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New Drug Evaluation: lifitegrast solution, ophthalmic

Date of Review: January 2017
Generic Name: lifitegrast
PDL Class: Not applicable

End Date of Literature Search: November 2016
Brand Name (Manufacturer): Xiidra™ (Shire US Inc.)
AMCP Dossier Received: Yes

Research Questions:

- Is there evidence that lifitegrast improves outcomes in patients with dry eye disease (DED), including improvement in symptoms of discomfort (as measured by patient symptom scores) and visual disturbance? If so, how does efficacy compare to other agents approved by the FDA for dry eye?
- Is there evidence that lifitegrast is safe in patients with DED? How do harms compare to other agents approved by the FDA for dry eye?
- Are there subpopulations of patients, such as those with Medicaid coverage, with DED that may benefit or experience more harms when treated with lifitegrast?

Conclusions:

- The U.S. Food and Drug Administration (FDA) approval of lifitegrast is based from three phase 3, double-blind, randomized controlled trials (OPUS – 1, 2, and 3) in patients with moderate to severe DED.[1, 2, 3] All studies were 12 weeks in duration and primary endpoints were assessed at that time. The majority of patients were white women, mean age of 59 years, with moderate DED symptoms. Small changes in primary endpoints between lifitegrast and placebo suggest no clinical benefit. Extensive exclusion criteria that include common conditions associated with DED limit the applicability of these findings to most patients.
- There is low quality and inconsistent evidence that lifitegrast may reduce inferior corneal staining scores (ICSS) (indicator of ocular surface damage, scores ranging from 0-4, 0 = none and 4 = confluent). Lifitegrast reduced ICSS from baseline by -0.75 compared to placebo +0.16 (mean difference [MD] 0.41; no confidence interval [CI] reported; p=0.0007) in one trial and by -0.73 compared to -0.71 with placebo (MD 0.02; no CI reported; p=0.6186) in a second trial.[1,2] Meaningful clinical changes in corneal staining scores have not been determined and the sensitivity of this test to detect differences is considered low.[4] ICSS scores have not been shown to be indicative of DED symptoms.
- There is low quality evidence that lifitegrast may decrease eye dryness scores (EDS).[2] The EDS visual analog scale (VAS) ranges from 0-100 (100 = maximal discomfort.[5] No minimally clinically important difference has been identified.[5]Lifitegrast decreased scores by -35.30 compared to -22.75 with placebo (MD 12.61; 95% CI, 8.51 to 16.70; p<0.0001).[2] A second study found lifitegrast decreased EDS by -37.9 points compared to -30.7 points for placebo (MD 7.16; 95% CI, 3.04 to 11.28; p=0.0007).[3] Such small mean differences between lifitegrast and placebo suggest changes may not be clinically meaningful.
- The most commonly occurring adverse reactions associated with lifitegrast use were eye irritation after installation, dysgeusia and reduced visual acuity. Early discontinuations were 3% higher in patients treated with lifitegrast compared to placebo (12% vs. 9%, respectively).[6]
- There is insufficient comparative evidence between lifitegrast and other treatments for DED and in subpopulations of patients with DED.

Recommendations:

- Restrict coverage of lifitegrast ophthalmic solution subject to prior authorization. Dry eye disease is not funded by the Oregon Health Plan (OHP).

Background:

It is estimated that over 20 million people in the United States have DED with estimated prevalence rates ranging anywhere from 5% to over 50%.[5] The cause of DED is not known but it is more common in the elderly and in post-menopausal women.[3] Dry eye disease results from disturbance of tear production and changes to the ocular surface that can cause visual disturbances and eye discomfort.[7] Dry eye disease is also known as keratoconjunctivitis sicca, dry eye syndrome and dysfunctional tear syndrome.[7] Symptoms associated with DED include burning, stinging, grittiness, itching and sometimes pain. Classification of DED is categorized as aqueous deficient or evaporative, with the potential for both conditions to occur concomitantly. Risk factors for DED include advanced age, female gender, poorer self-rated health, antidepressant or oral steroid use and Asian heritage.[5] Certain medical conditions are also known to increase the risk for DED:

