PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**CEQUA™**

Cyclosporine Ophthalmic Solution

Solution, 0.09% w/v

Anti-Inflammatory / Immunomodulator

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

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CEQUA (cyclosporine ophthalmic solution 0.09% w/v) is indicated to increase tear production in patients with moderate to severe keratoconjunctivitis sicca (dry eye).

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of CEQUA has not been established in pediatric patients; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

2 CONTRAINDICATIONS

CEQUA is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Section 5 Dosage Forms, Strengths, Composition and Packaging.
- Patients with active or suspected ocular or peri-ocular infections.
- Patients with ocular or peri-ocular malignancies or premalignant conditions.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

For topical ophthalmic use.

Each CEQUA vial is for single use in one patient only.

There are no special dosing considerations which need to be taken into account prior to initiating therapy with CEQUA.

3.2 Recommended Dose and Dosage Adjustment

Instill one drop of CEQUA twice daily (approximately 12 hours apart) into each eye.

The dose should not exceed two drops (administered 12 hours apart) in the affected eye(s) daily.

Limited data from clinical studies exists for long term administration of CEQUA (up to 12 months). It is expected that use of the product will continue long term.

Health Canada has not authorized an indication for pediatric use (see Sections 1.1 and 6.1.3

Pediatrics).

3.3 Administration

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.

Advise patients to wash their hands before each use and not to touch the tip of the vial to their eye or any other surface, in order to avoid eye injury or contamination of the solution (see Section 6 Warnings and Precautions).

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.

CEQUA can be used concomitantly with artificial tears, allowing a 15-minute interval between products.

3.4 Missed Dose

If a dose of this medication is missed, treatment should be continued on the next instillation as normal. Doses should not be doubled. Patients should be advised not to instill more than two drops in the affected eye(s) daily.

4 OVERDOSAGE

There is no information regarding topical overdose in patients taking CEQUA.

Excessive topical ocular use of cyclosporine would not be expected to contribute to ocular toxicity and due to low systemic concentrations of cyclosporine after topical ocular treatment, the likelihood of systemic intoxication from topical ocular overdose is remote.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Ophthalmic	Solution containing cyclosporine 0.09% w/v (0.9 mg/mL)	Octoxynol-40, polyoxyl 40 hydrogenated castor oil, polyvinylpyrrolidone, sodium chloride, sodium hydroxide or hydrochloric acid (to adjust pH), sodium phosphate dibasic anhydrous, sodium phosphate monobasic dihydrate, and water for injection.

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.

CEQUA 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.

6 WARNINGS AND PRECAUTIONS

General
CEQUA is for topical ophthalmic use only.

Resolve existing or suspected ocular or peri-ocular infections before initiating CEQUA treatment. If an infection occurs during treatment, CEQUA should be temporarily withheld until the infection has been resolved.

Carcinogenesis and Mutagenesis
See Section 14 Non-Clinical Toxicology.

Driving and Operating Machinery
The effects of CEQUA on a person's ability to drive and use of machines were not assessed. However, the ability of CEQUA to induce temporary blurred vision or other visual disturbances cannot be ruled out. Therefore, patients should be advised not to drive or use machinery until their vision has cleared after the administration of CEQUA.

Ophthalmologic
CEQUA has not been studied in patients with a history of *herpes keratitis*, end stage lacrimal gland disease, keratoconjunctivitis sicca (KCS) secondary to the destruction of conjunctival goblet cells such as occurs with Vitamin A deficiency, or scarring, such as occurs with cicatricial pemphigoid, alkali burns, Stevens Johnson syndrome, trachoma, or irradiation.

Patients with severe keratitis should be carefully monitored.

Potential for Eye Injury and Contamination
Advise patients not to touch the tip of the vial to their eye or any other surface, in order to avoid eye injury or contamination of the solution.

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.

Patients wearing contact lenses have not been studied.

