SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cequa® 0.9 mg/mL eye drops, solution in single-dose container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 0.9 mg of ciclosporin

One mL of the medicinal product contains 0.9 mg ciclosporin and each single-dose container contains 0.25 mL of drug product.

Therefore, each single-dose container contains 0.225 mg of ciclosporin. Accordingly, each eye drop (approximately 0.025 mL) contains 0.0225 mg of ciclosporin.

Excipient(s) with known effect

One drop of solution contains 0.159 mg phosphates.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution in single-dose container

Clear, colourless solution with a pH of 6.5 to 7.2 and osmolality of 160-190 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate-to-severe Dry Eye Disease (keratoconjunctivitis sicca) in adult patients who have not responded adequately to artificial tears (see Section 5.1).

4.2 Posology and method of administration

Treatment must be initiated by an ophthalmologist or a healthcare professional qualified in ophthalmology. The response to treatment should be reassessed at least every 3 months.

Posology

The recommended dose is one drop of this medicine twice daily (approximately 12 hours apart) into the affected eye(s).

Special populations

Elderly population

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

Patients with renal or hepatic impairment

The safety and efficacy of this medicine has not been studied in patients with hepatic or renal impairment. However, the systemic exposure to ciclosporin associated with the use of this medicine is very low (see section 5.2), and no special considerations are needed in these populations.

Paediatric population

The effect of this medicine has not been studied in children. There is no relevant use of this medicine in the treatment of signs of moderate to severe dry eye disease in the paediatric and adolescent population aged below 18 years.

Method of administration

For ocular use.

Precautions to be taken before administering the medicinal product

Patients should be instructed to first wash their hands.

Each Cequa single-dose container is for single use for both eyes in one patient only.

Patients should be instructed to use nasolacrimal occlusion and to close the eyelids for 2 minutes after instillation, to reduce the systemic absorption. This may result in an increase in local activity and decrease in systemic undesirable effects.

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

To avoid the potential for eye injury and contamination, advise patients not to touch the single-dose container tip to the eye or other surfaces.

4.3 Contraindications

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

Ocular or peri-ocular malignancies or premalignant conditions.

Active or suspected ocular or peri-ocular infection (see section 4.4).

4.4 Special warnings and precautions for use

Use with Contact Lenses

Cequa has not been studied in patients 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 this medicine ophthalmic solution.

Concomitant therapy

Ciclosporin treatment experience in patients with glaucoma is limited. When treating these patients concomitantly with this medicine it is recommended to have a regular clinical monitoring, especially with beta-blockers which are known to decrease tear secretion.

Infections

Resolve existing or suspected ocular or peri-ocular infections before initiating Cequa treatment. If an infection occurs during treatment, this medicine 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. A regular examination of the eye(s) is recommended.

Phosphates content

Cequa contains phosphates. Phosphates may cause in very rare cases cloudy patches on the cornea due to calcium build-up during treatment.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with this medicine.

Combination with other medicinal products that affect the immune system

Co-administration of ciclosporin with eye drops containing corticosteroids could potentiate the effects of ciclosporin on the immune system (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females.

Cequa is not recommended in women of childbearing potential not using effective contraception.

Pregnancy

There are no adequate and well-controlled studies of Cequa administration in pregnant women.

Studies in animals have shown reproductive toxicity following systemic administration of ciclosporin at exposure considered sufficiently in excess of the maximum human exposure indicating little relevance to the clinical use of this medicine.

This medicine is not recommended during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.

Breastfeeding

Information on the effects of ciclosporin in newborns/infants is very limited; considering the therapeutic doses of ciclosporin in eye drops, it is unlikely that sufficient amounts would be present in breast milk. Therefore, 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 ciclosporin and any potential adverse effects on the breast-fed child from ciclosporin.

Fertility

There are no data on the effects of ciclosporin on human fertility.

No impairment of fertility has been reported in animals receiving intravenous ciclosporin or oral ciclosporin up to high doses (see section 5.3).

4.7 Effects on ability to drive and use machines

Eye drops may induce temporary blurred vision and influence the ability to drive or operate machines. Patients should be advised not to drive or operate machines until their vision is cleared.

