Health Technology Briefing
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Ciclosporin ophthalmic solution for treating moderate-to-severe keratoconjunctivitis sicca (dry eye disease)

Company/Developer	Sun Pharmaceutical Industries Europe BV

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 10484	NICE ID: 8472	UKPS ID: 672065

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Ciclosporin A (CsA) ophthalmic solution is currently in clinical development for treating adult patients with moderate-to-severe Keratoconjunctivitis Sicca, also known as dry eye disease (DED). Dry eye is caused by a problem with tears and the ocular surface which develops when the eye does not produce enough tears, or the tears are not of the right quality, or the tears do not spread across the front of the eye properly when blinking. This would affect the quality of the tear film and cause potential damage to the ocular surface. DED is usually more common as people get older, although it can occur at any age, it is more common in women, especially after menopause or during pregnancy due to hormonal changes. Symptoms of DED include discomfort, redness, itchy, dryness, pain, foreign body sensation, irritation, and watery eyes. Typically, this condition does not cause a permanent change in vision but may blur eyesight for short periods. There is no cure for dry eye, but treatments can help the eyes feel more comfortable and keep symptoms at bay.

Ciclosporin A is a novel, unique nanomicellar solution formulation of CsA that delivers the drug to the ocular tissue. It has been shown to be effective in alleviating the symptoms of DED by reducing ocular surface inflammation and damage in clinical research. If licensed, Ciclosporin A would provide an additional treatment option for adult patients with DED.

Proposed Indication

Treatment of adults with keratoconjunctivitis sicca.[1,2]

Technology

Description

Ciclosporin A (Cequa, Seciera, OTX-101) is a calcineurin inhibitor that exerts immunomodulatory effects by blocking T-cell infiltration, activation, and the subsequent release of inflammatory cytokines. Ciclosporin A (CsA) enters the cytoplasm of T cells, binds to cyclophilin, and forms a ciclosporin/cyclophilin complex that prevents calcineurin-mediated de-phosphorylation of nuclear factor of activated T cells and the transcription of cytokine genes, including those of IL-2 and IL-4. CsA additionally inhibits p38 activation and JNK activation, which leads to IL-2 production. The subsequent reduction in IL-2 levels further reduces the function of effector T cells.[3] The action of CsA on T cells is the primary mechanism for DED symptom improvement. CsA protects human conjunctival epithelial cells via its anti-apoptotic action, as well as improves conjunctival goblet cell density and corneal surface integrity via its immunomodulatory activities.[4,5]

CsA is in clinical development for the treatment of adult patients with DED. In the phase III trial (NCT02688556), 0.09% ciclosporin nanomicellar ophthalmic solution was administered twice daily to treat DED in adult participants.[2]

Key Innovation

Drug delivery to the intraocular tissues continues to be a challenging task, further complicated by the poor aqueous solubility of CsA which presents technical challenges in drug delivery to the ocular surface. Recent advancements in nanotechnology-based novel delivery systems are being designed to fulfil these unmet needs.[4,6] Ciclosporin A ophthalmic solution is a unique formulation of CsA, a novel, patented nanomicellar drug delivery technology.[7] Ocular delivery of CsA is enhanced as the novel formulation optimises the encapsulation of CsA in the micelle core through hydrophobic interaction, thereby improving bioavailability and delivering the drug to the ocular surface.[8]

Topical CsA provides a broad-based approach to DED treatment by decreasing inflammation and improving ocular surface integrity with few systemic effects.[4] If licensed, CsA would provide an additional treatment option for adult patients with DED.

Regulatory & Development Status

Ciclosporin 0.09% ophthalmic solution does not currently have marketing authorisation in the EU/UK for any indication. Ciclosporin 1mg/ml ophthalmic emulsion is marketed in the EU/UK for severe DED.[9]

Oral ciclosporin is marketed in the EU/UK for the following indications: [9]

- Severe active rheumatoid arthritis
- severe atopic dermatitis
- Severe psoriasis
- Organ transplantation

- Nephrotic syndrome
- Prevention and treatment of graft-versus-host disease

Intravenous ciclosporin is marketed in the EU/UK for the following indications:[9]

- Severe acute ulcerative colitis
- Prevention and treatment of graft-versus-host disease

Ciclosporin 0.09% ophthalmic solution received marketing authorisation from the U.S. Food and Drug Administration (FDA) in 2018, for increase in tear production in adult patients with DED.[10]

Patient Group

Disease Area and Clinical Need

DED is a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play aetiological roles.[11] DED develops when natural tears are insufficient, or the tears aren't of the right quality, or if tears don't spread across the front of the eye properly. Blinking helps to spread a thin layer of liquid called the tear film, over the front surface of the eye. The tear film is made up of three layers: the mucin (mucous) layer, the aqueous (watery) layer, and the lipid (oily) layer. Each one of these layers is needed to keep the tear film healthy. Anything that affects the structure and balance of the tear film can potentially cause dry eye.[12] The risk factors for developing DED are blepharitis and meibomian gland dysfunction, some inflammatory health conditions like rheumatoid arthritis and Sjögren's syndrome, certain medications such as antihistamines, eye surgery or eye injury, cigarette smoking, alcohol, and environmental changes.[13,14] Symptoms of DED are itchy, sore, gritty, red, blurry, sensitive to light, and more watery eyes compared to normal.[13]