Hepatic
The effect of CEQUA has not been studied in patients with hepatic impairment. However, no special dose adjustment is needed in this population as systemic exposure to cyclosporine is low (see Section 9 Action and Clinical Pharmacology).

Immune
Ophthalmic medicinal products, which affect the immune system, including cyclosporine, may affect host defences against local infections and malignancies. Therefore, regular monitoring of the eye(s) is recommended when CEQUA is used long-term. Additionally, there is the potential to experience hypersensitivity to CEQUA. If an allergic reaction occurs, patients should be advised to discontinue the drug.

Renal
The effect of CEQUA has not been studied in patients with renal impairment. However, no special dose adjustment is needed in this population as systemic exposure to cyclosporine is low (see Section 9 Action and Clinical Pharmacology).

6.1 Special Populations

6.1.1 Pregnant Women

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

However, studies in animals have shown reproductive toxicity following systemic administration of cyclosporine at exposures sufficiently in excess of the maximum human exposure from ophthalmic use, indicating little relevance to the clinical use of CEQUA (see Section 14 Non-Clinical Toxicology).

CEQUA is not recommended during pregnancy unless the benefits outweigh the risks.

6.1.2 Breast-feeding

Cyclosporine is known to be excreted in human breast milk following systemic administration, however, excretion in human breast milk following topical administration of CEQUA has not been investigated. Cyclosporine blood concentrations are low following topical ocular administration of CEQUA (see Section 9 Action and Clinical Pharmacology - 9.3 Pharmacokinetics).

Administration of oral cyclosporine to rats during lactation did not produce adverse effects in offspring at clinically relevant doses (see Section 14 Non-Clinical Toxicology). There is no

information on the effects of CEQUA on breast-fed infants and milk production. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for CEQUA and any potential adverse effects on the breast-fed infants from cyclosporine.

Because many drugs are excreted in human breast milk, caution should be exercised when CEQUA is administered to a nursing woman.

6.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of CEQUA has not been established in pediatric patients; therefore, Health Canada has not authorized an indication for pediatric use.

6.1.4 Geriatrics

Geriatrics (>65 years of age): No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The most common adverse reaction reported in subjects following the use of CEQUA was pain on instillation of drops (22%).

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

OTX-101-2014-001 and OTX 101-2016-001 Pooled Safety Data
The primary assessment of safety is derived from two multicenter, randomized, double-masked, 12-week, vehicle-controlled trials of similar design in subjects with keratoconjunctivitis sicca. Study OTX-101-2016-001 was a pivotal Phase 3 study and study OTX-101-2014-001 was a supportive Phase 2b/3 study.

In the two clinical trials, 524 subjects (Safety Population) received at least 1 dose of CEQUA (i.e. cyclosporine ophthalmic solution 0.09% w/v). The majority of the treated subjects were female (83%) and the mean age was 59 years. Subjects in the CEQUA group had a higher incidence of adverse events (38.7% vs 27.1%) and treatment-related adverse events (25.2% vs 8.6%) compared with the Vehicle group. However, CEQUA was generally well tolerated with most adverse events considered mild and did not require treatment.

The most common adverse events (AEs) reported in greater than 1% of subjects (Table 2) were instillation site pain (22%) and conjunctival hyperemia (6%). The most common non-ocular AEs (≥ 1% of subjects in either group) were headache and urinary tract infection.

Table 2 Treatment-Emergent Adverse Events Reported in ≥ 1% of Subjects in Either Treatment Group - Pooled Data Set of Controlled Phase 3 and Phase 2b/3 Studies (Safety Population)

