NEW ZEALAND DATA SHEET

1 PRODUCT NAME

CEQUA™ ciclosporin 0.9 mg/mL (0.09% w/v) eye drops.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of CEQUA eye drops contains 0.9 mg of ciclosporin.

Excipients with known effects

This medicine contains 2.5 mg of phosphates in each ampoule which is equivalent to 10 mg/mL (4.7 mg of dibasic sodium phosphate and 5.3 mg of monobasic sodium phosphate dihydrate).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Eye drop. CEQUA is supplied as a sterile, clear, colourless solution for topical ophthalmic use. It has an osmolality of 160 to 190 mOsmol/kg and a pH of 6.5-7.2.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CEQUA is indicated to increase tear production in patients with moderate to severe keratoconjunctivitis sicca (dry eye) where prior use of artificial tears has not been sufficient.

4.2 Dose and method of administration

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

Instil 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 ampoule immediately after using in both eyes.

Response to treatment should be reassessed at least every 6 months.

4.3 Contraindications

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

Active or suspected ocular or peri-ocular infection (see Section 4.4 Special warnings and precautions for use).

Ocular or peri-ocular malignancies or premalignant conditions.

4.4 Special warnings and precautions for use

Potential for Eye Injury and Contamination

To avoid the potential for eye injury and contamination, advise patients not to touch the ampoule 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.

Patients wearing contact lenses have not been studied.

Careful monitoring of patients with severe keratitis is recommended.

Infections

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.

Effects on the immune system

Ophthalmic medicinal products, which affect the immune system, including ciclosporin, may affect host defences against local infections and malignancies. Therefore, regular examination of the eye(s) is recommended, e.g. at least every 6 months, when CEQUA is used for long periods.

Use in the elderly

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

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy – pregnancy Category B2

There are no adequate and well-controlled studies of CEQUA administration in pregnant women to inform a drug-associated risk. Oral administration of ciclosporin to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses (see Section 5.3 Preclinical safety data - animal data).

Lactation.

Ciclosporin blood concentrations are low following topical ocular administration of CEQUA (see Section 5.2 Pharmacokinetic properties). There is no information regarding the presence of ciclosporin in human milk following topical administration or on the effects of CEQUA on the breastfed infants and milk production. Administration of oral ciclosporin to rats during lactation did not produce adverse effects in offspring at clinically relevant doses (see Section 4.6 Fertility, pregnancy and lactation – Use in pregnancy). 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 breast-fed child from ciclosporin.

Fertility

Oral administration of ciclosporin 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).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

CEQUA was generally well tolerated. Across the pooled pivotal studies, subjects in the CEQUA group had a higher incidence of any adverse event (AE) (38.7% versus 27.1%) and of treatment-related AEs (25.2% versus 8.6%) compared with the Vehicle group. Most AEs, including ocular AEs, were mild (approximately 70% of all AEs in both the CEQUA and Vehicle groups) and did not require treatment. Serious adverse events were uncommon (1.1% in both treatment groups), and few subjects permanently discontinued study treatment due to an AE (CEQUA: 4.2 %, Vehicle: 1.7%).

Ocular AEs were reported in 30.9% of the CEQUA group and 17.9% of the Vehicle group. The disparity between the treatment groups was primarily driven by instillation site pain, the most common AE, which occurred in 21.8% of the CEQUA group versus 4.0% of the Vehicle group. The other common ocular AE (> 5%) was conjunctival hyperemia (CEQUA: 5.7%, Vehicle: 3.6%). All other ocular AEs were comparable between the treatment groups and were reported at low incidence (≤ 1.5%) in either group.

Non-ocular AEs were reported at a similar rate in the CEQUA and Vehicle groups (13.4% and 12.4%, respectively). The most common non-ocular AEs (> 1% of subjects in either group) were headache and urinary tract infection.

Clinical Trial Experience

OTX-101-2014-001 and OTX 101-2016-001 Pooled data
Safety data from the two 12-week pivotal studies, where a total of 524 subjects received CEQUA (Safety Population), were pooled to provide increased sensitivity and precision. Most subjects were treated between 9 and 13 weeks.

In the pooled data set, treatment-related adverse events (AEs) were reported by 132 subjects (25.2%) in the CEQUA group and 45 subjects (8.6%) in the Vehicle group. In both the CEQUA and Vehicle groups, nearly all treatment-related AEs were ocular (25.0% and 8.2%, respectively), with the only event occurring in > 2% of subjects in either group being instillation site pain. Treatment-related non-ocular AEs occurred at a similar frequency in the CEQUA and Vehicle groups (1.0% and 0.8%, respectively), and included headache, throat irritation, and dysgeusia. Refer to Table 1 for a tabulated summary of treatment-related AEs reported in ≥ 1% subjects in either treatment group.