- Diabetes mellitus
- Sjögren Syndrome
- Untreated thyroid disease
- Systemic inflammatory disease (e.g., graft-versus-host disease, rheumatoid arthritis, systemic lupus erythematosus, scleroderma)
- Lymphoma
- Sarcoidosis
- Chronic viral infections (e.g., hepatitis C, human immunodeficiency virus)
- Ocular surgery

A clinical practice guideline published by the American Academy of Ophthalmology recommends a comprehensive medical history and physical exam to determine if DED is present. Tear function, tear composition, and ocular surface alternations are evaluated to determine DED severity. Diagnosis of DED usually corresponds with 5 characteristics: 1) symptoms of discomfort 2) visual disturbance 3) tear film instability (potential for ocular surface damage) 4) increased osmolarity of tear film and 5) inflammation of the ocular surface.[5] Multiple tests have been used in the diagnosis of DED; however, clinical applicability and significance is unknown. Testing procedures, usually done by ophthalmologist, to aid in the diagnosis of dry eye are:

Schirmer's Test - The Schirmer tear test is used to determine tear section rate. Normal values of the Schirmer 1 test (anesthetic not used) are values greater than 10mm, with dry eye cutoff of 5 mm. This test is used to aid in the diagnosis of DED but is not considered a primary method.[8]

Ocular Surface Staining – Fluorescein staining is used to visualize the corneal surface. DED is associated with increased staining; however, there is low correlation to symptoms of dry eye.[9]

Ora Calibra Corneal and Conjunctival Staining score – Used to evaluate ocular surface staining (described above). Ora Calibra and Conjunctival Staining score is a validated scoring system with scores ranging from 0-4 (0 = none and 4 = confluent).[1] Each area is graded separately. The five areas are inferior, superior, central regions (relative to the cornea), temporal and nasal regions (relative to the conjunctiva). The inferior corneal staining score (ICSS) absorbs the most stain due to increased exposure to the environment.[10]

Tear Film Breakup Time (TFBUT) - The non-invasive tear film break-up time has been recommended as a test with moderately high sensitivity for diagnosing and monitoring DED.[5] Fluorescein is often used to visualize tear film since tear film instability is associated with DED if values are less than 5 seconds and may be a result of DED if less than 10 seconds; however, ocular surface damage does not always occur in DED and the sensitivity of this test to detect changes is considered low.[4,5]

Symptomatic tear-film break up time (SBUT) – The time between blinks when the patient is asked to stare is measured. Patients with dry eye have less corneal sensitivity and exhibit extended times between blinking.[11]

Outcomes used in the study of DED are not standardized and objective measurements do not consistently correlate with symptom severity.[5] Subjective assessment of DED is done by the use of questionnaires and is most indicative of efficacy of treatments. Patient assessment questionnaires that have been used in clinical trials are: McMonnies, Ocular Surface Disease Index (OSDI), Standard Patient Evaluation of Eye Dryness (SPEED), Symptom Assessment in Dry Eye survey (SANDE), Impact of Dry Eye on Everyday Life (IDEEL), Eye Dryness Score (EDS) and the Dry Eye Questionnaire (DEQ-5) (Table 1).[5] Minimum clinically important differences (MCID) in most questionnaires have not been established.

Table 1. Dry Eye Symptom Questionnaires[1,8,12]