Preferred Term	Pooled Data	
	CEQUA (N=524) n (%)	Vehicle (N=524) n (%)
Ocular AEs		
Instillation site pain	114 (21.8)	21 (4.0)
Conjunctival hyperaemia	30 (5.7)	19 (3.6)
Eye irritation	6 (1.1)	6 (1.1)
Blepharitis	5 (1.0)	0
Eye pruritus	2 (0.4)	8 (1.5)
Foreign body sensation in eyes	2 (0.4)	5 (1.0)
Vitreous floaters	2 (0.4)	5 (1.0)
Non-ocular AEs		
Headache	8 (1.5)	2 (0.4)
Urinary tract infection	6 (1.1)	4 (0.8)
Bronchitis	5 (1.0)	3 (0.6)
Sinusitis	4 (0.8)	5 (1.0)
Upper respiratory tract infection	4 (0.8)	5 (1.0)
Nasopharyngitis	1 (0.2)	5 (1.0)

Adverse events of severe intensity (1.7% vs 0.8%), and events that led to interruption (0.8% vs 0.4%) or discontinuation (4.2% vs 1.7%) of study drug were low. Serious adverse events were uncommon (1.1% in both treatment groups). One subject randomized to CEQUA in study OTX-101-2016-001 died from an unknown cause, but not considered to be related to study drug.

OTX-101-2016-002 Safety Extension Study

Long-term safety data are provided by a 12-month safety extension study i.e. OTX-101-2016-002. All 258 subjects from the Phase 3 study OTX-101-2016-001 who subsequently participated in the open-label 40-week OTX-101-2016-002 extension study were treated with CEQUA. Of these, 129 subjects had previously received CEQUA (Group 1) and another 129 subjects had received Vehicle (Group 2) during the 12-week OTX-101-2016-001 study period. At completion of the extension study, a total of 225 subjects had more than 6 months exposure to CEQUA including 138 subjects who had ≥12 months of total exposure. The overall mean duration of exposure was 10.42 months.

An analysis of adverse events in the full safety population for study OTX-101-2016-002 did not reveal any new findings. There were no changes to the serious adverse event profile. Instillation

site pain remained the most commonly reported adverse event. It was reported at a higher incidence, as expected, in subjects who had received Vehicle prior to being switched to CEQUA.

Besides instillation site pain (22.9%), conjunctival hyperemia (10.1%), and punctate keratitis (6.2%) were the most commonly reported treatment-emergent adverse events (Table 3). Punctate keratitis was reported by more subjects in Group 1, but it was considered unrelated to treatment in all cases but one, and the difference is attributed to the natural variability of the presentation of KCS. These events were predominantly of mild intensity, with only 1 subject (0.4%) reporting severe intensity.

Table 3 Treatment-Emergent Adverse Events Reported in ≥ 1% of Subjects in Safety Extension Study

Preferred Term	Group 1 (N=129) n (%)	Group 2 (N=129) n (%)	Overall (N=258) n (%)
Ocular AEs			
Instillation site pain	17 (13.2)	42 (32.6)	59 (22.9)
Conjunctival hyperaemia	12 (9.3)	14 (10.9)	26 (10.1)
Punctate keratitis	12 (9.3)	4 (3.1)	16 (6.2)
Blepharitis	3 (2.3)	4 (3.1)	7 (2.7)
Vitreous Detachment	5 (3.9)	2 (1.6)	7 (2.7)
Posterior capsule opacification	5 (3.9)	1 (0.8)	6 (2.3)
Eye irritation	2 (1.6)	2 (1.6)	4 (1.6)
Conjunctival hemorrhage	2 (1.6)	2 (1.6)	4 (1.6)
Instillation site lacrimation	1 (0.8)	3 (2.3)	4 (1.6)
Instillation site reaction	1 (0.8)	3 (2.3)	4 (1.6)
Intraocular pressure increased	2 (1.6)	1 (0.8)	3 (1.2)
Non-ocular AEs			
Bronchitis	2 (1.6)	4 (3.1)	6 (2.3)
Sinusitis	0	4 (3.1)	4 (1.6)
Osteoarthritis	3 (2.3)	1 (0.8)	4 (1.6)
Gastroenteritis viral	2 (1.6)	1 (0.8)	3 (1.2)
Urinary tract infection	2 (1.6)	1 (0.8)	3 (1.2)
Migraine with aura	1 (0.8)	2 (1.6)	3 (1.2)

Group 1 subjects continued with CEQUA in the Safety Extension Study.
Group 2 subjects began CEQUA treatment in the Safety Extension Study.