4.8 Undesirable effects

a. Summary of the safety profile

The primary assessment of safety for this medicine is based on vehicle-controlled studies. Supportive safety data are provided by the uncontrolled safety extension of one study for long term usage, and a Phase 1 study in healthy volunteers. In the vehicle controlled clinical studies over 520 patients were treated with this medicine. The most common adverse reactions are instillation site pain (21.6% vs 3.8% of subjects in the vehicle group), observed immediately after administration of this

medicine, conjunctival hyperaemia (5.7% vs 3.6% in the vehicle group), and eye irritation (1.1% vs 0.2% in the vehicle group).

The majority of adverse reactions reported in clinical studies with the use of this medicine were ocular and predominantly mild in intensity (approximately 70% of the AEs in both treatment groups were mild), **and in most cases resolved without treatment or sequelae.** Adverse events of severe intensity were uncommon.

AEs leading to discontinuation of study drug (4.2% versus 1.7%) were low across the OTX-101 and Vehicle groups.

Long term (9 to ≥12months exposure) safety data was available from 220 patients. No new adverse reactions were identified in these patients.

The following adverse reactions listed below were observed in clinical studies. They are ranked according to system organ class and classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data).

b. Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reactions
Eye disorders	Common	Conjunctival hyperaemia, eye irritation
	Uncommon	Increased lacrimation, punctate keratitis, photophobia, eye pain, conjunctival oedema, blepharitis, ocular and periocular infections
	Very rare	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.
General disorders and administration site conditions	Very common	Instillation site pain*
	Common	Instillation site reaction Instillation site lacrimation
	Uncommon	Instillation site dryness, instillation site pruritus, headache, and throat irritation

* See section 4.8c

c. Description of selected adverse reactions

Instillation site pain

Instillation site pain was very common observed in users of Cequa. Typically, it occurs immediately after instillation but is of a short duration (seconds to a few minutes), and resolves without further action being required.

Instillation pain was predominantly mild: of the 21.6% patients with instillation site pain, 17.8% experienced mild instillation site pain.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

A topical overdose is not likely to occur after ocular administration. If overdose with this medicine occurs, treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action and pharmacodynamic effects

Ciclosporin is a calcineurin inhibitor with immunosuppressant and anti-inflammatory activity. It inhibits the activation of transcription factors required for T-cell activation and inflammatory cytokine production, including interleukin 2 (IL-2) and T-cell growth factor (TCGF). It may also upregulate the release of anti-inflammatory cytokines.

In Dry Eye Disease (DED), which involves an inflammatory mechanism, ciclosporin absorbed into T-lymphocytes in the ocular surface inactivates calcineurin phosphatase, thus blocking the release of pro-inflammatory cytokines, such as IL-2.

Clinical efficacy Clinical trials

The efficacy and safety of Cequa was established in two separate, randomised, double-masked, vehicle-controlled, clinical trials involving a total of 1,200 adult patients with moderate to severe DED (SANDE score ≥40) and symptoms present for 6 months or longer. Of these, a total of 524 patients were treated with Cequa, 525 with vehicle. In the efficacy studies, patients were treated 2x daily for 12 weeks. Patients were also required to have bilateral DED supported by the presence of lissamine green conjunctival staining score of ≥ 3 to ≤ 9 out of 12 (NEI scale).

The results of these studies were consistent and are summarised in Table 1.