Questionnaire	Scoring	Description
McMonnies	14 questions with an index score of 0-45 (higher scores associated with dry eye). Scores >14.5 are recommended for DED diagnosis.	Gender, age, dry eye symptoms, previous treatments, secondary symptoms, medical conditions associated with DED, dryness of mucous membranes and medication use are assessed.
Ocular Surface Disease Index (OSDI)	Scores range from 0-100 with higher scores indicating more severity. Normal range (0-12 points), mild dry eye (13-22 points), moderate dry eye (23-32 points) and severe dry eye (33-100 points). Suggested minimally clinically important difference is a 7.0 to 9.9 when applied to the total score of up to 100 or 4.5-7.3 points for mild to moderate DED or 7.3 to 13.4 points for severe DED.	The OSDI assesses symptoms and vision-related functioning. The OSDI consists of 12 questions related to the following subscales: symptoms, visual-related function (VR-OSDI), and environmental triggers. The subscales are a composite of mean scores ranging from 0-4, with 0 indicating symptoms none of the time and 4 indicating symptoms all the time.
Standard Patient Evaluation of Eye Dryness Questionnaire (SPEED)	Not applicable.	Types of symptoms, time frame, frequency and eye drop use are assessed.
Symptom Assessment in Dry Eye (SANDE)	Uses a 100 mm visual analog scale (VAS).	Quantifies frequency and severity of DED symptoms.
Impact of Dry Eye on Everyday Life (IDEEL)	20-item IDEEL-symptom bother module reports a clinically meaningful difference of 12 points.	Impact of DED on quality of life and daily living.
Eye Dryness Score (EDS)	The scores range from 0 (no discomfort) to 100 (maximal discomfort). No minimally clinically important difference has been identified.	The EDS is used to quantify patient discomfort based on a VAS.
Dry Eye Questionnaire (DEQ-5)	Scores of >6 indicate DED and scores >12 suggest Sjögren Syndrome.	Assesses frequency of watery eyes, discomfort, dryness, and late day intensity of discomfort and dryness.

There is no cure for DED. Management of dry eye depends on the severity level. Avoiding medications, such as systemic antihistamines and anticholinergics, which may cause or aggravate DED can be helpful. In patients with moderate to severe DED, artificial tears, anti-inflammatories (topical glucocorticoids), corticosteroids, topical cyclosporine (Restasis 0.05%) and punctal plugs can be considered.[8,13] Artifical tears is considered first-line treatment for dry eye.[7] Lifitegrast and cyclosporine ophthalmic preparations require a prescription for use.[6] Lifitegrast prevents the pro-inflammatory process associated with DED by targeting cytokines which block binding of lymphocyte function-associated antigen-1 (LFA-1). LFA-1 is a cell surface protein found on leukocytes which interacts with other molecules to produce an immune response. Topical cyclosporine helps to increase tear production.[14] Studies of ophthalmic cyclosporine showed the drug increased tear production by about 10% increase.[14]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Lifitegrast ophthalmic 5% solution is used for the treatment of dry eye symptoms. The approved dosage is to instill 1 drop twice daily.[6] Lifitegrast was studied in two phase 3 trials (OPUS-1 and OPUS-2); but due to lack of consistency in findings and failure to meet co-primary endpoints, the FDA required a third phase 3 study (Table 3).[1,2,3] This study has not been published but data available from the FDA will be presented.[3]

OPUS-1

Patients over the age of 18 years with a history of bilateral dry eye were randomized to lifitegrast 5.0% or placebo given as 1 drop in each eye twice daily.[1] Patients satisfying initial screening were subjected to acute environmental stress (standardized temperature, humidity, air-flow, ambient light, and visual-tasking). To be included in the study, patients had to have worsening in inferior corneal fluorescein staining and ocular discomfort score (ODS). Subjects without worsening scores were excluded. One eye was designated to be enrolled in the study based on specified criteria. If both eyes qualified then the right eye would be the eligible study eye. Patients included in the study were a mean age of 61 years, predominately female (76%), 93% white, and they had moderate DED as indicated by a baseline ocular surface disease index OSDI score of 26. The primary outcome was change in inferior corneal staining lesions from baseline at 12 weeks, which has been shown to have a low correlation to symptoms.[1] Key secondary outcomes were changes in visual-related function subscale score of the Ocular Surface Disease Index (VR-OSDI) from baseline. The VR-OSDI measures vision related functions from 0 (none of the time) to 4 (all of the time). Study assessments were performed on days 14, 42 and 84. Results were analyzed on the modified intention-to-treat (mITT) population, using last observation carried forward (LOCF) for missing data. Lifitegrast reduced inferior corneal staining by -0.75 compared to placebo treated patients which increased by 0.16 (p=0.0007) (CI not provided). Numeric results were not provided for the visual related (VR) OSDI but changes from baseline for lifitegrast and placebo were not significantly different (p=0.7894). There were also 6 VAS subjective supportive endpoints that were evaluated and eye dryness was the only one that was found to be significantly less with lifitegrast compared to placebo (40.2% vs.41.6%); however, this is not clinically significant.[1] This endpoint was then used as a co-primary endpoint in future studies. Using corneal staining scores as a primary endpoint is limited because it is not considered a sensitive measure and does not correlate with dry eye symptoms. Limitations to the data include outcomes studied, a short term study of mostly white female patients and high level of reporting bias. There was also a chance for selection bias due to poor concealment of allocation procedures.

