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] 2018, Shtein 2020*). 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 tear production 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 2018).*
- 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 2018*).
- Medispan Therapeutic Classes: Ophthalmic Immunomodulators; Ophthalmic Integrin Antagonists

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 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

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 KCS		✔	
Treatment of the signs and symptoms of dry eye disease (DED)			✔

*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 2020, Cequa prescribing information 2019*)

- 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 ophthalmic immunomodulator products have not been directly compared in clinical trials and have primarily been compared to vehicle.
- 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 (AEs) 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 randomized controlled trials (RCTs) examined the efficacy and safety of topical cyclosporine for treatment of DED. All cyclosporine formulations proved safe for the treatment of DED. 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) (*Saccheti 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.
- A systematic review/meta-analysis of 30 randomized, controlled clinical studies (N = 4009) assessed the effectiveness and safety of topical cyclosporine in the treatment of DED. Eighteen studies compared cyclosporine 0.05% plus artificial tears (AT) vs AT alone. However, due to incomplete results data or considerable statistical heterogeneity, only a meta-analysis on mean conjunctival goblet cell density was conducted. The mean density (MD) was greater in the cyclosporine treated group (MD 22.5 cells per unit, 95% Confidence Interval [CI], 16.3 to 28.8). Additionally, the analysis could not demonstrate the benefit of cyclosporine for tear production and helping to reduce signs and symptoms of dry eye. The remaining 12 studies were not assessed due to inconsistent data reporting (*de Paiva et al 2019*).
- Two multicenter, randomized, controlled clinical studies evaluated the efficacy of cyclosporine ophthalmic solution 0.09% in 1048 patients with KCS. In both studies, there was a significantly ($p < 0.01$) higher percentage of eyes with increases of ≥ 10 mm from baseline in Schirmer wetting as compared to vehicle at day 84. This effect was seen in approximately 17% of patients treated with cyclosporine ophthalmic solution vs approximately 9% of patients treated with vehicle (*Cequa prescribing information 2018, Goldberg et al 2019, Luchs et al 2018, Sheppard et al 2020, Tauber et al 2018*).
- The safety and efficacy of lifitegrast ophthalmic solution for the treatment of DED 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 AT was not allowed during the studies. The clinical trials evaluated various endpoints related to signs and symptoms of DED. 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 AEs. Overall, 53.6% of participants receiving lifitegrast experienced ≥ 1 ocular treatment-emergent AE vs 34.2% in the placebo group; most treatment-emergent AEs 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*).
- A pooled analysis of 5 randomized trials (lifitegrast N = 1287, placebo N = 1177) evaluated the safety and tolerability of lifitegrast ophthalmic solution 5.0% for the treatment of dry eye. Overall, the majority of treatment related adverse events reported (> 5%) were: instillation site irritation, instillation site reaction and instillation site pain; the most common non-ocular adverse event reported was dysgeusia in 14.5% of patients receiving lifitegrast vs 0.3% in the placebo group. The analysis also noted that drop comfort scores in the lifitegrast treatment group improved within 3 minutes of instillation and continued to improve across visits through 1 year (*Nichols et al 2019*).

