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Horizon Scanning Research & Intelligence Centre

Lifitegrast for dry eye disease

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Lay summary

Lifitegrast is a new drug to treat the signs and symptoms of dry eye disease. Dry eye disease occurs when the eyes do not make tears properly, the tears are not of the correct consistency, or tears evaporate too quickly. This leads to inflammation in the front surface of the eye, and discomfort or problems with vision. Lifitegrast is taken as an eye drop and prevents inflammation of the eye.

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TARGET GROUP

- Dry eye disease: moderate to severe; patients for whom current therapeutic options are insufficient – second and subsequent line.

TECHNOLOGY

DESCRIPTION

Lifitegrast (Xiidra; lifitegrast sodium; SAR1118; SHP606; SPD606) is a lymphocyte function-associated antigen-1 (LFA-1) antagonist. It inhibits T-cell inflammation by blocking the binding of two key surface proteins (LFA-1 and ICAM-1) that mediate the chronic inflammatory cascade associated with dry eye disease. In a phase III clinical trial, lifitegrast 5% ophthalmic solution (50 mg/mL) is administered as a single 0.2mL eye drop twice a day into each eye for an 84 day treatment period[1,2].

Lifitegrast does not currently have Marketing Authorisation in the EU for any indication. Lifitegrast is licensed for use in the USA for treatment of the signs and symptoms of dry eye disease. The most common adverse reactions (incidence 5-25%) reported following the use of lifitegrast are instillation site irritation, dysgeusia, and decreased visual acuity[2].

INNOVATION and/or ADVANTAGES

If licensed, lifitegrast will offer an additional topical treatment option for the signs and symptoms of dry eye disease.

DEVELOPER

Shire Pharmaceuticals Limited.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Dry eye disease (also known as dry eye syndrome, keratoconjunctivitis sicca, dysfunctional tear syndrome, lacrimal keratoconjunctivitis, evaporative tear deficiency, aqueous tear deficiency, and LASIK-induced neurotrophic epitheliopathy) occurs when the eye does not produce tears properly, or when the tears are not of the correct consistency and evaporate too quickly[3]. Dry eye disease can be associated with: inflammation of the surface of the eye, the lacrimal gland, or the conjunctiva; any disease process that alters the components of the tears; an increase in the exposed surface area of the eye, as in thyroid disease when the eye protrudes forward; or cosmetic surgery, if the eyelids are opened too widely[3].

The symptoms of dry eye disease may include: stinging or burning of the eye; a sandy or gritty feeling as if something is in the eye; episodes of excess tears following very dry eye periods; a stringy discharge from the eye; pain and redness of the eye; episodes of blurred

vision; a feeling of heavy eyelids; inability to cry when emotionally stressed; discomfort on wearing contact lenses; decreased tolerance to reading, working on the computer, or any activity that requires sustained visual attention; and eye fatigue[3]. In addition, inflammation of the surface of the eye may occur along with dry eye disease [3]. If left untreated, this condition can lead to pain, ulcers, or scars on the cornea, and ultimately some loss of vision[3]. However, permanent loss of vision from dry eye disease is uncommon[3].

CLINICAL NEED and BURDEN OF DISEASE

The prevalence of dry eye disease is difficult to estimate as there is no defined diagnostic test[4]. Although it can affect people of any age, it is more prevalent in women and in older people[4]. The prevalence of dry eye disease in England has been estimated to be 965,794, with 6% of this population having severe dry eye disease that has not improved despite treatment with artificial tears (equating to 57,948 people)[4]. In 2014, there were 12,820 admissions for disorders of lacrimal system (H04) in England, resulting in 2,030 bed days and 12,879 finished consultant episodes[5].

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal. Ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears (TA369). December 2015.
- NICE advice. TearLab osmolarity system for diagnosing dry eye disease (MIB47). December 2015.
- NICE advice. LipiFlow thermal pulsation treatment for dry eyes caused by blocked meibomian glands (MIB29). April 2015.

NHS England Policies and Guidance

- NHS England. 2013/14 NHS Standard Contract for Specialised Ophthalmology (Adult). D12/S/a.
- NHS England. 2013/14 NHS Standard Contract for Ophthalmic Pathology Service (All Ages). D12/S(HSS)/b.
- NHS England. 2013/14 NHS Standard Contract for National Artificial Eye Service (All Ages). D01/S/e.

