

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208073Orig1s000**

**OTHER REVIEW(S)**

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** May 27, 2016  
**Requesting Office or Division:** Division of Transplant and Ophthalmology Products (DTOP)  
**Application Type and Number:** NDA 208073  
**Product Name and Strength:** Xiidra (lifitegrast) ophthalmic solution, 5%  
**Submission Date:** January 22, 2016  
**Applicant/Sponsor Name:** Shire  
**OSE RCM #:** 2016-198  
**DMEPA Primary Reviewer:** Michelle Rutledge, PharmD  
**DMEPA Team Leader:** Yelena Maslov, PharmD

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#### 1 PURPOSE OF MEMO

The Division of Transplant and Ophthalmology Products (DMIP) requested that we review the revised container label, foil labeling, carton labeling, prescribing information and instructions for use (IFU) for Xiidra (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

#### 2 CONCLUSION

DMEPA concludes that the revised labeling can be improved to promote the safe use of the product. We provide recommendations in Section 3 below and advise these are implemented prior to the approval of this NDA.

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<sup>1</sup> Vee S. Label and Labeling Review for Xiidra (NDA 208073). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 MAY 29. 2 p. OSE RCM No.: 2015-593.

In addition, on February 24, 2016, we note, the Agency provided the following recommendations via email to the applicant regarding the proposed single-use container label and foil pouch label:

The (b) (4) should use the correct established name, **Lifitegrast ophthalmic solution 5%**.

Regarding the proposed draft foil pouch artwork:

Recommend that Shire revise Usual dosage to read: **One drop twice a day in each eye. Use one single-use container immediately after opening and then discard.**

Recommend that Shire revise Storage to read: **Store at 25°C (77°F). Store remaining single-use containers in the original foil pouch."**

DMEPA recommends, for consistency, that these changes, where applicable, be added to the label and labeling, as well.

### **3 RECOMMENDATIONS FOR SHIRE**

We recommend the following be implemented prior to approval of this NDA:

#### **A. Instructions for Use**

1. Update Step #9 to reflect the Agency's recommendations provided in an email on February 24, 2016, regarding storage of this product to assist with the correct use of this product. For example revise, "Once you have applied a drop to both eyes, throw away the opened single use container with any remaining solution." to read, "Once you have applied a drop to both eyes, store remaining single-use containers in the original foil pouch. ..."

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/s/  
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MICHELLE K RUTLEDGE  
05/27/2016

YELENA L MASLOV  
05/31/2016

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** May 9, 2016

**To:** Christina Marshall, Regulatory Project Manager  
Division of Transplant and Ophthalmology Products (DTOP)

Ei Thu Z. Lwin, Regulatory Health Project Manager  
Division of Transplant and Ophthalmology Products (DTOP)

**From:** Meena Ramachandra PharmD, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** XIIDRA™ (lifitegrast ophthalmic solution) 5%; for topical ophthalmic use  
NDA 208073

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As requested in DTOP's consult dated February 8, 2016, OPDP has reviewed the draft PI and proposed carton and container labeling for XIIDRA™ (lifitegrast ophthalmic solution) 5%; for topical ophthalmic use.

OPDP reviewed the proposed substantially complete version of the PI as well as carton and container labeling titled, "NDA 208073 substantiallycomplete\_May2\_2016.docx" received via e-mail from Regulatory Health Project Manager Ei Thu Lwin on May 3, 2016. OPDP's comments on the draft PI are provided in the attached clean version of the substantially complete labeling. OPDP has no comments on the proposed carton and container labeling.

A combined OPDP and Division of Medical Policy Programs (DMPP) patient labeling review was conducted and comments on the Patient Package Insert (PPI) and Instructions For Use (IFU) will be provided under separate cover.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Meena Ramachandra (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

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MEENA RAMACHANDRA  
05/09/2016

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: May 9, 2016

To: Renata Albrecht, MD  
Director  
**Division of Transplant and Ophthalmology Products (DTOP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
  
Shawna Hutchins, MPH, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Sharon W. Williams, MSN, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
  
Meena Ramachandra, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)

Drug Name (established name): XIIDRA (lifitegrast ophthalmic solution) 5%

Dosage Form and Route: for topical ophthalmic use

Application Type/Number: NDA 208073

Applicant: Shire Development, LLC

## 1 INTRODUCTION

On February 25, 2015, Shire Development, LLC submitted for the Agency's review a New Drug Application for XIIDRA (lifitegrast ophthalmic solution) 5%. This application was originally submitted purpose of the submission is to seek approval for XIIDRA (lifitegrast ophthalmic solution) 5%, to be used for the treatment of signs and symptoms of dry eye disease (DED) (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Transplant and Ophthalmology Products (DTOP) on May 3, 2016, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for XIIDRA (lifitegrast ophthalmic solution) 5%.