7.3 Less Common Clinical Trial Adverse Reactions (< 1%)

Eye disorders: Conjunctival edema, eye pain, lacrimation increased, vision blurred

General disorders and administrative site conditions: Instillation site lacrimation, instillation site pruritus, instillation site reaction

Respiratory, thoracic and mediastinal disorders: Throat irritation

7.4 Post-Market Adverse Reactions

No post-marketing data is available.

8 DRUG INTERACTIONS

8.1 Overview

No drug interaction studies have been performed with CEQUA.

Drugs that affect cytochrome P-450 may alter cyclosporine metabolism. There is little to no detectable systemic absorption of cyclosporine following ocular administration (see Section 9 Action and Clinical Pharmacology – 9.3 Pharmacokinetics). Therefore, no interaction of topically applied cyclosporine with systemic drugs is expected to occur.

8.2 Drug-Drug Interactions

Interactions with other drugs have not been established with CEQUA.

Although many drugs are known to interact with orally administered cyclosporine, no systemic drug-drug interactions are likely to occur following topical ocular administration of CEQUA because of the very low cyclosporine dose (88 mcg/day) and low systemic levels seen in the ocular toxicology studies and in the clinical program conducted.

8.3 Drug-Food Interactions

Interactions with food have not been established with CEQUA.

8.4 Drug-Herb Interactions

Interactions with herbal products have not been established with CEQUA.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established with CEQUA.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Cyclosporine is a calcineurin inhibitor immunosuppressant agent when administered systemically. It is able to inhibit the activation of transcription factors required for T-cell activation and inflammatory cytokine production. 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. By suppressing the immune-based inflammation of the ocular surface, treatment with cyclosporine increases the ability of the lacrimal glands to produce tears, potentiating the return of a more stable tear film

and normal ocular surface. However, the exact mechanism of action in treating keratoconjunctivitis sicca (dry eye) is not known.

9.2 Pharmacodynamics

No studies of pharmacodynamic effects have been performed with CEQUA.

9.3 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. While numerically greater values were observed after multiple doses compared to a single dose, the maximum blood level observed was no greater than 0.200 ng/mL. This value is less than 0.1% of that at which systemic toxicity might be observed.

The mean ± SD for C_{max} was 0.173 ± 0.020 ng/mL and for $AUC_{(0\text{-}t)}$ was 0.526 ± 0.059 h∗ng/mL in human volunteers on Day 8 of the study, where only 4 of 16 subjects had ≥ 3 consecutive whole blood CsA concentrations ≥ lower limit of quantitation.

Special Populations and Conditions

Pediatrics (<18 years of age): The safety and efficacy of CEQUA has not been established in pediatric patients; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (>65 years of age): No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

Pregnancy and Breast-feeding: There is no information regarding the presence of cyclosporine in human milk following topical administration or on the effects of CEQUA on the breastfed infants and milk production (see Section 6.1 Special Populations - 6.1.2 Breast-feeding).

Hepatic Insufficiency: Based on the low systemic availability of cyclosporine, no increased risk in patients with impaired hepatic function would be expected to occur following the use of CEQUA.

Renal Insufficiency: Based on the low systemic availability of cyclosporine, no increased risk in patients with impaired renal function would be expected to occur following the use of CEQUA.

10 STORAGE, STABILITY AND DISPOSAL

CEQUA should be stored at room temperature (15°C to 25°C). Do not freeze. Keep out of the sight and reach of children. Store single-use vials in the original foil pouch. The ophthalmic 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 after administration.

11 SPECIAL HANDLING INSTRUCTIONS

Advise patients not to touch the tip of the vial to their eye or any other surface, in order to avoid eye injury or contamination of the solution (see Section 6 Warnings and Precautions).