OPUS-2

Adult patients were randomized to lifitegrast 5.0% or placebo in a phase 3, randomized, double-blind controlled trial lasting 12 weeks.[2] Patients entered a 14-day screening period before randomization. During screening exams at day -14 and day 0, the eye which tested the worse on the ICSS was designated the study

eye. This was most likely done because it would be easier to show a benefit in an eye that has worse test scores. After randomization, patients were assessed at day 14, 42 and 84. Patients included in the study were a mean age of 59 years, 77% were female, current users of artificial tears, self-reported DED and had moderate to severe DED as measured by the eye dryness score. Sixty-six percent of placebo treated patients and 65% of lifitegrast patients had baseline eye dryness scores of ≥ 60 at baseline. The co-primary endpoints were the changes in eye dryness score, measured by VAS in both eyes (questionnaire used not specified), and inferior corneal fluorescein staining score from the designated eye.[2] The VAS is a 7 item patient reported symptom scale ranging from 0-100, with 0 = no discomfort and 100 = maximal discomfort. A secondary outcome was change in ocular discomfort score (scale of 0-4, with 0 = no discomfort, 4 = severe discomfort) in the designated study eye.

The first co-primary endpoint, change in eye dryness score, was improved by -35.30 in the lifitegrast group compared to -22.75 in the placebo group (TE [treatment effect] 12.61; 95% CI, 8.51 to 16.70; p<0.0001). The second co-primary endpoint, ICSS in designated eye, was similar for lifitegrast and placebo (-0.73 and -0.71, respectively). The ocular discomfort score was improved by -0.91 in the lifitegrast group versus -0.57 in the placebo group (TE 0.34; 95% CI, 0.15 to 0.53; p=0.0005). Lifitegrast was more effective than placebo at decreasing the mean eye discomfort score (-26.46 and -16.73, respectively) (p<0.0001).[2] The co-primary outcomes ICSS and change in eye dryness score are limited by the unknown clinical significance of these tests. This study has the potential for selection bias since patients included into the study had to have a positive response to eye dryness by VAS to be enrolled and details of VAS questionnaire were not provided. Patients were self-diagnosed with DED which was not confirmed by a provider. The study was of short duration which limits applicability to a chronic eye condition. The study results would have the most applicability to white women.

OPUS-3 (unpublished; FDA analysis)
In a third phase 3 trial required by the FDA, lifitegrast 5.0% was compared to placebo in 711 patients in a randomized, double-blind fashion.[3] Patients were a mean age of 59 years, 75% female and 75% white. Most patients had an ICSS score greater than 1.5 and an eye dryness score greater than 60. The use of artificial tears within 30 days of study randomization was required. Patients had to be willing to suspend artificial tear use during the study, which suggests the symptoms of dry eye were not severe The primary endpoint was change in EDS, as assessed by VAS, from baseline at day 84. Key secondary endpoints were changes in EDS at day 14 and day 42. At day 84 the EDS decreased by 37.9 with lifitegrast compared to 30.7 with placebo (mean difference 7.16 points; 95% CI, 3.04 to 11.28; p=0.0007).[3] Lifitegrast was also associated with greater improvements in EDS compared to placebo at day 14 and 42 (p<0.0001 for both comparisons).[3] Limited details on study design provided by the FDA made assessment of bias incomplete. Prohibited medications were used by 3.9% of patients taking lifitegrast and 3.1% of patients taking placebo and 3.2% of total population were randomized even though they failed to meet study inclusion or exclusion criteria. The small difference in EDS between lifitegrast and placebo of 7.16 points represents only a small change on a 100 point scale, which suggest results are not clinically significant. Extensive exclusion criteria limits external validity.