Other Guidance

- The College of Optometrists. Dry Eye Management. 2013[6].
- American Academy of Ophthalmology. Dry Eye Syndrome Preferred Practice Pattern. 2013[7].

CURRENT TREATMENT OPTIONS

There is currently no cure for dry eye disease, therefore management aims to relieve discomfort and prevent damage to the cornea[4]. Some people may have recurring episodes for the rest of their lives. The exact treatment for dry eye disease depends on whether symptoms are caused by decreased production of tears, tears that evaporate too quickly or

are a complication of an underlying condition, which should also be managed to improve symptoms.

Current treatment options include[3,6,8]:

- Wearing glasses or sunglasses that fit close to the face or that have side shields – can help slow tear evaporation from the eye surfaces.
- Changing the air indoors – an air cleaner filters dust and other particles to help prevent dry eyes. A humidifier may help by adding moisture to the air.
- Avoiding dry conditions and allowing eyes to rest regularly.
- Omega-3 fatty acids supplements – decreases symptoms of irritation in some patients.
- Lubricant treatments – offer temporary relief and provide a replacement of naturally produced tears in patients with aqueous tear deficiency.
    - Preservative-free drops – for severe dry eye disease that requires long term regular applications or for soft contact lens wearers.
    - 'Oily' tear eye drops – for blepharitis or dry eye disease caused by tears evaporating too quickly. Oily eye drops replenish the oily part of the tear film and reduce evaporation from the surface of the eye.
    - Eye ointments – lubricates the eyes and keeps them moist overnight.
- Anti-inflammatory treatments – treat the inflammation in and around the eye which is a result of long-term dry eye disease. Expert opinion suggests that in the UK there are only a few clinical options available for the management of the inflammatory component of dry eye disease[a].
    - Corticosteroid eye drops and ointments – used in cases of severe dry eye disease; short term use decreases inflammation. Expert opinion notes that topical corticosteroid use can increase the risks of developing a cataract, raised intraocular pressure that could lead to a blinding optic neuropathy, and geographical ulceration in the presence of active herpes simplex virus in the cornea[a]. Topical corticosteroid treatments should not be prescribed without ophthalmological surveillance by the Hospital Eye Services[a].
    - Oral tetracyclines – low dose tetracyclines can be used as anti-inflammatory agents (the most common tetracycline used is doxycycline, but others, such as oxytetracycline and lymecycline, are sometimes also prescribed).
    - Ciclosporin – an immunosuppressive medication. It is the only drug specifically licensed to treat dry eye disease (licensed as Ikervis). It decreases corneal damage, increases basic tear production, and reduces symptoms of dry eye disease.
    - Topical tacrolimus – a dermal preparation which is used to the eyelid margin in severe immune-mediated dry eye disease. Tacrolimus is not licensed for ocular use.
- Lacrimal plugs – for severe dry eye disease cases. These plug the drainage holes at the inner corners of the eyelids where tears drain from the eye into the nose.
- Punctal cautery – for severe dry eye disease cases. This permanently closes the drainage holes.
- Serum eye drops may be required in very rare cases where all other medications have not worked. These are made using components of the patient's blood or blood from a donor. They provide nutritional factors which other lubricants do not provide (such as growth factors, anti-oxidants, vitamins and glucose); these factors have anti-inflammatory properties[a].
- Salivary gland autotransplantation – an uncommon procedure that is usually only recommended after all other treatment options have been tried. This procedure involves removing some of the glands that produce saliva from the lower lip and placing them

[a] Expert personal opinion

under the skin around the eyes. The saliva produced by the glands acts as a substitute for tears.

- Scleral contact lenses – contact lenses which are supported on the sclera lifted away from the cornea, they create a reservoir that captures natural tears or therapeutically applied lubricants and other treatments, to improve the health of the ocular surface. These are only available in highly specialised treatment centres[b].
- Amniotic membrane – amniotic membrane is stitched on to the surface of the eye to create a biological bandage. This can reduce inflammation, curbs scarring, and promotes healing[b].