## 2 MATERIAL REVIEWED

- Draft XIIDRA (lifitegrast ophthalmic solution) 5%, PPI and IFU received on February 25, 2015, and received by DMPP and OPDP on May 3, 2016.
- Draft XIIDRA (lifitegrast ophthalmic solution) 5%, Prescribing Information (PI) received on February 25, 2015 revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 4, 2016.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU documents using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/  
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SHARON W WILLIAMS  
05/09/2016

MEENA RAMACHANDRA  
05/09/2016

SHAWNA L HUTCHINS  
05/09/2016



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

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Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Memorandum**

**Date:** August 28, 2015

**From:** Suchitra M. Balakrishnan, MD, PhD. Medical Officer, Maternal Health  
Division of Pediatric and Maternal Health

**Through:** Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health  
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director  
Division of Pediatric and Maternal Health

**To:** Division of Transplant and Ophthalmology Products (DTOP)

**Drug:** Xiidra (lifitegrast ophthalmic solution, 5%)

**NDA:** 208073

**Applicant:** Shire Development, LLC

**Subject:** Pregnancy and Lactation Labeling

**Proposed**  
**Indication:** treatment of signs and symptoms of dry eye disease (DED) (b) (4)

**Materials Reviewed:**

- DPMH consult request dated August 4, 2015, DARRTS Reference ID 3801594
- Sponsor's submitted background package for NDA 208073, lifitegrast ophthalmic solution, 5%
- Nonclinical Team Primary Review, Xiidra, lifitegrast ophthalmic solution 5%, NDA 208073. Maria I Rivera & Lori E. Kotch, July 31, 2015. DARRTS Reference ID 3800708

**Consult Question:**

DTOP requests DPMH review, edits and concurrence on the Division's proposed language for PLLR language.

**INTRODUCTION**

On February 25, 2015, Shire Development LLC (Shire) submitted a 505(b)(1) new molecular entity (NME) new drug application (NDA) for Xiidra (lifitegrast 5.0% ophthalmic solution, hereafter referred to as lifitegrast) for the treatment of signs and symptoms of dry eye disease (DED). Lifitegrast is an anti-inflammatory small molecule antagonist of integrin lymphocyte function-associated antigen-1 (LFA-1), also known as CD11a/CD18 or  $\alpha$ L $\beta$ 2. Priority Review status was granted on April 7, 2015.

The Division of Transplant and Ophthalmology Products (DTOP) consulted the Division of Pediatric and Maternal Health (DPMH) on August 4, 2015, to review the Pregnancy and Lactation subsections of labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements and to provide comments to be included in the labeling that will be sent to the applicant.

The division has recently issued a discipline review letter to the applicant identifying deficiencies that preclude discussion of labeling changes and/or post-marketing requirements/commitments at this time<sup>1</sup>. The submitted studies (Phase 2 dry eye study, Phase 3 Studies OPUS-1, OPUS-2 and SONATA) support the safety of lifitegrast, but were not successful in demonstrating effectiveness in the treatment of dry eye disease<sup>2</sup>. DTOP has requested that DPMH complete its review of Section 8 of the package insert in this review cycle.

**BACKGROUND****Lifitegrast Drug Characteristics**

Lifitegrast binds to LFA-1, a cell surface protein found on leukocytes and blocks the interaction of LFA-1 with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 is over-expressed in corneal and conjunctival tissues in dry eye disease. LFA-1/ICAM-1 interaction contributes to formation of an immunological synapse resulting in T-cell activation and migration to target tissues. In vitro studies demonstrated that lifitegrast inhibits T-cell adhesion to ICAM-1 expressing cells, and thereby inhibits secretion of key inflammatory cytokines (IFN $\gamma$ , TNF $\alpha$ , IL-2) as well as other pro-inflammatory cytokines. However, the exact mechanism of action of lifitegrast in dry eye disease is not known<sup>3</sup>.

**Pharmacokinetics<sup>4</sup>:**

*Refer to the Clinical Pharmacology and Clinical Reviews referenced below for further details*

<sup>1</sup> IR- Discipline review letter dated August 27, 2015, Reference ID 3811847.

<sup>2</sup> Clinical Review by Dr. Rhea Lloyd dated August 11, 2015, Reference ID 3804559.