Clinical Safety:
Assessment of safety for lifitegrast is limited because the short duration of clinical trials; however, one safety study was conducted for 12 months. The most commonly occurring adverse reactions were irritation due to installation, dysgeusia and reduced visual acuity.[6] Other adverse reactions occurring in 1-5% of patients were the following: blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.[6] In the 12-month safety study, lifitegrast was associated with withdrawal due to adverse events in 12.3% compared to 9.0% of placebo treated patients.[15] Adverse events were similar to short term trials with no severe adverse reactions in either group.

Pharmacology and Pharmacokinetic Properties:

Table 2. Pharmacology of Lifitegrast.

Parameter	
Mechanism of Action	Lymphocyte function-associated antigen-1 (LFA-1) antagonist[6]
Absorption	NA
Distribution and Protein Binding	NA
Metabolism	NA
Half-Life	NA
Elimination	NA

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Ocular symptoms
2) Visual disturbances

Primary Study Endpoint:
1) ICSS change from baseline
2) EDS change from baseline

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. OPUS-1[1] RCT, DB, PC, PG, MC	1. Lifitegrast 5.0% solution 1 drop BID (L) 2. Placebo 1 drop BID (P) Duration: 12 weeks	Demographics: Age: 61 years Male: 24% White: 93% Cataract hx: 52% ICSS: 1.83 OSDI score: 26 Key Inclusion Criteria: • Age ≥18 years • bilateral dry eye disease • use of or desire to use artificial tears in previous 6 mo. • Conjunctival redness • Corneal fluorescein staining score of ≥2.0 • STT of ≥1 to ≤10 • Best-corrected visual acuity of ≥0.7 logarithm Key Exclusion Criteria: • Ocular inflammation • Ocular infection • Ocular surgery within 12 months • Contacts • Pregnancy	mITT: L: 293 P: 295 Attrition: L: 4% P: 4%	Primary Endpoint: Change from baseline in inferior corneal staining score: L: -0.75 P: 0.16 MD 0.91 (CI not reported) p=0.0007	NA	D/C due to Adverse Events: L: 10 (3.4%) P: 3 (1%) p=NR Instillation Site Irritation: L: 69 (24%) P: 12 (4%) p=NR Instillation Site Pain: L: 63 (22%) P: 11 (4%) p=NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (high) randomized 1:1 by unmasked independent statistician. There were 5% more males in the placebo group than the lifitegrast group and 4% more patient in the placebo group with history of cataracts compared to the lifiterast group. Performance Bias: (low) packaging of active and placebo treatments were identical. All study personnel and patients were masked to treatment assignment. Detection Bias: (unclear) blinding of outcome assessors was not described. Attrition Bias: (low) ITT with LOCF used for analysis. Low attrition rate in both groups. Reporting Bias: (high) all pre-specified endpoints reported but results and CI not provided. The study was funded by the manufacturer. **Applicability**: Patient: only applies to patients with DED and no other inflammatory eye conditions. Not all patients with DED have corneal lesions but this was required for study enrollment. ODSI score of 26 at baseline suggests moderate DED. Use of artificial tears had to be discontinued 72 hours prior to visit 1. Intervention: dosage appropriate according to FDA labeling. Comparator: placebo comparison appropriate to assess efficacy. Outcomes: primary endpoint does not always correlate with dry eye symptoms. Setting: 13 US sites.

