

## Therapeutic Class Overview

### Ophthalmic Immunomodulators

#### INTRODUCTION

- Dry eye syndrome refers to a group of disorders of the tear film that are due to reduced tear production or excessive tear evaporation (*American Academy of Ophthalmology [AAO] 2013*). The condition can be associated with discomfort and/or visual symptoms and may result in disease of the ocular surface. The ocular surface and tear-secreting glands are recognized to be responsible for the maintenance of the tear film and to clear tears. Therefore, disease or dysfunction results in an unstable and poorly maintained tear film that causes ocular irritation symptoms and an epithelial disease known as keratoconjunctivitis sicca (KCS). Decreased tear secretion and clearance initiates an inflammatory response on the ocular surface, which plays a role in the pathogenesis of KCS. Symptoms of KCS include, but are not limited to, dryness, discomfort, irritation/pain, foreign body sensation, and blurred vision (*AAO 2013*).
- Rare complications of severe dry eyes include ocular surface keratinization; corneal scarring, thinning, or neovascularization; microbial or sterile corneal ulceration with possible perforation; and severe visual loss.
- Frequent instillation of ophthalmic medications (eg, natural tears) may cause dry eye symptoms by preventing the normal maintenance of the tear film. Other factors known to exacerbate symptoms of dry eye include environmental factors such as reduced humidity, air drafts, air conditioning, or heating. Associated systemic diseases include Sjögren's Syndrome, rosacea, and viral infection. Common drug-induced causes of dry eye symptoms include systemic medications such as anticholinergics, antidepressants, antihistamines, diuretics, and retinoids (*AAO 2013*).
- Medispan Therapeutic Class: Ophthalmic Immunomodulators

**Table 1. Medications Included Within Class Review**

Drug	Generic Availability
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	-
Cequa (cyclosporine ophthalmic solution)	!
Xiidra (lifitegrast ophthalmic solution)	-

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

#### INDICATIONS

**Table 2. Food and Drug Administration Approved Indications**

Indication	Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	Cequa (cyclosporine ophthalmic solution)	Xiidra (lifitegrast ophthalmic solution)
To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca*	✓		
To increase tear production in patients with keratoconjunctivitis sicca		✓	
Treatment of the signs and symptoms of dry eye disease			✓

\*Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

(*Restasis prescribing information 2017; Restasis Multidose prescribing information 2016, Xiidra prescribing information 2017, Cequa prescribing information 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