<sup>3</sup> Pharmacology/Toxicology review by Dr. Maria Rivera in DAARTs dated July 31, 2015, Reference ID 3800708

<sup>4</sup>Clinical pharmacology review by Dr. Gerlie Gieser, April 17, 2015, Reference ID 3734645 and Clinical Review

In five healthy subjects treated twice daily for 10 days with lifitegrast 5.0% ophthalmic solution, the mean  $\pm$  SD (range) plasma lifitegrast C<sub>max</sub> was  $1.70 \pm 1.36$  ( $\leq 0.5 - 3.71$ ) ng/mL, achieved within 15 minutes post-dose. Plasma lifitegrast concentrations were below the LLOQ (0.5 ng/mL) of the PK assay after the 1 hour time point. On Day 10, both the mean plasma C<sub>max</sub> and AUC were approximately 3.5-fold higher than those measured on Day 1 of BID dosing. On Day 10, tear fluid lifitegrast concentrations in all these 5 healthy subjects were  $\geq 11.8$  ng/mL and  $\geq 164$  ng/mL at 24-hour post-dose and 8-hour post-dose, respectively.

In Study 1118-DRY-400 (SONATA), trough concentration of lifitegrast in plasma and pharmacodynamics (effect on whole blood CD3, CD4, and CD8 lymphocyte counts) was assessed at Days 0 (pre-dose), 180, and 360 in approximately 25% of subjects at selected participating sites. No formal pharmacokinetic profiling was conducted. There was no evidence of accumulation of lifitegrast in plasma over time; the mean trough concentration of lifitegrast in plasma was below the lower limit of quantification (0.5 ng/mL) at Days 0, 180, and 360. At approximately 180 days and/or 360 days of repeated topical ocular dosing, nine (~20%) of the patients included in the sub-study had detectable ( $\geq 0.5$  ng/mL) predose lifitegrast concentrations in the plasma. Of these 9 patients, 2 had pre-dose concentrations that exceeded the EC<sub>50</sub> (2.5 ng/mL) needed to inhibit T-cell adhesion in vitro, and an additional patient had potentially clinically important (PCI) treatment-emergent abnormalities in CD8 lymphocyte counts (i.e., CD8 < 220/mcL) measured on Day 180. The applicant stated that none of these 3 patients experienced systemic infections or immunosuppressive complications during the 12-month treatment period.

*Reviewer's Comment: It appears that systemic exposures to lifitegrast following repeated dosing at the proposed clinical dose are low, and do not produce clinically significant systemic chronic immunosuppression. However, the measured lifitegrast trough concentrations (and presumably, the peak concentrations) in some patients in the SONATA trial exceeded the EC<sub>50</sub> needed to inhibit T cell adhesion (3.69 nM = 2.5 ng/mL) in vitro. One patient developed PCI abnormalities in CD8 lymphocyte counts. There were no reported systemic infections or other AEs related to immunosuppression in any of these patients.*

### **Dry Eye disease:**

Dry eye disease (DED) is a multifactorial disease of the tears and ocular surface, accompanied by increased osmolarity of the tear film and inflammation of the ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface<sup>5</sup>. It is both a primary disease and a secondary result of many pathological states of the eye<sup>6</sup>. Left untreated, the chronic nature of DED can progress to corneal scarring, ulcers, and ultimately vision loss<sup>7</sup>. Current treatments include artificial

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<sup>5</sup> Lemp MA, Baudouin C, Baum J, Dogru M, Foulks GN, Kinoshita S, et al. (Definition and Classification Dry Eye WorkShop Subcommittee) 2007. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the International Dry Eye WorkShop. *Ocul Surf*; 5(2): 75-92.

<sup>6</sup> L. A. Vickers \_ P. K. Gupta, The Future of Dry Eye Treatment: A Glance into the Therapeutic Pipeline; *Ophthalmol Ther*, Published Online-August 20, 2015

<sup>7</sup> National Eye Institute 2013. Facts about dry eye. *Dry eye*. Viewed 04 Sep 2014, <http://www.nei.nih.gov/health/dryeye/factsaboutdryeye.pdf>

tears, punctal plugs, topical Cyclosporine (RESTASIS®) and topical corticosteroids (for acute exacerbations)<sup>8</sup>.

Overall US prevalence by self-reported dry eye symptoms has been estimated to be 7.8% of females aged 50 years and older<sup>9</sup> and 4.3% of males aged 50 years and older<sup>10</sup>. However, in recent years, a younger population is the most rapidly growing segment of dry eye sufferers, likely in part due to refractive surgery, shifts in lifestyles toward frequent computer and visual display tasking<sup>11</sup>.