2. OPUS-2[2] RCT, DB, PC, PG, MC	1. Lifitegrast 5.0% solution 1 drop BID (L) 2. Placebo 1 drop BID (P) Duration: 12 weeks	Demographics: Age: 59 years Male: 23% White: 85% Cataract hx: 35% ICSS: 2.40 Eye dryness score: 69 Key Inclusion Criteria: • Age ≥18 years • self-reported dry eye disease • artificial tear use within the previous 30 days • Corneal fluorescein staining score of ≥2.0 in ≥1 eye region • Conjunctival redness eye score ≥1 in ≥1 eye region • Eye dryness score ≥40 and positive response in >1 eye • Best-corrected visual acuity of >0.7 logarithm Key Exclusion Criteria: • Systemic or ocular steroid use • Immuno-deficient/ suppressed • Ocular inflammation • Ocular infection • Pregnancy • Topical cyclosporine • Ophthalmic meds • Aspirin or antihistamine use • LASIK last 12 months • Contact lens use	mITT: L: 358 P: 360 Attrition: L: 10% P: 3%	Co-Primary Endpoints: Change from baseline in EDS (VAS) in both eyes: L: -35.30 P: -22.75 MD 12.61 (95% CI, 8.51 to 16.70; p<0.0001) ICSS in designated eye: L: -0.73 P: -0.71 MD 0.03 (95% CI, -0.10 to 0.17; p=0.6186) Secondary Endpoint: Ocular Discomfort Score (study eye only): L: -0.91 P: -0.57 MD 0.34 (95% CI, 0.15 to 0.53; p=0.0005) Eye Discomfort Score (both eyes)*: L: -26.46 P: -16.73 MD 9.77 (95% CI, 5.27 to 14.28; p<0.0001) * The eye discomfort score is measured by VAS and reported as a single score for both eyes. The EDS score used the same scoring system but may have been comprised of different terms but methodology was not described.	NA NA NA NA	D/C due to Adverse Events: L: 26 (7.3%) P: 3 (0.83%) p=NR Instillation Site Irritation: L: 11 (3.1%) P: 1 (0.3%) p=NR Instillation Site Pain: L: 5 (1.4%) P: 1 (0.3%) p=NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (high) randomized 1:1 by interactive web response system. There were 6% more females in the lifitegrast group compared to placebo. Performance Bias: (low) packaging of active and placebo treatments were identical. All study personnel and patients were masked to treatment assignment. Detection Bias: (unclear) outcome assessment was not described. Attrition Bias: (low) mITT with LOCF used for analysis. Low attrition rate in both groups. Reporting Bias: (low) all pre-specified endpoints reported. Study was funded by the manufacturer. **Applicability**: Patient: patients had to respond to placebo treatment in screening phase to be included. Patients were self-diagnosed with DED and had used artificial tears. Extensive exclusion criteria, including conditions associated with DED, limits applicability to most patients. Intervention: dosage appropriate based on FDA labeling. Comparator: placebo comparison appropriate to assess efficacy. Outcomes: eye dryness score and ICSS commonly used in ophthalmic studies but clinically meaningful changes have not been identified. Outcome methodology was not clear. Setting: Thirty US sites.

3. OPUS-3[3] RCT, DB, PC, PG, MC	1. Lifitegrast 5.0% solution 1 drop BID (L) 2. Placebo 1 drop BID (P) Duration: 12 weeks	Demographics: Age: 58 years Male: 24% White: 77% Key Inclusion Criteria: See OPUS-1 Key Exclusion Criteria: See OPUS-2	mITT: L: 355 P: 356 Attrition: L: 10% P: 10%	Primary Endpoints: Change from baseline in EDS: L: -37.9 P: -30.7 TE 7.16 (95% CI, 3.04 to 11.28; p=0.0007) Secondary Endpoint: Change from baseline in EDS at day 42: L: -33.2 P: -23.9 MD 9.32 (95% CI, 5.44 to 13.20; p<0.0001) Change from baseline EDS at day 14: L: -22.9 P: -15.0 MD 7.85 (95% CI, 4.33 to 11.37; p<0.0001)	NA NA NA	D/C due to Adverse Events: L: 22 (6.2%) P: 9 (2.5%) p=NR Instillation Site Irritation: L: 65 (18.2%) P: 11 (3.1%) p=NR Instillation Site Pain: L: 8 (2.2%) P: 0 p=NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) randomization not reported. Performance Bias: (unclear) no details on masking of drug allocation or physician and patient blinding. Detection Bias: (unclear) outcome assessment was not described. Attrition Bias: (low) mITT with LOCF used for analysis. Low attrition rate in both groups. Reporting Bias: (low) pre-specified endpoints reported. Study funded by the manufacturer. **Applicability**: Patient: majority of patients had an inferior corneal staining score of >1.5 and an eye dryness score of ≥60. Patients were users of artificial tears at study entry but willing to suspend treatment while in study, suggesting moderate symptoms. Extensive exclusion criteria, including conditions associated with DED, limits applicability to most patients. Intervention: dosage appropriate based on FDA labeling. Comparator: placebo comparison appropriate to assess efficacy. Outcomes: eye dryness score commonly used in ophthalmic studies but clinically meaningful changes have not been identified. Setting: Forty-two US sites.