Table 1 Summary of Key Efficacy Results

Parameter		OTX-101-2014-001[1]	OTX-101-2016-001

		OTX-101	Vehicle	P-value	OTX-101	Vehicle	p-Value
N[2] (Enrolled/completed)		152/140	152/144		372/347	373/361	
Schirmer's Test increase ≥10mm (%)[3]							
Overall		16.8%	8.6%	0.0021	**16.6%**	**9.2%**	**0.0001**
B/L <5mm		20.8	8.9		20.4	10.2	
B/L 5 - 9mm		18.8	10.8		17.3	10.1	
B/L ≥ 10mm		13.9	6.8		14.8	8.5	
Mean Schirmer's Test (mm)							
Mean (SD)	B/L	12.3 (8.67)	12.2 (8.25)		11.89 (7.77)	12.09 (7.73)	
LS Mean (SE)	Δ B/L	3.5 (0.61)	0.4 (0.60)	0.0003	2.80 (0.28)	0.99 (0.27)	<0.0001
LGS Total (Max score = 12)							
Mean (SD)	B/L	5.40 (1.75)	5.52 (1.665)		5.42 (1.714)	5.52 (1.767)	
LS mean (SE)	Δ B/L	**-1.57 (0.133)**	**-0.83 (0.131)**	**<0.0001**	-1.54 (0.082)	-1.15	0.0007
LGS Temporal zone (Max Score = 4)							
Mean (SD)	B/L	0.92 (0.612)	0.90 (0.627)		0.92 (0.639)	1.00 (0.666)	
LS mean (SE)	Δ B/L	-0.34 (0.042)	-0.11 (0.041)	0.0001	-0.33 (0.027)	-0.21 (0.027)	0.0030
LGS Complete Clearing (Temporal zone) [3]							
		55.4%	37.2%	≤0.0001	52.9%	45.6%	0.0049
CFS score Total (Max Score = 20**)**							
Mean (SD)	B/L	4.40 (2.847)	4.42 (2.636)		4.06 (2.374)	4.30 (2.650)	
LS mean (SE)	Δ B/L	-1.33 (0.149)	-0.43 (0.147)	<0.0001	-1.47 (0.075)	-1.11 (0.074)	0.0007
CFS Score Central (Max Score =4)							
Mean (SD)	B/L	0.76 (0.708)	0.75 (0.704)		0.60 (0.597)	0.69 (0.705)	
LS mean (SE)	Δ B/L	-0.28 (0.039)	-0.09 (0.039)	0.0005	-0.30 (0.019)	-0.24 (0.019)	0.0159
CFS Complete Clearing central (%)[3]							
		50.7%	43.8%	0.0777	65.0%	56.9%	0.0022

B/L = Baseline; Δ B/L = Change from Baseline; LGS = Lissamine Green Staining (Conjunctiva), CFS = Corneal Fluoresceine Staining

1 Reanalysed to facilitate comparison with OTX-101-2016-001.

2 N= Intent to Treat population

3 n = number of subjects with only one eye + 2 times number of subjects with both eyes responding. Denominator is 2 times the number of subjects.

OTX-101-2014-001, was a dose finding study with 2 co-primary efficacy endpoints of mean change from baseline at Day 84 for total conjunctival staining score in the

designated study eye and Global SANDE symptom score. In OTX-101-2016-001, the primary efficacy endpoint was the proportion of patients with an increase of ≥10mm from baseline in Schirmer's test score at Day 84 based on data for both eyes. Other key secondary and additional efficacy variables 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.

The results from both clinical studies were consistent (See Table 1). Cequa was superior to its vehicle with respect to increased tear production: a higher proportion of subjects treated with Cequa responded with an increase in Schirmer's test of ≥10mm compared to vehicle treated subjects, and the increase in LS Mean Schirmer's results was higher in the Cequa treated group. Cequa treated patients showed superior improvement in corneal damage using fluorescein staining (decrease in LS Mean Total CFS score, Clearing of CFS in the central region of the cornea and reduction of LS Mean CFS Score for central region) compared to vehicle treated subjects. Conjunctival damage (with lissamine green staining) in the Cequa treated group was reduced more significantly than in the vehicle treated group as demonstrated by comparison of LS Mean LGS scores for overall and for the temporal region of the conjunctiva, and of clearing of LGS in the temporal region. The effect noted for ocular surface improvement (both corneal and conjunctival staining) was noted within 28 days and was maintained for the duration of the studies.

Both Cequa and its Vehicle improved symptoms (SANDE score) by approximately 30% with no statistical difference between them.

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. Blood ciclosporin levels remained much lower than therapeutic/toxic levels, and never exceeded 0.2 ng/mL.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogolglycerol
hydroxystearate Octoxynol-40
Sodium dihydrogen phosphate dihydrate (E339)
Disodium phosphate (E339)
Sodium chloride
Povidone (E1201)
Hydrochloric acid (for pH adjustment) (E507)
Sodium hydroxide (for pH adjustment) (E524)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf life: 24 months
Shelf life after first opening of the aluminium pouch: 5 days

6.4 Special precautions for storage

Store below 25°C. Do not freeze. Store the single-dose containers in the polyfoil aluminium pouch.

Any opened individual single-dose container with any remaining solution should be discarded immediately after use.

6.5 Nature and contents of container

Cequa 0.9 mg/mL eye drops, solution, is packaged in single-dose, low-density polyethylene (LDPE) containers. Each single-dose container contains 0.25 mL of the solution.

Cequa single-dose containers are packaged in cartons of 60 single-dose containers: 10 single-dose containers (2 cards of 5 single-dose containers) are packaged in a polyfoil aluminium pouch; 6 pouches (60s) are packaged in the cartons.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 14894/0821

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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