### **Dry eye disease and Pregnancy:**

A search of published literature in PubMed was performed, and no publications were found describing outcomes of pregnancy in patients with dry-eye syndrome *per say*. Since lifitegrast is an ophthalmic solution and systemic exposures are limited based on available clinical data, published literature on the impact of multisystem autoimmune diseases (e.g., Sjogren's syndrome or systemic lupus erythematosus) on fetal and maternal outcomes during pregnancy was not reviewed.

### **Pregnancy and Nursing Mothers Labeling**

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”<sup>12</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>13</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR did take effect on June 30, 2015; however, at this time applicants may voluntarily convert labeling to PLLR format for applications submitted prior to this date.

## **DISCUSSION**

### **Nonclinical Experience<sup>14</sup>**

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<sup>8</sup> Laura E. Downie and Peter R. Keller' A Pragmatic Approach to the Management of Dry Eye Disease: Evidence into Practice, *Optom Vis Sci* , 2015; 92: 957-966

<sup>9</sup> Schaumberg DA, Sullivan DA, Buring JE, Dana MR 2003. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol*; 136(2): 318-26.

<sup>10</sup> Schaumberg DA, Dana R, Buring JE, Sullivan DA 2009. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. *Arch Ophthalmol*; 127(6): 763-8.

<sup>11</sup> Raoof D, Pineda R. Dry eye after laser in situ keratomileusis. *Semin Ophthalmol*. 2014;29(5–6):358–62

<sup>12</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>13</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

<sup>14</sup> Pharmacology/Toxicology review by Dr. Maria Rivera in DAARTs dated July 31, 2015, Reference ID 3800708

In a fertility and embryofetal development toxicity study in rats, a fetal effect was apparent at the high dose (30 mg/kg), as reflected by an increase in mean preimplantation loss and increased incidence of several minor skeletal variations and malformations limited to 1 or 2 fetuses and litters. In males, there was a slight decrease in prostate (16%) and seminal vesicle (19%) weights at 30 mg/kg, but no effects were noted in fertility index. The NOAEL for male and female fertility was the high dose of 30 mg/kg; the NOAEL for embryofetal development was the mid dose of 10 mg/kg. The non-clinical reviewer opines that based on AUC, the exposure margin for the fetal findings is 460-fold, indicating minimal clinical concern.

In a rabbit embryofetal development study, omphalocele was noted in a single fetus at the low dose of 3 mg/kg/day and the high dose of 30 mg/kg/day. In addition, there was an increased incidence of subclavian vein-supernumerary branch at the high dose, and bipartite ossification of the sternbrae at the mid dose and high dose. Omphalocele is an extremely rare malformation (i.e., noted in 1 fetus each in 2 litters from a total of 2237 litters in the historical database). Based on the finding of omphalocele at the low dose and high dose, a fetal NOAEL was not identified in this study. As 2 litters had an affected fetus in the current study, the non-clinical reviewer is of the opinion that it is difficult to definitely rule out a test article-related effect. However, she again indicates that based on AUC, the exposure margin at the low dose of 3 mg/kg/day is 400-fold, indicating minimal clinical concern.

Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation. The applicant has been asked to reduce the specification for (b) (4), a potentially genotoxic impurity, to as low as reasonably possible.

### **Lifitegrast and Pregnancy**

The applicant did not conduct studies with lifitegrast in pregnant women. Pregnant or lactating females were excluded from participation in all clinical studies and women of childbearing potential had to use acceptable methods of birth control or had to agree to abstain from sexual intercourse. Despite these criteria, one subject randomized to placebo reported pregnancy during the lifitegrast clinical development program. On Day 86, the subject had a positive pregnancy test result. Her last menstrual period was on Day 51. Treatment with the investigational product was permanently discontinued due to the pregnancy. The outcome of the pregnancy is unknown.

A search of published literature for available human pregnancy data with topical cyclosporine (Restasis) was also conducted and no studies were found. However, systemic cyclosporine is prescribed to pregnant women post-transplant<sup>15</sup> or with auto-immune disorders<sup>16</sup> with no reported increase in congenital malformations compared to the general population risk, although intra-uterine growth restriction remains a concern.

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<sup>15</sup> Bar Oz B, Hackman R, Einarson T, *et al.* Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. *Transplantation*. 2001;71:1051–1055.