- The pivotal trials for cyclosporine ophthalmic emulsion were 2 randomized, placebo-controlled trials that included 877 patients and an open-label, extension trial that included 412 patients (*Barber et al 2005, Sall et al 2000*). All patients were diagnosed with moderate-to-severe KCS and decreased tear production based on the Schirmer tear test. The combined results of the 2 placebo-controlled trials demonstrated that cyclosporine ophthalmic emulsion 0.05% and 0.1% were associated with significant improvements from baseline in corneal staining, Schirmer tear test scores, Ocular Surface Disease Index (OSDI) scores, Subjective Facial Expression Rating Scale scores, and various dry eye related symptoms (*Sall et al, 2000*). Specifically compared to placebo, at 4 months, improvements in corneal staining were significant in both cyclosporine ophthalmic emulsion groups compared to placebo ( $p \leq 0.044$ ), and at 6 months, only the cyclosporine ophthalmic emulsion 0.05% group demonstrated significance over placebo ( $p = 0.008$ ). Additionally, at 6 months, improvements in Schirmer tear test scores were significantly greater for both cyclosporine ophthalmic emulsion groups compared to placebo ( $p \leq 0.05$  for both) and from baseline scores ( $p$  values not reported). Improvements in OSDI and Subjective Facial Expression Rating Scale scores were significant compared to baseline for all treatment groups ( $p < 0.001$ ), but there were no significant differences among these groups ( $p$  values not reported). Improvements in blurred vision were significantly greater in the cyclosporine ophthalmic emulsion 0.05% group than placebo at all follow-up visits ( $p \leq 0.014$ ), and significant improvements were achieved at all time points within all treatment groups when compared to baseline for relief of dry eye symptoms including dryness ( $p < 0.001$ ), sandy/gritty feeling ( $p < 0.001$ ), and itching ( $p \leq 0.038$ ). A Chinese, double-blind study used similar subjective ratings for dry eye symptoms and found that cyclosporine ophthalmic emulsion 0.05% improved measures over 8 weeks (*Chen et al 2010*).
- An open-label, extension trial was also conducted to determine the long-term safety of cyclosporine ophthalmic emulsion. After 3 consecutive 12-month periods, results demonstrated that cyclosporine ophthalmic emulsion was safe and well tolerated. Over 3 years, adverse events were found in 65.3% (269/412) of patients with ocular burning reported most commonly (12.1%). This trial also demonstrated sustained efficacy of cyclosporine ophthalmic emulsion over an extended period of time (*Barber et al 2005*).
- A trial comparing cyclosporine ophthalmic emulsion to punctal plugs or a combination of both demonstrated that both treatments improved the symptoms of dry eye, but punctal plugs achieved results more rapidly than cyclosporine ophthalmic emulsion (*Roberts et al 2007*).
- A systematic review of 18 RCTs examined the efficacy and safety of topical cyclosporine for treatment of dry eye disease. All cyclosporine formulations proved safe for the treatment of dry eye disease. Symptoms improved in 100% (9/9 RCTs), tear function improved in 72% (13/18 RCTs) and ocular surface damage was ameliorated in 53% (9/17 RCTs) (*Sacchetti et al 2014*).
  - Statistical comparison of cyclosporine efficacy through a meta-analysis of data was not possible due to a lack of standardized criteria and comparable outcomes among studies.
- Two multicenter, randomized, controlled clinical studies evaluated the efficacy of cyclosporine ophthalmic solution 0.09% in 1048 patients with keratoconjunctivitis sicca. In both studies, there was a significantly ( $p < 0.01$ ) higher percentage of eyes with increases of  $\geq 10$  mm from baseline in Schirmer wetting as compared to vehicle at day 84. This effect was seen in approximately 17% of Cequa-treated vs approximately 9% of vehicle-treated patients (*Cequa prescribing information 2018*).
- The safety and efficacy of lifitegrast ophthalmic solution for the treatment of dry eye disease were assessed in a total of 1181 patients (1067 of which received lifitegrast 5%) in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (*Semba et al 2012, Sheppard et al 2014, Tauber et al 2015, Holland et al 2017*). The use of artificial tears was not allowed during the studies. The clinical trials evaluated various endpoints related to signs and symptoms of dry eye disease. However, the Food and Drug Administration (FDA) approval relied on an assessment of symptoms based on change from baseline in patient reported eye dryness score (EDS; 0 to 100 visual analogue [VAS] scale) and an assessment of signs based on the inferior corneal staining score (ICSS; 0 to 4 scale).
- A larger reduction in EDS favoring lifitegrast was observed in all studies at day 42 and day 84.

- EDS was used as a primary symptom endpoint in 2 of the 4 studies (OPUS-2 and OPUS-3); the other 2 evaluated EDS as a secondary endpoint.
- In OPUS-1, the primary symptom endpoint was the visual-related function subscale score of the Ocular Surface Disease Index (VR-OSDI) questionnaire. No difference between lifitegrast and placebo was seen in the mean change from baseline to day 84 ( $p = 0.7894$ ) (*Sheppard et al 2014*).
- At day 84, a larger reduction in ICSS favoring lifitegrast was observed in 3 of the 4 studies (no statistically significant difference between lifitegrast and placebo was found in the OPUS-2 study).
- In a 1-year safety study (N = 331: 220 lifitegrast; 111 placebo), there were no serious ocular treatment-emergent adverse events (TEAEs). Overall, 53.6% of participants receiving lifitegrast experienced  $\geq 1$  ocular TEAE vs. 34.2% in the placebo group; most TEAEs were mild to moderate in severity, with burning, instillation site reaction, reduced visual acuity, dry eye, and dysgeusia reported most commonly (*Donnenfeld et al 2016*).
- Ocular comfort of lifitegrast was also assessed in OPUS-3 (n = 711). Drop comfort scores (0 = very comfortable, 10 = very uncomfortable) were assessed immediately after instillation and at 1, 2, and 3 minutes post-instillation. The results showed that drop comfort scores with lifitegrast improved within 3 minutes of instillation with scores approaching that of placebo (*Nichols et al 2018*).

## CLINICAL GUIDELINES

- Clinical guidelines consider cyclosporine ophthalmic emulsion to be an appropriate therapy for patients with moderate dry eye syndrome, and also in the treatment of severe atopic KCS or for those patients with atopic KCS who have failed conventional therapy (AAO 2013). However, depending on patient preference and physician experience, any of the recognized treatment options for dry eye syndrome may be used to treat the disease regardless of the severity rating. The guidelines have not yet been updated to include lifitegrast.

