▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – CEQUA™ (CICLOSPORIN) EYE DROPS

1 NAME OF THE MEDICINE

Ciclosporin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CEQUA contains ciclosporin 900 microgram/mL as the active ingredient. It has an osmolality of 160 to 190 mOsmol/kg and a pH of 6.5-7.2.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Eye drops.

CEQUA is a sterile, clear, colourless solution, practically free from visible particulates.

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

For topical ophthalmic use.

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

Instil one drop of CEQUA twice daily (approximately 12 hours apart) into the affected eye(s).

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

CEQUA can be used concomitantly with artificial tears, allowing a 15-minute interval between products. Discard the ampoule immediately after using in both eyes.

4.3 CONTRAINDICATIONS

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

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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No data available.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Male and female fertility were unaffected by ciclosporin in rats at oral doses up to 15 mg/kg/day (more than 1500 times higher than the maximum recommended human ophthalmic dose, based on body surface area-adjusted doses for a 50 kg subject).

Use in pregnancy – Pregnancy Category C

There are no adequate and well-controlled studies of CEQUA administration in pregnant women. Studies in animals do not indicate a likely risk of embryofetal harm with ophthalmic

use of ciclosporin. No embryofetal toxicity was observed with ciclosporin at oral doses of 17 mg/kg/day in the rat and 30 mg/kg/day in the rabbit, which are approximately 1800 and 6200 times higher than the maximum recommended human ophthalmic dose (based on body surface area-adjusted doses for a 50 kg subject). Embryo- and fetotoxicity; as increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations, were observed in animals at higher oral doses that were maternally toxic (30 mg/kg/day in rats and 100 mg/kg/day in rabbits). The offspring of pregnant rabbits given ciclosporin subcutaneously at 10 mg/kg/day had reduced numbers of nephrons and exhibited renal hypertrophy, systemic hypertension and progressive renal insufficiency postnatally.

Use in 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. While systemically absorbed ciclosporin is excreted in milk, ciclosporin blood concentrations are low following topical ocular administration of CEQUA (see Section 5.2 Pharmacokinetic properties). Adverse effects in breast-fed infants are not expected given the low level of potential exposure but cannot be excluded. 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 OTX-101 0.09% (Safety Population), were pooled to provide increased sensitivity and precision. Most subjects were treated between 9 and < 13 weeks.

Subjects in the OTX-101 0.09% group had a higher incidence of any AE (38.7% versus 27.1%) and treatment-related AEs (25.2% versus 8.6%) compared with the Vehicle group. However, OTX-101 0.09% was generally well tolerated, with most AEs (approximately 70%), including ocular AEs, considered mild and did not require treatment. The most common AE was instillation site pain (OTX-101: 21.8%, Vehicle: 4.0%).

AEs 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 OTX-101 0.09% in OTX-101-2016-001 died from an unknown cause, but not considered to be related to study drug. Table 1 presents treatment-emergent adverse events (TEAEs) reported in ≥ 2% of subjects in the Safety Population.

Table 1: TEAEs reported in ≥ 2% of subjects in either treatment group in the Safety Population

	Pooled data		**OTX-101-2014-001**		**OTX-101-2016-001**	
Preferred Term	**OTX-101 0.09% (N=524)**	**Vehicle (N=524)**	**OTX-101 0.09% (N=152)**	**Vehicle (N=152)**	**OTX-101 0.09% (N=372)**	**Vehicle (N=372)**
Any ocular AE, n (%)	**162 (30.9)**	**94 (17.9)**	**37 (24.3)**	**28 (18.4)**	**125 (33.6)**	**66 (17.7)**
Instillation site pain	114 (21.8)	21 (4.0)	23 (15.1)	5 (3.3)	90 (24.2)	16 (4.3)
Conjunctival hyperaemia	30 (5.7)	19 (3.6)	0	0	30 (8.1)	19 (5.1)
Eye irritation	6 (1.1)	6 (1.1)	3 (2.0)	1 (0.7)	3 (0.8)	5 (1.3)
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 (%)	**70 (13.4)**	**65 (12.4)**	**21 (13.8)**	**32 (21.1)**	**49 (13.2)**	**33 (8.9)**
Upper respiratory tract infection	4 (0.8)	5 (1.0)	3 (2.0)	2 (1.3)	1 (0.3)	2 (0.5)
Nasopharyngitis	1 (0.2)	5 (1.0)	1 (0.7)	4 (2.6)	0	1 (0.3)

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 OTX-101 0.09%. Of these, 129 subjects had previously received OTX-101 0.09% (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 OTX-101 0.09%, including 138 subjects who had ≥12 months of total exposure. The overall mean duration of exposure was 10.42 months.

An analysis of 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 AE. It was reported at a higher incidence, as expected, in subjects who had received Vehicle prior to being switched to OTX-101 0.09%.

Besides instillation site pain (22.9%), conjunctival hyperemia (10.1%), and punctate keratitis (6.2%) were the most commonly reported TEAEs. 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. Table 2 presents the TEAEs reported in ≥ 2% of total subjects.

