

Therapeutic Class Overview

Ophthalmic Immunomodulators

INTRODUCTION

- Dry eye disease (DED) 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[a], Shtein 2021*). 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[a]).
 - 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[a]).
 - Eysuvis (loteprednol etabonate ophthalmic suspension) 0.25% is a corticosteroid indicated for the short-term use for up to 2 weeks for the treatment of the signs and symptoms of DED (*Eysuvis prescribing information 2020*). This product is reviewed with the ophthalmic corticosteroids with the other formulations of loteprednol etabonate.
- Ocular allergy includes 5 subtypes such as seasonal and perennial allergic conjunctivitis, vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis, and giant papillary conjunctivitis. VKC is a chronic, bilateral, severe form of inflammation on the ocular surface that can result in corneal scarring and vision loss if not treated properly (*Hamrah and Dana 2021*).
 - VKC typically affects those living in warm, dry, subtropical climates. The prevalence in these areas is approximately 0.03% of the population. Males are more commonly affected than females (ratio, 3.2:1) as are patients < 20 years of age. The most common concomitant atopic diseases are asthma and allergic rhinitis.
 - Pruritus is the primary symptom, but patients may also experience photophobia, thick mucus discharge, tearing, burning, foreign body sensation, pain, and blurred vision. Symptoms tend to occur most commonly in the spring. Bilateral signs of VKC include giant cobblestone-like papillae on the conjunctiva of the upper eyelid.
 - Treatment of VKC typically consists of trigger avoidance and the use of over-the-counter ophthalmic antihistamine/mast cell stabilizer products, followed by an oral antihistamine. If VKC is not well-controlled, ophthalmic corticosteroids may be considered. Ophthalmic immunomodulators may be added for patients who have an inadequate response to ophthalmic corticosteroids.
- Medispan Therapeutic Classes: Ophthalmic Immunomodulators; Ophthalmic Integrin Antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cequa (cyclosporine ophthalmic solution) 0.09%	-
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion) 0.05%	-
Verkazia (cyclosporine ophthalmic emulsion) 0.1%	-
Xiidra (lifitegrast ophthalmic solution) 5%	-

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Cequa (cyclosporine ophthalmic solution)	Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	Verkazia (cyclosporine ophthalmic emulsion)	Xiidra (lifitegrast ophthalmic solution)
To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS*		✓		
To increase tear production in patients with KCS	✓			
Treatment of the signs and symptoms of DED				✓
Treatment of VKC in children and adults			✓	

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

(Prescribing information: Cequa 2019, Restasis 2017, Restasis Multidose 2016, Verkazia 2021, Xiidra 2020)

- 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. Indirect comparisons are very challenging since the inclusion criteria, endpoints, use of artificial tears, and vehicles differed among the trials (Holland et al 2019, Nichols et al 2021). In addition, signs and symptoms of DED correlate poorly.
- DED**
 - 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 0.1%. 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 Restasis (cyclosporine ophthalmic emulsion) 0.05% 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 0.05% (*Roberts et al 2007*).
- A systematic review of 18 randomized controlled trials (RCTs) examined the efficacy and safety of topical cyclosporine 0.05% to 2% with or without artificial tears 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) (*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.
- A systematic review and meta-analysis of 30 randomized, controlled clinical studies (N = 4009) assessed the effectiveness and safety of topical cyclosporine 0.05 % in the treatment of DED. Eighteen studies compared cyclosporine 0.05% plus artificial tears vs artificial tears 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 Cequa (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, Sheppard et al 2020, Tauber et al 2018*).
- A systematic review and meta-analysis of 11 RCTs (N = 1085) evaluated the effect of cyclosporine 0.05% in diverse dosages with or without artificial tears for DED. Pooled results showed that cyclosporine had better tear-breakup time (mean difference [MD] 0.94; 95% CI, 0.08 to 1.80) when compared to artificial tears; however, high heterogeneity was noted ($I^2 = 85\%$). In a subgroup analysis, results showed significant treatment effect for cyclosporine only when treatment duration was > 3 months (*Tuan et al 2020*).
- 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 (*Holland et al 2017, Semba et al 2012, Sheppard et al 2014, Tauber et al 2015*). The use of artificial tears 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 adverse events. Overall, 53.6% of participants receiving lifitegrast experienced ≥ 1 ocular treatment-emergent AE vs 34.2% in the placebo group; most treatment-emergent adverse events 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*).

