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APPLICATION NUMBER:

208073Orig1s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, MD , MPH
Subject	Deputy Office Director Decisional Memo
NDA#	208073
Applicant Name	Shire Development, LLC
Date of Submission	February 25, 2015/January 22, 2016
PDUFA Goal Date	July 22, 2016
Proprietary Name / Established (USAN) Name	Xiidra / (lifitegrast ophthalmic solution) 5%
Dosage Forms / Strength	Topical ophthalmic solution
Action:	Approval
Approved Indication	Treatment of the signs and symptoms of dry eye disease

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer Review	Rhea Lloyd, MD
Statistical Review	Solomon Chefo, PhD
Pharmacology Toxicology Review	María I. Rivera, PhD
Clinical Pharmacology Review	Gerlie Gieser, PhD
MMPP/OPDP	Sharon W. Williams, MSN, BSN, RN/Meena Ramachandra, PharmD
OSI	Roy Blay, Ph.D.
OSE/DMEPA	Michelle Rutledge, PharmD
Clinical Outcomes Assessment	Selena Daniels, PharmD, MS
Pediatric and Maternal Health	Suchitra M. Balakrishnan, MD, PhD
CDTL Review	William Boyd, MD
Deputy Division Director Review	Wiley Chambers, MD

Quality Review Team

Drug Substance	Monica Cooper	OPQ/ONDP/DNDAPI/NDBI
Drug Product	Shrikant Pagay	OPQ/ONDP/DNDPI/NDPBIII
Process	Edwin Jao	OPQ/OPF/DPAIII/PABVII
Microbiology	Denise Miller	OPQ/OPF/DMA/MABII
Facility	Frank Wackes	OPQ/OPF/DIA/IABII
Biopharmaceutics	Elsbeth Chikhale	OPQ/ONDP/DB/BBI
Regulatory Business Process Manager	Erin Andrews	OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang	OPQ/ONDP/DNDPI/NDPBIII
ORA Lead	Paule Perdue	OGROP/ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	James Laurenson	OPQ/ONDP

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Dry eye disease is a condition in which either the quality or quantity of natural tears are insufficient. Clear vision is dependent on having a thin tear film over the central cornea. Discomfort and/or pain will occur if the tear film is absent from the cornea and/or conjunctiva for a prolonged period of time. The cornea and/or conjunctiva are at higher risk of infection or other injury when not covered by a tear film, including sight threatening injury. There is an unmet need for new drug products to treat the signs and symptoms of dry eye disease.

Lifitegrast (LIF) ophthalmic solution 5% is an antagonist of LFA-1 (also known as CD11a/CD18 or αLβ2) formulated as an unpreserved (b) (4) sterile eye drop. LIF is thought to act by binding to the LFA-1 T-cell surface antigen and preventing interaction with its cognate ligand, ICAM-1 (also known as CD54), ultimately resulting in a reduction of the expression of pro-inflammatory cytokines. NDA 208073 for LIF 5% was originally submitted on February 25, 2015 and received a Complete Response on October 16, 2015. Based on the original NDA review, the review team concluded and I concurred that there was a lack of substantial evidence of efficacy due to the lack of consistent findings for the primary sign and symptom endpoints. In addition, there were deficiencies concerning the acceptance limit for (b) (4) and specification standards for impurities, particulates, and leachables.

In this resubmission, the applicant includes the results of an additional adequate and well-controlled trial, OPUS-3, and addresses the product quality deficiencies. I concur with the Clinical Reviewer, Statistical Reviewer, CDTL, and Deputy Division Director that this resubmission provides substantial evidence of efficacy for the treatment of the signs and symptoms of dry eye disease in adults. The concerns regarding consistency of efficacy findings that arose in the review of the initial submission have been addressed. The product quality deficiencies have been adequately addressed.

