

## 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] Dry Eye Syndrome, 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 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 Dry Eye Syndrome, 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, such as natural tears, may also 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 systemic retinoids (AAO Dry Eye Syndrome, 2013).
- Medispan Therapeutic Class: Ophthalmic Immunomodulators

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

Drug	Manufacturer	FDA Approval Date	Generic Availability
RESTASIS® (cyclosporine ophthalmic emulsion)	Allergan	December 23, 2002	-
XIIDRA® (lifitegrast ophthalmic solution)	Shire	July 11, 2016	-

(Drugs@FDA, 2017)

#### INDICATIONS

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

Drug	Indication
RESTASIS (cyclosporine ophthalmic emulsion)	To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca*
XIIDRA (lifitegrast ophthalmic solution)	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, 2013; XIIDRA prescribing information, 2016)

Information on indications, mechanism of action, pharmacokinetics, 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 two 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 two 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 four months, improvements in

corneal staining were significant in both cyclosporine ophthalmic emulsion groups compared to placebo ( $P \leq 0.044$ ), and at six months, only the cyclosporine ophthalmic emulsion 0.05% group demonstrated significance over placebo ( $P = 0.008$ ). Additionally, at six 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 eight weeks (Chen et al, 2010).

- An open-label, extension trial was also conducted to determine the long term safety of cyclosporine ophthalmic emulsion (Barber et al, 2005). After three consecutive 12-month periods, results demonstrated that cyclosporine ophthalmic emulsion was safe and well tolerated. Over three 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.
- 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.
- The safety and efficacy of lifitegrast ophthalmic solution for the treatment of dry eye disease were assessed in a total of 1,181 patients (1,067 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; XIIDRA prescribing information 2016). 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 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 one-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 versus 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).
- 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 Dry Eye Syndrome, 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 of the product.
  - 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, remove contact lenses prior to the administration of the emulsion. Reinsert lenses 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, visual disturbance (blurring), and other local ocular effects.

- **Lifitegrast ophthalmic solution**

- There are no contraindications.
- 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	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
RESTASIS (cyclosporine ophthalmic emulsion)	Ophthalmic emulsion: 0.05% (30 single-use vials each containing 0.4 mL)	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.  Discard vial immediately after use.
XIIDRA (lifitegrast ophthalmic solution)	Ophthalmic solution: 5% (60 single-use polyethylene containers each containing 0.2 mL)	Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container.	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.

## SPECIAL POPULATIONS

**Table 4. Special Populations**

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
RESTASIS (cyclosporine ophthalmic emulsion)	No overall difference in safety or effectiveness has been observed between elderly and younger patients.	Safety and efficacy in children <16 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required.	Pregnancy category C*  Yes, excreted in breast milk with systemic administration (% unknown); use with caution.
XIIDRA (lifitegrast ophthalmic solution)	No overall differences in safety or effectiveness have been observed between elderly	Safety and efficacy in pediatric patients <17 years of age have not	No dosage adjustment required.	No dosage adjustment required.	There are no available data on lifitegrast use in pregnant women to inform any drug associated risks.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	and younger adult patients.	been established.			There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low.

\* Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

## CONCLUSION

- RESTASIS (cyclosporine ophthalmic emulsion) is the first ophthalmic emulsion FDA-approved to increase tear production in patients with keratoconjunctivitis sicca (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 two 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 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 three years (Sall et al, 2000; Barber et al, 2005; Roberts et al, 2007).
- 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 one-year safety exposure study (Donnenfeld et al, 2016; Semba et al, 2012; Sheppard et al, 2014; Tauber et al, 2015; XIIDRA prescribing information 2016).
- Clinical guidelines consider cyclosporine ophthalmic emulsion to be an appropriate therapy for patients with moderate to severe dry eye syndrome (AAO Dry Eye Syndrome, 2013; AOA Ocular Surface Disorders, 2010). Lifitegrast has not yet been incorporated into the guidelines.
- There are no comparative trials of cyclosporine ophthalmic emulsion and lifitegrast ophthalmic solution.

## REFERENCES

- American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Dry Eye Syndrome. San Francisco, CA: American Academy of Ophthalmology; 2013. Available at: <http://www.aao.org/preferred-practice-pattern/dry-eye-syndrome-ppp--2013>. Accessed January 5, 2017.
- American Academy of Ophthalmology Cornea/External Disease Panel. Preferred practice pattern. Conjunctivitis. San Francisco, CA: American Academy of Ophthalmology; 2013. Available at: <http://www.aao.org/preferred-practice-pattern/conjunctivitis-ppp--2013>. Accessed January 5, 2017.
- American Optometric Association. Optometric clinical practice guideline. Care of the patient with conjunctivitis. 2<sup>nd</sup> ed. St. Louis, MO: American Optometric Association; 2002, Reviewed in 2007. Available at: <http://www.aoa.org/documents/optometrists/CPG-11.pdf>. Accessed January 5, 2017.
- American Optometric Association. Optometric Clinical Practice Guideline. Care of the patient with Ocular Surface Disorders. St. Louis, MO: American Optometric Association; 2010. Available at: <http://www.aoa.org/documents/optometrists/CPG-10.pdf>. Accessed January 5, 2017.
- 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;112:1790-4.
- 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):361-6.
- 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):741-8.

- Drugs@FDA. Food and Drug Administration. Available at: <https://www.accessdata.fda.gov/scripts/cder/drugsatfda/>. Accessed January 5, 2017.
- RESTASIS prescribing information. Allergan, Inc. Irvine, CA. June 2013.
- Roberts C, Carniglia P, Brazzo B. Comparison of topical cyclosporine, punctal occlusion and a combination for the treatment of dry eye. *Cornea*. 2007;26:805-9.
- 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):1016-22.
- 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):631-9.
- 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):1050-60.
- 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):475-83.
- 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):2423-31.
- XIIDRA prescribing information. Shire, Lexington, MA. June 2016.

Publication Date: January 12, 2017