Table 1: Treatment-related Adverse Events reported in ≥ 1% subjects in either treatment group in Pooled Data Set - (Safety Population)

	Pooled data		OTX-101-2014-001		OTX-101-2016-001	
Preferred Term	CEQUA (N=524)	Vehicle (N=524)	CEQUA (N=152)	Vehicle (N=152)	CEQUA (N=372)	Vehicle (N=372)
Any ocular AE, n (%)	131 (25.0)	43 (8.2)	30 (19.7)	12 (7.9)	101 (27.2)	31 (8.3)
Instillation site pain	113 (21.6)	20 (3.8)	23 (15.1)	4 (2.6)	89 (23.9)	16 (4.3)
Conjunctival hyperaemia	6 (1.1)	2 (0.4)	0	0	6 (1.6)	2 (0.5)
Eye irritation	6 (1.1)	1 (0.2)	3 (2.0)	1 (0.7)	3 (0.8)	5 (1.3)
Installation site reaction	4 (0.8)	3 (0.6)	0	1 (0.7)	4 (1.1)	2 (0.5)
Instillation site lacrimation	4 (0.8)	0	0	0	4 (1.1)	0
Eye pruritis	2 (0.4)	8 (1.5)	1 (0.7)	4 (2.6)	1 (0.3)	5 (1.3)

Any non-ocular AE, n (%)	5 (1.0)	4 (0.8)	0	1 (0.7)	5 (1.3)	3 (0.8)
No individual non-ocular AEs ≥ 1% in any treatment group						

OTX-101-2016-002 Safety Extension Study

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 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 treatment-related AEs in the full safety population for OTX-101-2016-002 did not reveal any new findings. There were no changes to the SAE profile. Instillation site pain remained the most commonly reported treatment-related AE. It was reported at a higher incidence, as expected, in subjects who had received Vehicle prior to being switched to CEQUA. Refer to Table 2 for a tabulated summary of treatment-related AEs reported in ≥ 1% subjects in either treatment group.

Table 2: Treatment-related Adverse Events reported in ≥ 1% of subjects in the OTX-101-2016-002 safety extension study – (Safety Population)

Prefered Term	Group 1 (N=129)	Group 2 (N=129)	Total (N=258)
Instillation site pain	17 (13.2)	42 (32.6)	59 (22.9)
Conjunctival hyperaemia	2 (1.6)	5 (3.9)	7 (2.7)
Installation site reaction	1 (0.8)	3 (2.3)	4 (1.6)
Instillation site lacrimation	1 (0.8)	3 (2.3)	4 (1.6)
Eye irritation	1 (0.8)	2 (1.6)	3 (1.2)
Lacrimation increased	0	2 (1.6)	2 (1.6)

Cases of corneal calcification have been reported very rarely in association with the use of phosphate-containing eye drops in some patients with significantly damaged corneas.

Post-Marketing Experience
Infections and Infestations
Urinary Tract Infection

Reporting of suspected adverse reactions

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 https://nzphvc.otago.ac.nz/reporting/}

4.9 Overdose

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

Pharmacotherapeutic group: Calcineurin inhibitors.

ATC code: S01XA18.

Mechanism of action

Ciclosporin 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 ciclosporin is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

Clinical efficacy and safety

Two multicentre, randomised, vehicle-controlled clinical studies treated 1,048 patients with keratoconjunctivitis sicca (OTX-101-2014-001 and OTX-101-2016-001). 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 3 presents data from the studies.

Tear Production				
	OTX-101-2014-001		OTX-101-2016-001	
	CEQUA N = 152	Vehicle N = 152	CEQUA N = 371	Vehicle N = 373
≥ 10-mm increase in tear production (% of eyes) at Day 84	16.8%	8.6%	16.6%	9.2%
Difference (95% CI), p-value	8.2% (1.9%, 14.6%), <0.01		7.3% (3.3%, 11.3%), <0.01	

5.2 Pharmacokinetic properties

Absorption

Blood concentrations of ciclosporin 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.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure that may occur with CEQUA indicating little relevance to clinical use.

Genotoxicity

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

Carcinogenicity

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.

Toxicity to reproduction and development

Oral administration of ciclosporin 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 21000 times higher than the maximum recommended human ophthalmic dose (MRHOD) of 1.5 mcg/kg/day, respectively. No adverse embryofoetal effects were observed in rats or rabbits receiving ciclosporin 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 ciclosporin (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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CEQUA eye drops contain the following excipients:

PEG-40 hydrogenated castor oil
octoxinol 40
povidone
dibasic sodium phosphate
monobasic sodium phosphate dihydrate
sodium chloride
water for injections
sodium hydroxide (for pH adjustment)
hydrochloric acid (for pH adjustment).

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C. Do not freeze. Store the ampoules in the original foil pouch. Protect from light.

6.5 Nature and contents of container

CEQUA ophthalmic solution is packaged in single-use LDPE ampoules. Each ampoule contains 0.25 mL of the solution.

CEQUA ampoules are packaged in cartons of 10 or 60 ampoules: 10 ampoules (2 cards of 5 ampoules) are packaged in a polyfoil aluminum pouch; 1 pouch (10s) or 6 pouches (60s) are packaged in the cartons.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

CARSL Consulting
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9 DATE OF FIRST APPROVAL

9 February 2023

10 DATE OF REVISION OF THE TEXT

10/03/2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Updated Post-Marketing Experience to include Urinary Tract Infection under Infections and Infestations