Table 2: TEAEs Reported in ≥ 2% of subjects in the OTX-101-2016-002 Safety Extension Study

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	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)
Bronchitis	2 (1.6)	4 (3.1)	6 (2.3)
Posterior capsule opacification	5 (3.9)	1 (0.8)	6 (2.3)
Instillation site reaction	1 (0.8)	3 (2.3)	4 (1.6)
Instillation site lacrimation	1 (0.8)	3 (2.3)	4 (1.6)
Osteoarthritis	3 (2.3)	1 (0.8)	4 (1.6)
Sinusitis	0	4 (3.1)	4 (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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

Clinical trials

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.

Table 3

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

Genotoxicity

Ciclosporin was not 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. An *in vitro* sister chromatid exchange (SCE) assay using human lymphocytes gave indications of a positive effect for ciclosporin at high concentrations.

Carcinogenicity

Systemic carcinogenicity studies were carried out in mice and rats. A 78-week mouse study, at oral doses of 1, 4, and 16 mg/kg/day, revealed a trend for increased incidences of lymphomas at the highest dose studied. In another study with ARK mice treated with ciclosporin at 150 mg/kg in the diet, ciclosporin accelerated the development of lymphomas.

In a 24-month rat study, conducted at oral doses of 0.5, 2, and 8 mg/kg/day, no significant increase in tumour incidence was observed. Adjusted for body surface area, the highest doses without tumourigenic effect in the mouse and rat are approximately 210 and 830 times higher than the maximum recommended ophthalmic dose of ciclosporin provided by CEQUA therapy.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

PEG-40 hydrogenated castor oil, octoxinol 40, povidone, dibasic sodium phosphate, monobasic sodium phosphate dihydrate, sodium chloride, water for injections and sodium hydroxide or hydrochloric acid to adjust pH.

6.2 INCOMPATIBILITIES

CEQUA should not be administered to patients while they are wearing contact lenses (see Section 4.4 Warnings and precautions for use).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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. The carton of 10 ampoules is a sample pack only.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

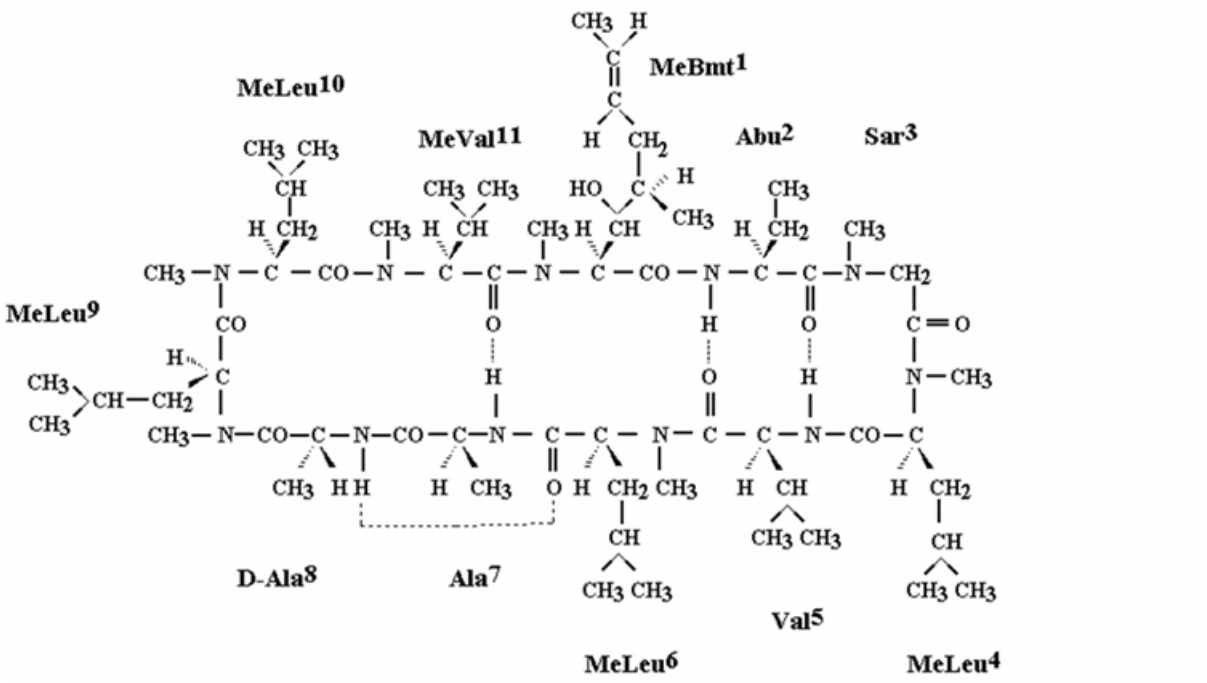
In Australia, any unused medicine or waste material can be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Ciclosporin is a white powder that is insoluble in water and freely soluble in ethanol.

Chemical structure

Mol. Formula: $C_{62}H_{111}N_{11}O_{12}$ Mol. Wt.: 1202.6



CAS number

59865-13-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only medicine.

8 SPONSOR

Sun Pharma ANZ Pty Ltd
12 Waterloo Road
Macquarie Park, Sydney NSW 2113
Australia

Tel: 1800 726229
Email: customerservice.aus@sunpharma.com

9 DATE OF FIRST APPROVAL

31 January 2020

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information