• VKC

- The Vernal Keratoconjunctivitis Study (VEKTIS) was a double-blind, multi-center, Phase 3, RCT that evaluated the safety and efficacy of Verkazia (cyclosporine ophthalmic emulsion) 0.1% in the treatment of active VKC in 169 children and adolescents aged 4 to < 18 years. Patients had severe keratitis according to the corneal fluorescein staining (CFS) score of 4 or 5 on the modified Oxford scale (range, 0 to 5 with higher scores indicating more severe disease). Patients were randomized to cyclosporine ophthalmic cationic emulsion 0.1% instilled as 1 drop 4 times daily (high-dose group), 1 drop twice daily plus vehicle twice daily (low-dose group), or vehicle 4 times daily for 4 months (*Bremond-Gignac et al 2020, Leonardi et al 2019[a]*).
- The primary endpoint was the mean composite score of CFS score, use of rescue medication with dexamethasone 0.1% 4 times daily and corneal ulceration over 4 months. The composite scores of the high-dose and low-dose groups were significantly higher, favoring the active treatment groups vs vehicle. The mean differences from vehicle were 0.76 (95% CI, 0.26 to 1.27; $p = 0.007$) for the high-dose group and 0.67 (95% CI, 0.16 to 1.18; $p = 0.010$) for the low-dose group.
 - The secondary endpoints, mean change from baseline in CFS score and mean number of rescue medication courses, were significantly improved in the high-dose cyclosporine group. The mean numbers of corneal ulcerations were not significantly different vs vehicle (0.001 and 0.003 per month in the high-dose and low-dose cyclosporine groups, respectively). Corneal ulcers occurred in 4 (7.0%), 3 (5.6%), and 3 (5.2%) patients in the high-dose, low-dose, and vehicles groups, respectively.
 - A total of 142 patients entered the 8-month DB follow-up period in which patients remained on their allocated regimen of high-dose or low-dose cyclosporine. Patients originally randomized to vehicle who completed the 4-month treatment period ($n = 49$) were allocated to either the high-dose ($n = 22$) or low-dose ($n = 26$) groups which was pre-determined with the initial randomization. The mean CFS scores remained stable to month 12. The percentages of patients requiring rescue medications were stable in both groups through month 8, but higher rates of patients required rescue medication in months 10 to 12 for the high-dose and low-dose groups (18.3% and 20.0%, respectively). The changes in months 10 to 12 were primarily due to patients using cyclosporine intermittently. The most common adverse events through month 12 were instillation site pain (13.9%) and instillation site pruritus (6.9%).

CLINICAL GUIDELINES

• DED

- The AAO Preferred Practice Pattern for Dry Eye Syndrome makes treatment recommendations based on disease severity (*AAO 2018[a]*).
 - 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 adverse events 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) recommends a step-wise approach based on disease severity (*Jones et al 2017*).
 - 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: punctal occlusion (most widely used tear conservation approach), pulsed light therapy, moisture goggles
- Pharmacological: topical antibiotic for blepharitis, limited duration topical corticosteroid, topical cyclosporine, topical 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, punctal occlusion or other surgical approaches.

• VKC

- The AAO Conjunctivitis Preferred Practice Patterns recommend ophthalmic and oral antihistamines/mast cell stabilizers, and environmental changes to reduce allergen or irritant exposure. For acute exacerbations, patients should be treated with ophthalmic corticosteroids to control severe symptoms and signs. Topical compounded cyclosporine 2% has demonstrated a reduction in the signs and symptoms of VKC vs placebo. Restasis (cyclosporine ophthalmic emulsion) 0.05% with more frequent dosing (ie, 4 to 6 times daily) has been shown to be effective for the treatment of severe VKC and/or atopic keratoconjunctivitis. Ophthalmic cyclosporine may allow for reduced use of ophthalmic steroids (AAO 2018[b]).
- The European Academy of Allergy and Clinical Immunology (EAACI) position paper on ocular allergy aligns with the AAO guidelines for the recommendations of the step-wise approach to treatment for VKC (Leonardi et al 2019[b]).