According to Vidal-Rohr et al (2023), approximately one-third of the adult UK population have DED, female sex, systemic/ocular health conditions, short sleep duration, and prolonged outdoor leisure time are positive predictors of DED.[15] In England in 2022-2023, there were 7,537 finished consultant episodes (FCE) for disorders of the lacrimal system (ICD-10 code H04) resulting in 7,483 hospital admissions, 1,069 FCE bed days, and 6,636 day cases.[16]

Recommended Treatment Options

NICE recommendations include:[17,18]

- Artificial tears eyedrops containing Hypromellose or carbomers or polyvinyl alcohol for mild DED (preservative-free tear replacement is preferred);
- Ocular lubricants containing sodium hyaluronate, hydroxypropyl guar, or carmellose sodium for moderate to severe DED;
- Eye ointments containing liquid paraffin with white soft paraffin and wool alcohol for recurrent corneal epithelial erosion (preferably at night) in addition to other options to lubricate the eye surface;
- Ciclosporin 1mg/ml for treating severe keratitis that has not improved despite treatment with artificial tears.

Clinical Trial Information

Trial	**Emerald;** NCT02688556; A randomised, multicentre, double-masked, vehicle-controlled study of the safety and efficacy of OTX-101 in the treatment of keratoconjunctivitis sicca. **Phase III** - Completed **Location** - US **Study completion date** - December 2016
Trial Design	Randomised, double-masked, parallel assignment
Population	N=745; adult participants 18 years and older; a history of keratoconjunctivitis sicca (KCS) for at least 6 months and clinical diagnosis of bilateral KCS.
Intervention(s)	0.09% cyclosporine nanomicellar ophthalmic solution, 1 drop of OTX-101 in both eyes twice daily.[19]
Comparator(s)	Placebo-vehicle of cyclosporine nanomicellar ophthalmic solution
Outcome(s)	Primary outcome(s): • Tear production [time frame: baseline and 12 weeks]: percentage of eyes with increase from baseline of ≥ 10 mm in Schirmer's Test Score See trial record for full list of other outcomes.
Results (efficacy)	The primary endpoint was achieved; a significantly greater percentage of eyes in the OTX-101 0.09% treatment group achieved an increase of 10 mm or more in the Schirmer test score at day 84 (OTX-101 0.09%, 16.6%; vehicle, 9.2%; $P < 0.001$). Significant improvements relative to vehicle also were observed for corneal (days 28, 56, and 84) and conjunctival (days 56 and 84) staining.[20]
Results (safety)	The OTX-101 0.09% formulation was well tolerated. Treatment-emergent adverse events were primarily mild in intensity.[20]

Clinical Trial Information	
Trial	NCT02254265; A randomized, multicentre, double-masked, vehicle-controlled, dose-ranging study of the safety and efficacy of OTX-101 in the treatment of keratoconjunctivitis sicca **Phase II/III** - Completed **Location** - US **Study completion date** - May 2015
Trial Design	Randomised, double-masked, parallel assignment
Population	N= 455; adult participants 18 years and older; a history of KCS for at least 6 months and clinical diagnosis of bilateral KCS.
Intervention(s)	OTX-101 0.05% ophthalmic solution 1 drop in both eyes twice a day for 84 days OTX-101 0.09% ophthalmic solution 1 drop in both eyes twice a day for 84 days
Comparator(s)	Vehicle of OTX-101 ophthalmic solution 1 drop in both eyes twice a day for 84 days

Outcome(s)	Primary outcome(s): • Conjunctival staining [time frame: baseline to 84 days]: mean change from baseline at day 84 for the lissamine green conjunctival staining score in the designated study eye. • Global symptom score [time frame: baseline to 84 days]: mean change from baseline at day 84 for the global symptom score. See trial record for full list of other outcomes.
Results (efficacy)	Subjects treated with active drug experienced greater improvement in conjunctival staining than vehicle-treated patients (P<0.01 for both concentrations). All groups demonstrated improvements in global symptom score, but there were no differences among groups. Nominally significant differences were found between the active drug arms and vehicle for corneal staining scores and Schirmer's test scores. OTX-101 0.09% demonstrated a notable impact on multiple signs of KCS relative to the vehicle.[21]
Results (safety)	Most treatment-emergent adverse events were mild in severity; no serious ocular adverse events were reported.[21]

Estimated Cost

The cost of CsA is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Ciclosporin 1mg/ml (Ikervis) for treating dry eye disease that has not improved despite treatment with artificial tears. (TA369) December 2015

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Specialised Ophthalmology (adults) D12/S/a

Other Guidance

- NHS Bath and Northeast Somerset, Swindon and Wiltshire Together. Prescribing guidelines for dry eye. 2023[22]
- NHS Commissioning Alliance (North place) Crawley, East Surrey, Horsham and mid-Sussex. Prescribing guidelines for dry eye management agreement. 2019.[23]

Additional Information

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