## SAFETY SUMMARY

- Cyclosporine ophthalmic emulsion
  - Cyclosporine ophthalmic emulsion is contraindicated in patients with known or suspected hypersensitivity to any ingredient in the formulation.
  - Warnings include the risk of eye injury and contamination when administering the medication if the vial tip touches the eye or other surfaces and use with contact lenses. Cyclosporine ophthalmic emulsion should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of cyclosporine ophthalmic emulsion.
  - Ocular burning is the most frequently reported adverse event. Other adverse events reported include ocular pain, conjunctival hyperemia, discharge, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).
- Cyclosporine ophthalmic solution
  - The ophthalmic solution has no contraindications for use.
  - Cyclosporine ophthalmic solution has similar warnings as the ophthalmic emulsion formulation.
  - Pain on drop instillation was the most frequently reported adverse event followed by conjunctival hyperemia. Other adverse events included blepharitis, eye irritation, headache, and urinary tract infection.
- Lifitegrast ophthalmic solution
  - Lifitegrast ophthalmic solution is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.
  - The most commonly reported adverse events reported in 5 to 25% of patients were instillation site irritation, dysgeusia, and reduced visual acuity.
  - Other adverse events reported in 1 to 5% of patients included blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

## DOSING AND ADMINISTRATION

**Table 3. Dosing and Administration**

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	Ophthalmic emulsion	oph	To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca: Ophthalmic emulsion: instill 1 drop in each eye twice daily approximately 12 hours apart	Cyclosporine ophthalmic emulsion can be used concomitantly with artificial tears; however, patients should allow for a 15-minute interval between the products.  To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces.  Restasis (single-dose vial): Discard vial immediately after use.  Restasis Multidose is packaged in a multi-dose preservative-free 10 mL bottle containing 5.5 mL.
Cequa (cyclosporine ophthalmic solution)	Ophthalmic solution	oph	Instill 1 drop twice daily (approximately 12 hours apart)	Cyclosporine ophthalmic solution can be used concomitantly with artificial tears; however, patients should allow for a 15-minute interval between the products.  To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces.  Discard the vial immediately after use.
Xiidra (lifitegrast ophthalmic solution)	Ophthalmic solution	oph	Instill 1 drop twice daily (approximately 12 hours apart)	Contact lenses should be removed prior to the administration of lifitegrast and may be reinserted 15 minutes following administration.  Discard the single-use container immediately after using in each eye.

See the current prescribing information for full details

## CONCLUSION

- Restasis (cyclosporine ophthalmic emulsion) is the first ophthalmic emulsion FDA-approved to increase tear production in patients with KCS. Although the exact mechanism of action of this agent is unknown, it is assumed that it acts as a partial immunomodulator.
- Xiidra (lifitegrast ophthalmic solution) is the second prescription treatment to receive FDA-approval for treatment of dry eye disease. Lifitegrast is a novel small molecule integrin antagonist that inhibits T cell-mediated inflammation by blocking the binding of 2 important cell surface proteins (lymphocyte function-associated antigen 1 [LFA-1] and intercellular adhesion molecule 1 [ICAM-1]), thus lessening overall inflammatory responses. However, the exact mechanism of action of lifitegrast in dry eye disease is unknown.
- In August 2018, the FDA approved Cequa (cyclosporine ophthalmic solution) to increase tear production in patients with KCS (*Cequa prescribing information 2018*). This is the first cyclosporine product to utilize nanomicellar technology. This formulation allows the drug molecule to overcome solubility difficulties, penetrate the eye's aqueous layer, and prevent the release of active lipophilic molecule prior to penetration.
- In clinical trials, cyclosporine ophthalmic emulsion demonstrated significant increases in tear production and decreases in dry eye symptoms compared to placebo and demonstrated safety for up to 3 years (*Sall et al 2000, Barber et al 2005*,

Roberts et al 2007). For the new cyclosporine ophthalmic solution, there was a significantly ( $p < 0.01$ ) higher percentage of eyes with increases of  $\geq 10$  mm from baseline in Schirmer wetting as compared to vehicle at day 84 (Cequa prescribing information 2018).

- Lifitegrast also demonstrated significant improvements in the signs and symptoms of dry eye disease compared with placebo in clinical trials. Lifitegrast was well tolerated with no unexpected adverse events in a 1-year safety exposure study (Donnenfeld et al 2016, Holland et al 2017, Semba et al 2012, Sheppard et al 2014, Tauber et al 2015).
- Clinical guidelines consider cyclosporine ophthalmic emulsion to be an appropriate therapy for patients with moderate to severe dry eye syndrome (AAO 2013, AOA 2010). Lifitegrast and the recently approved cyclosporine ophthalmic solution have not yet been incorporated into the guidelines.
- There are no comparative trials of cyclosporine ophthalmic emulsion or solution and lifitegrast ophthalmic solution.

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