SAFETY SUMMARY

- Restasis / Restasis Multidose (cyclosporine ophthalmic emulsion) 0.05%
 - 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 adverse events included ocular pain, conjunctival hyperemia, discharge, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).
- Cequa (cyclosporine ophthalmic solution) 0.09%
 - 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 adverse events included blepharitis, eye irritation, headache, and urinary tract infection.
- Verkazia (cyclosporine ophthalmic emulsion) 0.1%
 - There are no contraindications in the labeling for Verkazia.
 - The most common adverse events with Verkazia include eye pain (12%) and eye pruritis (8%).
- Xiidra (lifitegrast ophthalmic solution) 5%
 - 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.
 - Post marketing adverse events 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
Cequa (cyclosporine ophthalmic solution) 0.09%	Ophthalmic solution	Ophthalmic	Instill 1 drop twice daily (approximately 12 hours apart)	<p>Cyclosporine ophthalmic solution can be used concomitantly with artificial tears; however, patients should allow for a 15-minute interval between the products.</p> <p>To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces.</p> <p>Discard the vial immediately after use.</p>
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion) 0.05%	Ophthalmic emulsion	Ophthalmic	Instill 1 drop twice daily (approximately 12 hours apart)	<p>Cyclosporine ophthalmic emulsion can be used concomitantly with artificial tears; however, patients should allow for a 15-minute interval between the products.</p> <p>To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces.</p> <p>Restasis (single-dose vial): Discard vial immediately after use.</p> <p>Restasis Multidose is packaged in a multi-dose preservative-free 10 mL bottle containing 5.5 mL.</p>
Verkazia (cyclosporine ophthalmic emulsion) 0.1%	Ophthalmic emulsion	Ophthalmic	Instill 1 drop 4 times daily	<p>Contact lenses should be removed prior to the administration of Verkazia and may be reinserted 15 minutes following administration.</p> <p>If ≥ 1 ophthalmic product is used, the eye drops should be administered ≥ 10 minutes apart to avoid diluting products. Verkazia should be administered 10 minutes prior to any eye ointment, gel or other viscous eye drops.</p> <p>To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces.</p> <p>Discard vial immediately after use.</p>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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

- Agents in this class are indicated for the treatment of the signs and/or symptoms of DED or for the treatment of VKC.
- Direct comparative studies of the 3 cyclosporine formulations are not available. The vehicles of each of the cyclosporine products differ.
- **DED**
 - Restasis (cyclosporine ophthalmic emulsion) 0.05% was the first ophthalmic emulsion FDA-approved to increase tear production in patients with KCS. In August 2018, the FDA approved Cequa (cyclosporine ophthalmic solution) 0.09% 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, Restasis (cyclosporine ophthalmic emulsion) 0.05% demonstrated significant increases in tear production and decreases in dry eye symptoms compared to placebo and demonstrated safety for up to 3 years (*Barber et al 2005, Roberts et al 2007, Sall et al 2000*). For Cequa (cyclosporine ophthalmic solution) 0.09%, 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, Sheppard et al 2020, Tauber et al 2018*).
 - Xiidra (lifitegrast ophthalmic solution) is indicated for the treatment of the signs and symptoms 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.
 - 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 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*).
 - Ophthalmic immunomodulators improve signs of DED in patients who are inadequately treated with artificial tears 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.
- **VKC**
 - VKC is a bilateral chronic form of allergic conjunctivitis that presents in childhood and is associated with allergy and atopy (*AAO 2018[b]*). Treatment options include environmental changes to minimize allergen or irritant exposure, cold compresses, eye lubricants, and ophthalmic antihistamines/mast cell stabilizers. For acute exacerbations, topical corticosteroids are administered to reduce the signs and symptoms.
 - Verkazia (cyclosporine ophthalmic emulsion) 0.1% is indicated for the treatment of VKC. Cyclosporine ophthalmic emulsion) 0.1% improved signs and symptoms of VKC over 4 months compared to vehicle and demonstrated safety over 12 months.
 - For patients with VKC who are inadequately treated, intolerant, or require tapering with ophthalmic corticosteroids, Verkazia (cyclosporine ophthalmic emulsion) 0.1% offers an additional treatment option for the patient with VKC.

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