EFFICACY and SAFETY

Trial	NCT00926185, 1118-KCS-100; lifitegrast vs placebo; phase II.	OPUS-1, NCT01421498, 1118-KCS-200; lifitegrast vs placebo; phase III.	OPUS-2, NCT01743729, 1118-DRY-300; lifitegrast vs placebo; phase III.
Sponsor	Shire.	Shire.	Shire.
Status	Published.	Published.	Published.
Source of information	Publication[9], trial registry[10].	Publication[11], Trial registry[12].	Publication[13], trial registry[14].
Location	USA.	USA.	USA.
Design	Randomised, placebo-controlled.	Randomised, placebo-controlled.	Randomised, placebo-controlled.
Participants	n=230; aged ≥18 yrs; patient-reported history of dry eye disease in both eyes; positive response when exposed to the Controlled Adverse Environment (CAE) model.	n=588; aged ≥18 yrs; patient-reported history of dry eye disease in both eyes; pts demonstrate a positive response when exposed to the CAE model.	n=718; aged ≥18 yrs; patient-reported history of dry eye disease in both eyes; artificial tear use within the past 30 days.
Schedule	Randomised to lifitegrast 0.1% ophthalmic solution; lifitegrast 1.0% ophthalmic solution; lifitegrast 5.0% ophthalmic solution; or placebo ophthalmic solution; all given as eye drops twice daily.	Randomised to lifitegrast 5.0% ophthalmic solution; or placebo ophthalmic solution; both given as eye drops twice daily.	Following 14 days placebo ophthalmic solution, randomised to lifitegrast 5.0% ophthalmic solution; or placebo ophthalmic solution; both given as eye drops twice daily.
Follow-up	Active treatment for 84 days, follow up 86 days.	Active treatment for 84 days, follow-up 84 days.	Active treatment for 84 days, follow-up 84 days.
Primary outcomes	Corneal fluorescein staining score before CAE exposure.	Inferior corneal fluorescein staining; visual-related function subscale of OSDI; safety and tolerability, including incidence and severity of ocular and non-ocular adverse events (AEs).	Eye dryness score and inferior corneal fluorescein staining score.
Secondary outcomes	Ocular symptoms pre- and post-chamber; lissamine green staining; conjunctival redness; tear film break-up time; blink rate; Ocular Surface Disease Index (OSDI)	STT; total corneal staining; OSDI score; ocular discomfort score.	Ocular discomfort score; eye discomfort score; total corneal staining score; nasal conjunctival lissamine green staining score.

[b] Expert personal opinion

	score; ocular protection index; Schirmer Tear Test (STT); corneal sensitivity; safety; ocular discomfort score.		
Key results	Mean change from baseline to day 84 showed significant improvements (p<0.05) in corneal staining score, total OSDI, and visual-related function OSDI scores for lifitegrast groups compared to placebo; improvements in tear production and symptoms were observed as early as day 14 (p<0.05).	The study met the primary objective efficacy inferior corneal staining score end point in demonstrating superiority of lifitegrast compared with placebo (p=0.0007). Lifitegrast significantly reduced corneal fluorescein staining (superior, p=0.0392; total cornea, p=0.0148) and conjunctival lissamine staining (nasal, p=0.0039; total conjunctiva, p=0.0086) at day 84 versus placebo. Significant (p<0.05) improvements in nasal and total lissamine scores were observed at day 14 and maintained through day 84. The study did not meet the visual-related function subscale score of the Ocular Surface Disease Index measure (p=0.7894). However, significant improvements were observed at day 84 in ocular discomfort (p=0.0273) and eye dryness (p=0.0291), the most common and severe symptoms reported at baseline in both groups.	Lifitegrast-treated subjects experienced greater improvement in eye dryness (p<0.0001), ocular discomfort (p=0.0005) and eye discomfort (p<0.0001) than placebo-treated subjects. There was no significant between-group difference in inferior corneal staining, total corneal staining, or nasal lissamine staining.
Adverse effects (AEs)	AEs were mild and transient in nature with no serious ocular adverse events. Lifitegrast 5.0% showed increased instillation site adverse events relative to placebo but were limited to the initial dose.	There were no unanticipated or serious ocular AEs. The most frequent reported ocular AEs were transient intermittent instillation site symptoms (irritation, discomfort) primarily on the initial lifitegrast dose.	More lifitegrast-treated subjects (33.7%) than placebo-treated subjects (16.4%) experienced ocular treatment-emergent adverse events (TEAEs); no ocular TEAEs were serious.