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BID = twice daily; CI = confidence interval; DED = dry eye disease; EDS = eye dryness score (ranges from 0-100, higher scores indicating more eye discomfort); ICSS = inferior corneal staining score; ITT = intention to treat; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OSDI = Ocular Surface Disease Index; PP = per protocol; STT = Schirmer's tear test; TE = treatment effect; VAS = visual analog scale used in EDS; VR-OSDI = visual-related function subscale score of the Ocular Surface Disease Index (range 0-4).

References:

1. 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. doi:10.1016/j.ophtha.2013.09.015.
2. 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. doi:10.1016/j.ophtha.2015.08.001.
3. Food and Drug Administration. Xiidra (lifitegrast opthalmic solution) Medical Review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208073Orig1s000MedR.pdf. Published June 24, 2015. Accessed September 14, 2016.
4. Savini G, Prabhawasat P, Kojima T, Grueterich M, Espana E, Goto E. The challenge of dry eye diagnosis. *Clin Ophthalmol*. 2008;2(1):31-55.
5. Chao W, Belmonte C, Benitez del Castillo JM, et al. Report of the inaugural meeting of the TFOS i2 = initiating innovation Series: targeting the unmet need for dry eye treatment. *The Ocular Surface*. 2016;14(2):264-316. doi:10.1016/j.jtos.2015.11.003.
6. Xiidra (lifitegrast ophthalmic solution) [Prescribing Information]. Lexington, MA: Shire US Inc. June 2016.
7. Shtein R. Dry Eyes - UpToDate. *UpToDate*. December 22, 2015. Accessed November September 14, 2016.
8. Foulks G, Forstot L, Donshik P, et al. Clinical guidelines for management of dry eye associated with SjÖgren Disease. *Ocular Surface*. 2015;13(2):118-132.
9. Abelson MB, Holly FJ. A tentative mechanism for inferior punctate keratopathy. *Am J Ophthalmol*. 1977;83(6):866-869.
10. Ousler GW, Abelson MB, Nally LA, et al. Evaluation of the time to “natural compensation” in normal and dry eye subject populations during exposure to a controlled adverse environment. *Adv Exp Med Biol*. 2002;506(Pt B):1057-1063.
11. Abelson MB, Welch D, Netwig B. Symptomatic break-up time (SBUT) in dry eye patients with normal vs. low corneal sensitivity. *Investigative Ophthalmology and Visual Science*. 2009;13.
12. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol*. 2010;128(1):94-101. doi:10.1001/archophthalmol.2009.356.
13. American Academy of Ophthalmology. Dry eye syndrome summary benchmark - 2015. American Academy of Ophthalmology. http://www.aao.org/summary-benchmark-detail/dry-eye-syndrome-summary-benchmark--october-2012. Published November 1, 2015. Accessed September 15, 2016.
14. Restasis (cyclosporine ophthalmic emulsion) [Prescribing Information]. Irvine, CA: Allergan, Inc. June 2013.
15. 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. doi:10.1097/ICO.0000000000000803.

Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XIIDRA safely and effectively. See full prescribing information for XIIDRA.

XIIDRA™ (lifitegrast ophthalmic solution) 5%, for topical ophthalmic use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------
Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist indicated for the treatment of the signs and symptoms of dry eye disease (DED). (1)

----------DOSAGE AND ADMINISTRATION----------
One drop twice daily in each eye (approximately 12 hours apart). (2)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution containing lifitegrast 5% (50 mg/mL). (3)

----------CONTRAINDICATIONS----------
None (4)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence 5-25%) following the use of Xiidra were instillation site irritation, dysgeusia and decreased visual acuity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov./medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2016