The primary symptom endpoint used in the clinical trials is an appropriate measure of clinical benefit (how patients feel and function) for adult patients with dry eye disease. OPUS-3 demonstrated robust superiority for LIF 5% over vehicle for the pre-specified primary symptom endpoint. The findings of OPUS-3, supported by the findings of the OPUS-1 and OPUS-2 trials, constitute substantial evidence of efficacy. Strongly supportive of this consistent finding of clinical benefit measured by the symptom endpoint in OPUS-1, OPUS-2, and OPUS-3, are consistent findings of superiority for LIF 5% over vehicle for the sign endpoint observed in three trials. The adverse drug reactions observed in clinical trials were application site reactions, dysgeusia, and reduced visual acuity and would be expected to be of short duration. I conclude that the overall benefit-risk supports approval of LIF 5% for the treatment of the signs and symptoms of dry eye disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• I concur with the Deputy Division Director that: "Dry eye disease is a condition in which either the quality or quantity of natural tears are insufficient to provide a thin tear film over the cornea and conjunctiva for at least as long as the interval between one blink and the next. The condition occurs in both men and women, is frequently associated with increasing age and is most common in post-menopausal women. It rarely occurs in children. The cause is unknown."	I concur with the Deputy Division Director that: "The severity of dry eye disease depends on the duration of time that the cornea and/or conjunctiva is not covered by a tear film. Clear vision is dependent on having a thin tear film over the central cornea. Discomfort and/or pain will occur if the tear film is absent from the cornea and/or conjunctiva for a prolonged period of time. The cornea and/or conjunctiva are at higher risk of infection or other injury when not covered by a tear film, including sight threatening injury."
Current Treatment Options	• I concur with the Deputy Division Director that: "There are no approved therapies for the treatment of the signs and symptoms of dry eye disease. There are drug products that meet the conditions described in the over-the-counter monograph that are available for temporary relief of burning and irritation due to dryness of the eye. There is one approved product for increasing tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation."	I concur with the Deputy Division Director that there is an unmet need for new drug products to treat the signs and symptoms of dry eye disease.
Benefit	• For the indication: "treatment of the signs and symptoms of dry eye disease", the Agency recommended to the applicant that efficacy trials evaluate both a sign and symptom endpoint. For this application, the following endpoints were used in clinical trials and important in demonstrating efficacy: o Sign – The Inferior Corneal Staining Score (ICSS). Scores range from 0 to 4 (0 = no staining, 4 = severe; 0.5-point increments; in the superior, central, and inferior corneal zones) o Symptom – The Visual Analog Scale Symptom Index – Eye	I concur with the Clinical Reviewer, Statistical Reviewer, CDTL, and Deputy Division Director that this resubmission provides substantial evidence of efficacy for the treatment of the signs and symptoms of dry eye disease in adults. The concerns regarding consistency of efficacy findings that arose in the review of the initial submission have been addressed.

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	Dryness Score; Eye Discomfort Score (EDS). Patients are asked to subjectively rate each ocular symptom (burning/stinging, itching, foreign body sensation, eye discomfort, eye dryness, photophobia, and pain) by placing a vertical mark on a horizontal line ranging from 0% (no discomfort) to 100% (maximal discomfort). The Clinical Outcome Assessment Reviewer concluded that, based on face validity, the EDS measures the appropriate key symptoms of patient-reported dry eye and discomfort and appeared fit for purpose for this drug development program. • The Phase 2 trial KCS-100, and the Phase 3 trials OPUS-1, OPUS-2 and OPUS-3 were submitted to provide evidence of efficacy. The four trials were multicenter, randomized, double-masked, vehicle-controlled studies conducted in adult patients with dry eye disease in the U.S. and were similar in design. Each trial was 14 weeks in duration with five trial visits at Days -14, 0, 14, 42, and 84. There was a two week open label vehicle run-in screening period followed by a 12 week treatment period. Treatment in each trial was administered as a single drop twice daily (AM and PM) in each eye for 12 weeks. For each trial, the primary analysis was performed in the ITT population using the last observation carried forward (LOCF) method for imputing missing data. ○ Trial KCS-100: 230 patients with dry eye were randomized to LIF 0.1, 1, 5% or vehicle ophthalmic solution. The primary efficacy endpoint was the ICSS of the designated trial eye at Day 84. None of the LIF groups achieved a statistically significant difference compared to vehicle. The mean reduction in ICSS at Day 84 in the LIF 5% treated group was higher than in the vehicle treated group by about a quarter unit, and this difference was marginally significant (p = 0.049). The change in symptom scores at Day 84 including	The EDS as a primary symptom endpoint is an appropriate measure of clinical benefit (how patients feel and function) for adult patients with dry eye disease. OPUS-3 demonstrated robust superiority for LIF 5% over vehicle for the pre-specified primary endpoint of mean change in EDS from baseline at Day 84. While OPUS-1 and OPUS-2 failed their pre-specified co-primary endpoints, I find the robust treatment difference for LIF 5% over vehicle for this same endpoint of mean change in EDS from baseline at Day 84 in OPUS-1 and OPUS-2 to be strongly supportive. Thus, the findings of OPUS-3, supported by the findings of OPUS-1 and OPUS-2, constitute substantial evidence of efficacy. Strongly supportive of this consistent finding of clinical benefit measured by the symptom endpoint in OPUS-1, OPUS-2, and OPUS-3, are consistent findings of superiority for LIF 5% over vehicle for the sign endpoint of the mean change in ICCS from baseline at Day 84 in OPUS-1, KCS-100, and OPUS-3. While there are statistical uncertainties (failed co-primary endpoint OPUS-1, borderline statistical significance KCS-100, post-hoc analysis OPUS-3), I find the consistency of the findings to be persuasive and supportive of clinical