If there is any presence of leakage, visible particulate matter, or damage to the vial, the vial should not be used and is to be discarded.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Cyclosporine (USP); Ciclosporin and Ciclosporin A (Ph.Eur.)

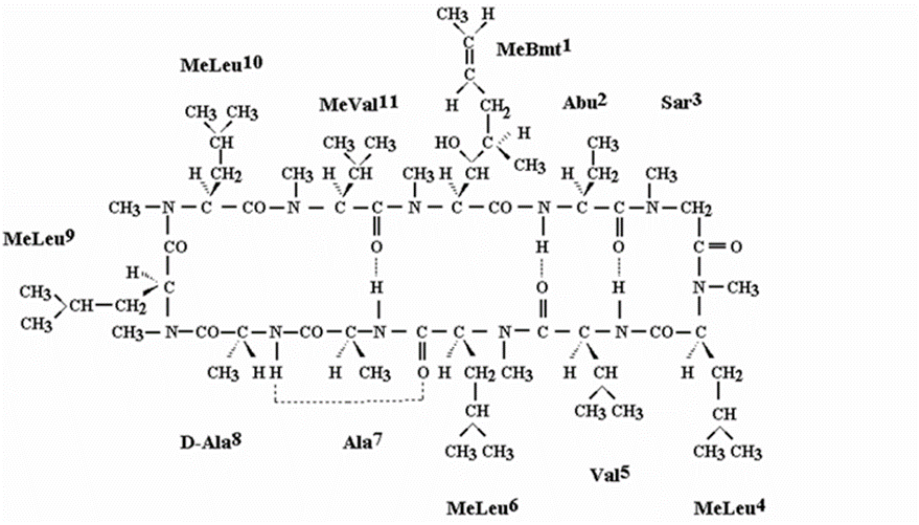
Chemical name: Cyclosporine A

Cyclo[[(E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]

Molecular formula: $C_{62}H_{111}N_{11}O_{12}$

Molecular mass: 1202.6

Structural formula:



Physicochemical properties: Cyclosporine A is white or almost white odorless powder. It is insoluble in water, soluble in most organic solvents (methanol, ethanol, acetone, chloroform and diethylether) with the exception of aliphatic hydrocarbons (n-hexane). The anhydrous product is hygroscopic.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Two multicenter, randomized, double-masked, vehicle-controlled trials (i.e. OTX-101-2014-001 and OTX-101-2016-001) of similar design were conducted to evaluate the safety and efficacy of CEQUA (cyclosporine ophthalmic solution 0.09% w/v) in the treatment of patients with keratoconjunctivitis sicca (KCS). Both studies were identical with respect to duration (12 weeks), dosing regimen (1 drop in each eye, twice daily), and inclusion/exclusion criteria.

Patients enrolled in both studies had a subject-reported history of ≥ 6 months of KCS. All patients had a clinical diagnosis of bilateral KCS, based on a lissamine green conjunctival staining score of ≥ 3 to ≤ 9 out of a total possible score of 12 (scoring excluded superior zones 2 and 4) in the same eye at Screening and Baseline. Patients had self-rated global symptom scores of ≥ 40 on a scale of 100 for dryness and/or irritation.

Study OTX-101-2016-001 was a pivotal Phase 3 study that compared cyclosporine ophthalmic solution 0.09% w/v against vehicle in 744 subjects. A single primary efficacy endpoint was designated i.e. increased tear production as measured by proportion of subjects with ≥ 10-mm increases in Schirmer's test score at Day 84 from baseline based on data for both eyes.

Study OTX-101-2014-001 was a supportive Phase 2b/3 study that compared two concentrations of cyclosporine ophthalmic solution, 0.05% w/v and 0.09% w/v, against vehicle in 455 subjects. Two co-primary efficacy endpoints measured the mean change from baseline at Day 84 for total conjunctival staining score in the designated study eye and Symptom Assessment iN Dry Eye (SANDE) global symptom score. Based on the results of study OTX-101-2014-001, cyclosporine ophthalmic solution 0.09% w/v was selected for further development.