CLINICAL GUIDELINES

- The American Academy of Ophthalmology (AAO) Preferred Practice Pattern for Dry Eye Syndrome makes treatment recommendations based on disease severity (*AAO 2018*).
    - For mild disease, education and environmental modifications, aqueous enhancement using artificial tears, gels or ointments, and eyelid therapy with warm compresses and eyelid scrubs are recommended.
    - For moderate disease, the AAO recommends in addition to the treatments for mild disease, anti-inflammatory agents such as topical cyclosporine, lifitegrast, and corticosteroids; punctal plugs; or spectacle side shields and moisture chambers.
        - Low-dose topical corticosteroid therapy should be used at infrequent intervals for short periods of time (ie, several weeks) to suppress ocular surface inflammation. Patients prescribed corticosteroids for dry eye should be monitored for AEs such as increased intraocular pressure and cataract formation.
    - For severe disease, the AAO recommends in addition to all the previously mentioned treatments, systemic cholinergic agonists or anti-inflammatory agents, mucolytic agents, autologous serum tears, contact lenses, permanent punctal occlusion, or tarsorrhaphy.
- Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) (*Jones et al 2017*)
    - A step-wise approach is recommended based on disease severity.
        - Step 1: education, lid hygiene, warm compress, modification of environmental factors, omega-3 fatty acid supplementation, or ocular lubricants. Ocular lubricants are considered mainstay of treatment, however, they only offer palliative relief with no disease modifying potential.
        - Step 2 (if above inadequate):
            - Non-pharmacological: punctual occlusion (most widely used tear conservation approach), pulsed light therapy, moisture goggles
            - Pharmacological: topical antibiotic for blepharitis, limited duration topical corticosteroid, topical cyclosporine, lifitegrast.
        - Step 3(if above inadequate): oral secretagogues, allogenic serum eye drops, or therapeutic contact lenses
        - Step 4(if above inadequate): longer duration topical steroid, membrane grafts, punctual occlusion or other surgical approaches.

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 was the most frequently reported AE. Other AEs included 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 AE followed by conjunctival hyperemia. Other AEs 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 AEs reported in 5 to 25% of patients were instillation site irritation, dysgeusia, and reduced visual acuity.
  - Other AEs 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.
  - Post marketing AEs reported include rare serious cases of hypersensitivity (anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis), eye swelling, and rash.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	Ophthalmic emulsion	Ophthalmic	Instill 1 drop 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	Ophthalmic	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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				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	Ophthalmic	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 DED. 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 DED 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 nanomicellar cyclosporine ophthalmic solution, there was a significantly ($p < 0.01$) higher percentage of eyes with increases of ≥ 10 mm from baseline in Schirmer wetting as compared to vehicle at day 84 *(Cequa prescribing information 2018, Goldberg et al 2019, Luchs et al 2018, Sheppard et al 2020, Tauber et al 2018)*.
- Lifitegrast also demonstrated significant improvements in the signs and symptoms of DED compared with placebo in clinical trials. Lifitegrast was well tolerated with no unexpected AEs 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*).
- Ophthalmic immunomodulators improve signs of DED in patients who are inadequately treated with AT and other therapies. Lifitegrast demonstrated improvement in symptoms of DED; however, cyclosporine has not consistently improved symptoms in DED compared to placebo. Direct comparative data between cyclosporine products and lifitegrast are lacking.

REFERENCES

- American Academy of Ophthalmology Cornea/External Disease Panel, Preferred Practice Pattern Guidelines. Dry Eye Syndrome. San Francisco, CA: American Academy of Ophthalmology; 2018. https://www.aao.org/preferred-practice-pattern/dry-eye-syndrome-ppp-2018. Accessed August 11, 2020.
- Barber L, Pflugfelder S, Tauber J, Foulks G. Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. *Ophthalmology.* 2005;112(10):1790-1794.
- Cequa prescribing information. Sun Pharmaceuticals: Canbury, NJ; October 2019.
- Chen M, Gong L, Sun X, et al. A comparison of cyclosporine 0.05% ophthalmic emulsion versus vehicle in Chinese patients with moderate to severe dry eye disease: an eight-week, multicenter, randomized, double-blind, parallel-group trial. *J Ocul Pharmacol Ther*. 2010 Aug;26(4):361-366.
- ClinicalTrials.gov. Web site. https://clinicaltrials.gov. Identifier: NCT02254265, NCT02688556. Accessed August 11, 2020.