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	the EDS were numerically better for the treatment arm. ○ Trial OPUS-1: 588 patients were randomized to LIF 5% or vehicle. The primary efficacy co-primary endpoints were the mean change in ICSS from baseline at Day 84 and the patient-reported symptom endpoint of the Visual-Related Function Subscale of the Ocular Surface Disease Index (VR-OSDI) score mean change from baseline at Day 84. The mean change in ICSS at Day 84 treatment difference (LIF 5.0% minus vehicle) was -0.23 (95% CI: -0.36, -0.09) in favor of LIF (p-value = 0.0007). The mean change in VR-OSDI score at Day 84 treatment difference was -0.01 (95% CI: -0.12, 0.10) and not statistically significant. The EDS was a secondary endpoint for OPUS-1. In OPUS-1, the mean change in EDS at Day 84 treatment difference was -4.7 (95% CI: -8.9, -0.4; p-value = 0.0311) in favor of LIF. ○ Trial OPUS-2: 718 patients were randomized to LIF 5% or vehicle. Based on history of artificial tear use and patient-reported symptom scores, OPUS-2 enrolled patients who appear somewhat more symptomatic than the patients enrolled in KCS-100 or OPUS-1. The primary efficacy co-primary endpoints were the mean change in ICSS from baseline at Day 84 and the mean change in EDS from baseline at Day 84. In OPUS-2, both groups demonstrated comparable mean reductions in ICSS at Day 84; the treatment difference was -0.03 (95% CI: -0.16, 0.10) and not statistically significant. The mean change in EDS at Day 84 treatment difference was -12.3 (95% CI: -16.4, -8.3) and was statistically significant (p-value < 0.0001) in favor of LIF.	benefit. While not pre-specified, I find the ANCOVA modeling to be useful to understand the overall consistency of results of these trials demonstrating clinical benefit. Section 14 of the prescribing information illustrates trial results using figures based on ANCOVA modeling. I agree that this is appropriate as the trial results will be more easily understood by health care providers.

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	○ Trial OPUS-3: 711 patients were randomized to LIF 5% or vehicle. Similar to OPUS-2, all patients enrolled in this trial had documented history of artificial tear use within 30 days prior to the screening visit on Day -14 and EDS ≥ 40 at baseline. OPUS-3 included a single primary efficacy endpoint: the mean change in EDS from baseline at Day 84. The mean change in EDS at Day 84 was -38 (95% CI: -41, -35) in the treatment arm and was -31 (95% CI: -33, -28) in the vehicle arm; the treatment difference was -8 (95% CI: -12, -4) and was statistically significant (p-value = 0.0003). Although mean change in ICSS at Day 84 was pre-specified as a safety analysis, the Statistical Reviewer performed a post-hoc analysis at the request of the review team and found the mean change in ICSS at Day 84 in the treatment arm was -0.80 (-0.90, -0.70) and in the vehicle arm was -0.63 (-0.73, -0.54); the treatment difference was -0.17 (95% CI: -0.30, -0.03; p-value = 0.0135). • As there were differences in pre-specified analytic plans among trials, the Statistical Reviewer also used analysis of covariance (ANCOVA) modeling to assess the efficacy trials. In the ANCOVA models, the change in EDS (or the change in ICSS) from baseline at Day 84 was used as the response variable; and treatment, baseline EDS (or the baseline ICSS), and stratification factor (specific to the Phase 3 studies) were used as covariates in the models. ○ In OPUS-2 and OPUS-3, patients treated with LIF 5% demonstrated statistically superior improvement in EDS early on and continued improvement throughout the study compared to vehicle treated patients. At the end of the treatment period on Day 84, the improvement in EDS observed in the LIF 5% treated group was higher than in the vehicle treated group by about 12 units in	