Key secondary and additional efficacy variables compared between cyclosporine ophthalmic solution and vehicle in the two clinical studies included: mean change from baseline in Schirmer's test score, mean change from baseline in total and temporal lissamine green conjunctival staining score, clearing of temporal lissamine green staining, mean change from baseline in total and central corneal fluorescein staining score, and clearing of central corneal staining.

Patient demographics for the pivotal and supportive vehicle-controlled studies conducted in patients with keratoconjunctivitis sicca are provided in Table 4. All studies were conducted with cyclosporine solution administered via the ophthalmic route on a twice daily schedule. In these studies, 1199 patients with keratoconjunctivitis sicca were included in the ITT Population (cyclosporine ophthalmic solution or vehicle).

Table 4 Summary of Patient Demographics for Clinical Trials in Patients with Keratoconjunctivitis Sicca (ITT Population)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
OTX-101-2016-001	Phase 3, multicenter, randomized, double-masked, vehicle-controlled	0.09% cyclosporine, or vehicle twice daily in each eye as ophthalmic solution for 12 weeks (84 days)	Cyclosporine 0.09%: n=371 Vehicle n=373 Total: n=744	59.0 (18 – 90)	M=118 (15.9%) F=626 (84.1%)
OTX-101-2014-001	Phase 2/3, multicenter, randomized, double-masked, vehicle-controlled, dose-ranging	0.05%, 0.09% cyclosporine, or vehicle twice daily in each eye as ophthalmic solution for 12 weeks (84 days)	Cyclosporine 0.05%: n=151 0.09%: n=152 Vehicle n=152 Total: n=455	60.1 (22 – 91)	M=94 (20.7%) F=361 (79.3%)

The supportive OTX-101-2014-001 study failed to meet the co-primary efficacy endpoint of mean change from baseline in the global symptom score at Day 84. Therefore, the responder analysis performed for the primary efficacy endpoint in pivotal study OTX-101-2016-001 i.e. an increase of ≥ 10 mm from baseline in Schirmer's test, was performed as a post hoc analysis utilizing the average of eyes in study OTX-101-2014-001. These data were subsequently reanalyzed using the statistical methods of OTX-101-2016-001 (i.e. analysis of the data for both eyes of each subject using methods that account for within subject correlation) to support the primary efficacy results of pivotal Phase 3 study OTX-101-2016-001.

13.2 Study Results

In both studies, compared to vehicle at Day 84, CEQUA-treated patients showed 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 5).

Table 5 Results of Studies OTX-101-2014-001 and OTX-101-2016-001 in Patients with Keratoconjunctivitis Sicca: Schirmer's Test at Day 84 (ITT Population)

Tear Production				
	OTX-101-2014-001		OTX-101-2016-001	
	CEQUA N = 152	Vehicle N = 152	CEQUA N = 371	Vehicle N = 373
Number of eyes	304	304	742	746
Eyes with ≥ 10 mm increase in tear production, n (% of eyes)	51 (16.8%)	26 (8.6%)	123 (16.6%)	69 (9.2%)
Difference (95% CI)	8.2% (1.9%, 14.6%)		7.3% (3.3%, 11.3%)	
p-value versus vehicle	0.0113		0.0003	

14 NON-CLINICAL TOXICOLOGY

Repeat-Dose Toxicity

The systemic toxicologic profile of cyclosporine (CsA) is well established and the cyclosporine drug product formulation contains no novel excipients.

The nonclinical toxicity studies performed to support the ocular safety of cyclosporine ophthalmic solution included ocular tolerability studies of up to 6 days duration and repeat-dose ocular toxicity and toxicokinetic studies of 28 days, 13 weeks and 26 weeks in which up to 0.1% concentrations of cyclosporine ophthalmic solution were administered up to four times daily (QID).