Trial	OPUS-3, NCT02284516, SHP606-304; lifitegrast vs placebo; phase III.	SONATA, NCT01636206, 1118-DRY-400; lifitegrast vs placebo; phase III.
Sponsor	Shire.	Shire.
Status	Complete but unpublished.	Published.
Source of information	Trial registry[15], manufacturer.	Publication[16], trial registry[17].
Location	USA.	USA.

Design	Randomised, placebo-controlled.	Randomised, placebo-controlled.
Participants	n=700 (planned); aged ≥18 yrs; patient reported history of dry eye disease in both eyes; use of over the counter artificial tears within the past 30 days.	n=331; aged ≥18 yrs; patient reported history of dry eye disease in both eyes.
Schedule	Randomised to lifitegrast 5% ophthalmic solution; or placebo ophthalmic solution; both given as eye drops twice daily.	Randomised to lifitegrast 5% ophthalmic solution; or placebo ophthalmic solution; both given as eye drops twice daily.
Follow-up	Active treatment 84 days, follow-up 91 days.	Active treatment 360 days, follow-up 360 days.
Primary outcomes	Patient-reported eye dryness score.	Ocular and non-ocular AEs.
Secondary outcomes	Patient-reported symptom scores; adverse events.	Ocular safety measures: corneal fluorescein staining, drop comfort, best-corrected visual acuity, slit-lamp biomicroscopy, and intraocular pressure.
Key results	Not reported.	Ocular safety parameters for lifitegrast were similar to placebo. The mean plasma lifitegrast concentration at 360 days was below the limit of detection. There was no indication of systemic toxicity or localised infectious complications secondary to chronic immunosuppression.
Adverse effects (AEs)	Not reported.	There were no serious ocular TEAEs. Overall, 53.6% of pts receiving lifitegrast experienced ≥1 ocular TEAEs vs 34.2% in the placebo group; most TEAEs were mild to moderate in severity. Rates of discontinuation because of TEAEs were 12.3% (lifitegrast) vs 9.0% (placebo). The most common (>5%) TEAEs in both treatment groups were instillation site irritation (burning), instillation site reaction, visual acuity reduced, dry eye, and dysgeusia.
Expected reporting date	Previously reported as October 2015. Company anticipate publication in Q4 2016.	-

ESTIMATED COST and IMPACT

COST

The cost of lifitegrast is not yet known. Ciclosporin (Ikervis) costs £72.00 for 30 ampules, representing treatment for one month[4].

IMPACT - SPECULATIVE

Impact on Patients and Carers

- ☐ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☐ Other
- ☐ No impact identified

Impact on Health and Social Care Services

- ☑ Increased use of existing services: *expert opinion suggests that outcomes from lifitegrast use should be measured regularly using the ocular surface disease staining score (which is patient reported) and the Oxford corneal staining system of Ocular surface staining score*[c].
- ☐ Decreased use of existing services
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☐ Other
- ☐ None identified

Impact on Costs and Other Resource Use

- ☐ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☐ Other increase in costs
- ☐ Other reduction in costs
- ☑ Other: *uncertain unit cost compared to existing treatments.*
- ☐ None identified

Other Issues

- ☑ Clinical uncertainty or other research question identified: *there is a question of whether this treatment is most appropriate for immune-mediated dry eye disease over simple dry eye disease, and expert opinion suggests that it would be most appropriate to use lifitegrast in patients with the most severe dry eye disease*[c].

  Expert opinion also suggests outcome measures should include more objective markers of disease activity: tear film osmolarity, expression of HLA-DR on impression cytology of the conjunctiva, and changes in ocular surface features through immunohistochemical analysis for goblet cells, conjunctival keratinisation, and dysplasia[c].

  Expert opinion also raised questions over whether the long term modulation of LFA-1 will impact upon ocular surface health, i.e. whether it will cause neoplastic change. There are questions over whether lifitegrast is a long term maintenance treatment, or like steroids, should it be reserved as either pulse therapy for exacerbations, or medium term with ophthalmological review[c].
- ☐ None identified

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[c] Expert personal opinion

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