- De Paiva CS, Pflugfelder SC, Ng SM, et al. Topical cyclosporine A therapy for dry eye. *Cochrane Database Syst Rev*. 2019;13(9): doi: 10.1002/14651858.CD010051.pub2.
- Donnenfeld ED, Karpecki PM, Majmudar PA, et al. Safety of lifitegrast ophthalmic solution 5.0% in patients with dry eye disease: a 1-year, multicenter, randomized, placebo-controlled study. *Cornea.* 2016;35(6):741-748.
- Drugs@FDA. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed August 11, 2020.
- Goldberg DF, Malhotra RP, Schechter BA et al. A Phase 3, Randomized, Double-Masked Study of OTX-101 Ophthalmic Solution 0.09% in the Treatment of Dry Eye Disease. *Ophthalmology*. 2019;126(9):1230-1237.
- Holland EJ, Luchs J, Karpecki PM, et al. Lifitegrast for the treatment of dry eye disease: results of a phase III, randomized, double-masked, placebo-controlled Trial (OPUS-3). *Ophthalmology*. 2017;124(1):53-60.
- Luchs J. Phase 3 clinical results of cyclosporine 0.09% in a new nanomicellar ophthalmic solution for treatment of keratoconjunctivitis sicca [abstract]. Presented at: American Society of Cataract and Refractive Surgery – American Society of Ophthalmic Administrators Annual Meeting; April 13 to 17, 2018; Washington DC. https://ascrs.confex.com/ascrs/18am/meetingapp.cgi/Paper/45230. Accessed August 11, 2020.
- Nichols KK, Holland E, Toyos MM, et al. Ocular comfort assessment of lifitegrast ophthalmic solution 5.0% in OPUS-3, a Phase III randomized controlled trial. *Clin Ophthalmol*. 2018;12:263-270. doi: 10.2147/OPTH.S152841.
- Nichols KK, Donnenfeld ED, Karpecki PM, et al. Safety and tolerability of lifitegrast ophthalmic solution 5.0%: Pooled analysis of five randomized controlled trials in dry eye disease. *Eur J Ophthalmol.* 2019;29(4):394-401.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration. https://www.accessdata.fda.gov/scripts/cder/ob/. Accessed August 11, 2020.
- Restasis prescribing information. Allergan, Inc. Irvine, CA. July 2017.
- Restasis Multidose prescribing information. Allergan, Inc. Irvine, CA. October 2016.
- Roberts C, Carniglia P, Brazzo B. Comparison of topical cyclosporine, punctal occlusion and a combination for the treatment of dry eye. *Cornea*. 2007;26(7):805-809.
- Sacchetti M, Mantelli F, Lambiase A, Mastropasqua A, Merlo D, Bonini S. Systematic review of randomised clinical trials on topical ciclosporin A for the treatment of dry eye disease. *Br J Ophthalmol*. 2014;98(8):1016-1022.
- Sall K, Stevenson OD, Mundorf T, Reis B, et al. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *Ophthalmology.* 2000;107(4):631-639.
- Semba CP, Torkildsen GI, Lonsdale JD, et al. A phase 2 randomized, double-masked, placebo-controlled study of novel integrin antagonist (SAR 118) for the treatment of dry eye. *Am J Ophthalmol*. 2012;153(6):1050-1060.
- Sheppard J, Kannarr S, Luchs, J et al. Efficacy and Safety of OTX-101, a Novel Nanomicellar Formulation of Cyclosporine A, for the Treatment of Keratoconjunctivitis Sicca: Pooled Analysis of a Phase 2b/3 and Phase 3 Study. *Eye Contact Lens*. 2020;46:S14-S19.
- Sheppard JD, Torkildsen GL, Lonsdale JD, et al. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study. *Ophthalmology*. 2014;121(2):475-483.
- Shtein RM. Dry eye disease. UpToDate website. www.uptodate.com Updated April 16, 2020. Accessed August 11, 2020.
- Tauber J, Karpecki P, Latkany R, et al. Lifitegrast ophthalmic solution 5.0% versus placebo for treatment of dry eye disease: results of the randomized phase III OPUS-2 study. *Ophthalmology*. 2015;122(12):2423-2431.
- Tauber J, Schechter BA, Bacharach J et al. A Phase II/III, randomized, double-masked, vehicle-controlled, dose-ranging study of the safety and efficacy of OTX-101 in the treatment of dry eye disease. *Clin Ophthalmol*. 2018; 12:1921-1929.
- Xiidra prescribing information. Shire. Lexington, MA. June 2020.

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