Ocular administration of cyclosporine ophthalmic solution at CsA concentrations up to 0.1% QID to New Zealand White (NZW) rabbits for periods of up to 13 weeks, and at CsA concentrations up to 0.09% QID for 26 weeks, resulted in transient minimal to mild irritation of periocular membranous tissues. No effects were observed in intraocular pressure or electroretinography measurements in any study. There were no histologic changes except as related to the observed transient mild irritation in ocular or periocular tissues. The margin of exposure for ocular effects in NZW rabbits administered cyclosporine ophthalmic solution 0.09% QID for 26 weeks (total daily dose of 83 mcg/eye/day, administered at a dose volume of 35 µL/eye/dose) was ~1.9-fold compared to the maximum recommended human ophthalmic dose (MRHOD) (total daily dose of 44 mcg/eye/day; 22 mcg/eye/dose given BID at a dose volume of 24.4 µL).

Ocular administration of cyclosporine ophthalmic solution 0.09% QID for 26 weeks to NZW rabbits resulted in low CsA blood concentrations ($AUC_{(0-4)}$ of 5.20 ±1.43 and 8.52 ± 2.77 h∗ng/mL and C_{max} values of 2.06 ± 0.67 and 3.30 ± 0.98 ng/mL, for females and males, respectively); safety margins of systemic exposure based on whole blood $AUC_{(0-4)}$ concentrations of CsA vs. human systemic exposure at the MRHOD were 16.2- and 9.9-fold for male and female rabbits, respectively. No systemic effects related to CsA administration were noted after ocular administration of cyclosporine ophthalmic solution to animals.

The ocular tissue distribution and systemic absorption of CsA was assessed following single topical ocular administration (35 µL) of cyclosporine ophthalmic solution 0.05% (17.5 mcg CsA/eye/day) and repeat QID topical ocular administration of cyclosporine ophthalmic solution 0.01%, 0.05%, and 0.1% (daily doses of 14, 70, and 140 mcg CsA/eye/day) for 7 days to NZW rabbits. Following completion of the dosing phase, blood, tears and ocular tissues were collected for analysis of CsA levels. CsA was extensively distributed in ocular tissues but exhibited minimal systemic exposure (mean $C_{max} \leq 6.2$ ng/mL). Ocular and periocular CsA tissue levels increased in a dose-responsive manner. There was an increase in $AUC_{(0-t)}$ with repeat dosing of cyclosporine ophthalmic solution 0.05% indicating accumulation in all ocular tissues with repeat daily dosing compared to a single dose.

Systemic exposure to CsA also increased upon repeat QID dosing of cyclosporine ophthalmic solution 0.05% compared to a single dose. However, the CsA mean C_{max} value (2.01 ng/mL) in blood following repeat dosing of cyclosporine ophthalmic solution 0.05% in the 7-day tissue distribution study was comparable to the mean C_{max} values observed at the same dose level in the 28-day, 13-week and 26-week toxicity studies (1.35, 1.76, 1.51 ng/mL, respectively). In addition, there was no apparent systemic CsA accumulation over the 28-day, 13-week and 26-week dosing period. Overall, these data indicated that there was no systemic CsA accumulation following repeat-dose ocular administration of CsA up to 26 weeks.

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 (MRHOD) of 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 assay using human lymphocytes.

Reproductive Toxicology
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 surface area) were approximately 3200 and 21000 times higher than the MRHOD of 1.5 mcg/kg/day, respectively. No adverse embryo-fetal 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 1620 times greater than the MRHOD).

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 1620 times higher than the MRHOD, normalized to body surface area).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

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Pr**CEQUA™**

Cyclosporine Ophthalmic Solution

Read this carefully before you start taking **CEQUA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CEQUA**.

What is CEQUA used for?