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	OPUS-2, 8 units in OPUS-3, 5 units in OPUS-1, and 7 units in KCS-100. ○ In KCS-100 and OPUS-1, vehicle treated patients showed worsening in ICSS at Day 84 whereas LIF 5.0% treated patients in these trials showed no change from baseline on average. In both trials, the mean reduction in ICSS at Day 84 in the treatment arm was higher than in the vehicle arm by about a quarter unit, and this difference was statistically significant in OPUS-1 ($p < 0.001$) and was marginally significant in KCS-100 ($p = 0.048$). In OPUS-2 and OPUS-3, both vehicle and LIF 5% treated patients demonstrated at least half unit improvement early on (at Day 14) and continued improving throughout the study. At the end of the treatment period on Day 84; both groups in OPUS-2 showed equal amount of improvement (about 0.7 units) from baseline on average, and LIF 5% treated patients in OPUS-3 showed about 0.8 unit improvement from baseline while vehicle treated patients showed about 0.6 unit improvement from baseline.	
Risk	• The overall safety data base included 1,287 patients exposed to LIF. There were 2 deaths assessed by the Clinical Reviewer as unrelated to study drug. The Serious Adverse Event rate was similar for LIF and vehicle, and assessed by the Clinical Review as not related to study drug. The most common adverse reactions following installation of LIF 5% occurring with an incidence greater than 5% were: dysgeusia (15%), instillation site irritation (15%), installation site reaction (12%), instillation site pain (10%) and visual acuity reduced (5%). These adverse reactions would be expected to be of short duration. • Product Quality deficiencies concerning the acceptance limit for [redacted] (b) (4) and specification standards for impurities, particulates, and leachables were adequately addressed in this resubmission.	I concur with the review team, CDTL, and Deputy Division Director that there are no safety issues precluding approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• See above	I concur with the Clinical Reviewer, CDTL, and Deputy Division Director that risks can be adequately mitigated through labeling and that standard post-marketing safety surveillance is expected to be adequate to monitor for rare and unexpected adverse events.

2. Further discussion to support regulatory action

Product Quality

Quality Micro and Biopharmaceutics Reviewers recommended approval of the NDA. All Complete Response Letter issues including drug substance, drug product and process were deemed to have been satisfactorily resolved. The Office of Process and Facilities (OPF) had provided an overall recommendation of "acceptable" for the facilities on Feb 26, 2016. The NDA was recommended for approval from the Product Quality perspective.

Nonclinical Pharmacology/Toxicology

The Pharmacology Toxicology Reviewer recommended approval. She noted that the Complete Response Letter deficiencies regarding the acceptance limit for (b) (4) and impurity identification/standards had been adequately addressed.

During the initial review cycle, repeat dose ocular toxicity studies, intravenous toxicity studies in dogs and rats, a fertility and embryofetal development study in rats and a rabbit embryofetal development study had been reviewed. No issues were identified that would preclude approval.

Clinical Pharmacology

The Clinical Pharmacology Reviewer recommended approval. The clinical pharmacology data in this NDA (reviewed during the initial cycle) consists of plasma PK and tear fluid PK in healthy subjects enrolled in a Phase 1 trial, sparse plasma PK and PD (lymphocyte counts) in a subset of dry eye disease patients enrolled in the SONATA trial, and *in vitro* data on LIF metabolism in human hepatocytes, protein binding, and CYP2C9 inhibitory potential, as well as *in vitro* primary pharmacodynamic and cardiovascular safety pharmacology.

There were 9 patients with detectable ($\geq$ 0.5 ng/mL) plasma LIF trough concentrations (C_{trough}) in the SONATA trial. Two of these patients had pre-dose concentrations that exceeded the EC50 (2.5 ng/mL) for inhibiting T-cell adhesion in vitro, and an additional patient had a CD8 count < 220/µL measured on Day 180. The applicant stated that these 3 patients did not experience systemic infections or immunosuppressive complications during the 12 month treatment period.

Advisory Committee Meeting

As there were no efficacy or safety issues that would benefit from an Advisory Committee discussion, an Advisory Committee was not convened to discuss this NDA.

Pediatrics

Because dry eye disease does not occur in sufficient numbers in the pediatric population, LIF has not been studied in clinical studies with pediatric patients. This application was presented at the Pediatric Review Committee (PeRC) during the first review cycle. PeRC concurred that a waiver of required pediatric assessments was appropriate as necessary studies are impossible or highly impracticable.

Other Relevant Regulatory Issues

The proposed proprietary name, Xiidra, was re-reviewed and found acceptable from both a promotional and safety perspective.

Risk Evaluation and Mitigation Strategies

The Division of Risk Management (DRISK) and the review team concurred that a REMS is not necessary.

Postmarketing Requirements and Commitments

No Postmarketing Requirements or Commitments will be included in the Approval Letter. Standard post-marketing safety surveillance is expected to be adequate to monitor for rare and unexpected adverse events.

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/s/

JOHN J FARLEY
07/11/2016