolerated in the phase 4 study. In total, 58 patients (43.3%) reported at least one treatment-emergent adverse event (AE), although most (73.8%) were mild. Instillation site irritation and instillation site pain were the most common treatment-related AEs. No new safety signals appeared in the trial.

SUMMARY

The phase 4 study of the CEQUA clinical trial supported and replicated the outcomes of the phase 2b/3 trials in showing that CEQUA offers a treatment for DED that is at once fast-acting, comfortable, and sustained in its ability to improve the signs and symptoms of the disease.[11-16] Assessments of this trial are ongoing, but so far, CEQUA has shown consistent performance in safety and efficacy measurements. ■

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SUN OPHTHALMICS

IMPORTANT SAFETY INFORMATION (CONT.)

WARNINGS AND PRECAUTIONS (CONT.)

Use with Contact Lenses: CEQUA 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 CEQUA ophthalmic solution.

ADVERSE REACTIONS

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

Please see additional Important Safety Information and the enclosed Brief Summary.

Brief Summary of Prescribing Information for CEQUA® (cyclosporine ophthalmic solution) 0.09%, for topical ophthalmic use

CEQUA® (cyclosporine ophthalmic solution) 0.09%
See package insert for Full Prescribing Information.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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.

Use with Contact Lenses

CEQUA 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 CEQUA ophthalmic solution.

ADVERSE REACTIONS

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, 769 patients received at least 1 dose of cyclosporine ophthalmic solution. The majority of the treated patients were female (83%).

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of CEQUA 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.

Data

Animal Data

Oral administration of cyclosporine oral solution (USP) 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 3200 and 21,000 times higher than the maximum recommended human ophthalmic dose (MRHOD) of 1.5 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 1800 and 6400 times higher than the MRHOD, respectively).

An oral dose of 45 mg/kg/day cyclosporine (approximately 4800 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 dams or offspring were observed at oral doses up to 15 mg/kg/day (approximately 1600 times greater than the MRHOD).

Lactation

Risk Summary

Cyclosporine blood concentrations are low following topical ocular administration of CEQUA. There is no information regarding the presence of cyclosporine in human milk following topical administration or on the effects of CEQUA on breastfed infants and milk production. Administration of oral cyclosporine to rats during lactation did not produce adverse effects in offspring at clinically relevant doses. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CEQUA and any potential adverse effects on the breastfed child from cyclosporine.

Pediatric Use

The safety and efficacy of CEQUA ophthalmic solution have not been established in pediatric patients below the age of 18.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

PATIENT COUNSELING INFORMATION

Handling the Vial

Advise patients to not 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.

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.

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 Pharmaceutical Industries Limited
By: Laboratoire Unither 1 rue de l'Arquerie 50200 Coutances France
Cyclosporine (active ingred.) Product of Czech Republic.
Product of France
Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512

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