- CEQUA is used to treat a condition called keratoconjunctivitis sicca also known as dry eye disease.
- CEQUA makes your eyes produce more tears.

How does CEQUA work?

CEQUA contains cyclosporine. Cyclosporine is a medicine that decreases inflammation in the eye.

What are the ingredients in CEQUA?

Medicinal ingredients: cyclosporine
Non-medicinal ingredients: octoxynol-40, polyoxyl 40 hydrogenated castor oil, polyvinylpyrrolidone, sodium chloride, sodium hydroxide or hydrochloric acid to adjust pH, sodium phosphate dibasic anhydrous, sodium phosphate monobasic dihydrate, and water for injection

CEQUA comes in the following dosage forms:

As a solution containing cyclosporine 0.9 mg / mL (0.09% w/v).

Do not use CEQUA if you:

- are allergic to cyclosporine or any of the other ingredients in CEQUA
- have an eye infection
- have a cancer or a precancerous condition in or around your eye

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CEQUA. Talk about any health conditions or problems you may have, including if you:

- have had a viral infection of the eye called herpes keratitis
- have any other eye disease

Other warnings you should know about:

Do not allow the tip of the vial to touch your eye or any other surface. Doing so may contaminate the solution or cause injury to the eye.

Contact Lenses:

Do not put CEQUA in your eyes while you are wearing contact lenses. Patients with dry eyes

should not typically wear contact lenses. If you must wear contact lenses, remove the lenses before applying CEQUA. Wait 15 minutes before you put your contact lenses back in.

Driving and using machines:
After applying CEQUA, your vision might be blurry for a while. If this happens, wait until your vision clears before you drive or use machinery.

Pregnancy and breastfeeding:
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you receive this medicine. If you are pregnant, CEQUA may pass to your baby in the womb. It may also pass to your baby through your breast milk. If you are pregnant or breastfeeding, your doctor will decide if you can receive this medicine.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take CEQUA:
- CEQUA is for use in the eyes only.
- Wash your hands before using CEQUA.
- Use CEQUA immediately after you open the vial. Each vial is for single use and the CEQUA solution should be used immediately after opening. You must discard whatever is left in the vial after you have applied your CEQUA drops to your eye(s).
- Do not let the tip of the vial touch your eye or any other surface.
- Always use CEQUA exactly as your healthcare professional has told you. Ask your healthcare professional if you are not sure.
- If you are using any other eye drops, wait at least 15 minutes after using them before using CEQUA. If you apply CEQUA first, wait 15 minutes before applying any other product, including artificial tears, to your eyes.
- Do not use this medication if the solution has visible particulate matter, or the vial is leaking or seems damaged.

Usual adult dose:
Apply one drop into each affected eye twice a day about 12 hours apart. Do not exceed two drops per day in the affected eye(s).

Overdose:

If you think you have taken too much CEQUA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to use CEQUA, skip that dose and continue with the next dose as planned. Do not double your dose to make up for the dose you forgot.

What are possible side effects from using CEQUA?
These are not all the possible side effects you may feel while using CEQUA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Eye pain
- Irritation or redness in or around the eye
- Swelling or redness on the edge of the eyelid
- Increased pressure in the eye
- Headache
- Swelling, itching or discomfort in or around the eye
- A feeling that there is something in your eye
- Watering of your eyes
- Blurred vision
- Sore throat

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Urinary tract infection: blood in urine, cloudy urine, frequent urination, pain or burning sensation when urinating, pain in the pelvis, strong smelling urine.		✓	
RARE			
Allergic Reaction: difficulty breathing, difficulty swallowing, fever, hives, itchy skin, loss of consciousness, rash, swelling of your tongue, throat or face.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature (15°C to 25°C). Do not freeze. Store single-use vials in the original foil pouch. Use contents immediately after opening a vial. Discard vial and unused contents after use.

Keep out of reach and sight of children.

If you want more information about CEQUA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sunpharma.com/canada, or by calling 1-844-924-0656.

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