<sup>16</sup> Coscia LA, Constantinescu S, Davison J. Immunosuppressive drugs and fetal outcome. *Best Pract Res Clin*

The Applicant-proposed labeling recommends that lifitegrast (b) (4) (b) (4) DPMH concludes that there is insufficient information to make a clear assessment of risk since systemic exposures are low but exceeded the EC50 needed to inhibit T cell adhesion (3.69 nM = 2.5 ng/mL) *in vitro* in some patients and there are no human data available in pregnant women. Therefore, DPMH recommends inclusion of a statement about the lack of human data to adequately inform drug associated risk.

### **Lactation**

A search of published literature in the Drugs and Lactation Database (Lactmed)<sup>17</sup> and Pubmed for available human lactation data was performed to update the Lactation subsection of labeling for this application. There is no information in published literature on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. No animal studies have been conducted.

DPMH agrees that breastfeeding should not be contraindicated during drug therapy with lifitegrast, and concurs with the required Lactation Risk Summary statement: “The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Xiidra and any potential adverse effects on the breastfed infant from Xiidra or from the underlying maternal condition.”



### **CONCLUSIONS AND RECOMMENDATIONS**

Lifitegrast labeling has been revised to comply with the PLLR. DPMH has the following recommendations for lifitegrast labeling. DPMH refers to the final NDA action for final labeling.:

- **Pregnancy, Section 8.1**

- The “Pregnancy” subsection of lifitegrast labeling was formatted in the PLLR format to include, “Risk Summary” and “Data” subsections<sup>18</sup>.

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Obstet Gynaecol. 2014;28:1174–1187.

<sup>17</sup>The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

<sup>18</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

- **Lactation, Section 8.2**

- The “Lactation” subsection of lifitegrast labeling was formatted in the PLLR format to include the “Risk Summary” subsection<sup>19</sup>.

## FULL PRESCRIBING INFORMATION

### 8.1 Pregnancy

#### Risk Summary



#### Data

##### *Animal Data*

(b) (4)  
(b) (4). Lifitegrast administered daily by IV injection to rats from pre-mating through gestation day 17, (b) (4) (b) (4) caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at (b) (4) 5400-fold the plasma exposure at the RHOD (b) (4), based on AUC. (b) (4) (b) (4) were observed in the rat at 10 mg/kg/day (460-fold the plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the plasma exposure at the RHOD, based on AUC), when given by IV injection daily from gestation day 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified.

### 8.2 Lactation

#### Risk Summary

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 [see *Clinical Pharmacology (12.3)*]. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need

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<sup>19</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

for Xiidra and any potential adverse effects on the breastfed infant from Xiidra or from the underlying maternal condition.

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/s/  
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SUCHITRA M BALAKRISHNAN  
09/10/2015

TAMARA N JOHNSON  
09/11/2015

LYNNE P YAO  
09/16/2015

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL INSPECTION SUMMARY**

**DATE:** June 25, 2015

**TO:** Christina Marshall, Regulatory Project Manager  
Rhea Lloyd, M.D., Medical Officer  
William Boyd, M.D., Medical Team Leader  
Division of Transplantation and Ophthalmology Products

**FROM:** Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**THROUGH:** Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
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Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 208073

**APPLICANT:** Shire

**DRUG:** Lifitegrast

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** Treatment of dry eye

CONSULTATION REQUEST DATE: March 2, 2015  
 CLINICAL INSPECTION SUMMARY DATE: July 10, 2015  
 DIVISION ACTION GOAL DATE: October 23, 2015  
 PDUFA DATE: October 25, 2015

**I. BACKGROUND:**

The Applicant submitted this NDA to support the use of lifitegrast for the treatment of dry eye.

The pivotal studies 1118-KCS-200 entitled, “A Phase 3, Multicenter, Randomized, Double-Masked and Placebo-Controlled Study Evaluating the Efficacy of a 5.0% Concentration of SAR 1118 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye (OPUS-1)”, and 1118-DRY-300 entitled, “A Phase 3, Multicenter, Randomized, Double-Masked and Placebo-Controlled Study Evaluating the Efficacy of a 5.0% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Currently Using Artificial Tears (OPUS-2)”, and 1118-DRY-400 entitled, “A Phase 3, Multicenter, Randomized, Double-Masked and Placebo-Controlled Study Evaluating the Safety of a 5.0% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye (SONATA)” were inspected in support of this application.

These sites were selected for inspection as they were among the higher enrollers for their respective studies.

**II. RESULTS (by Site):**

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
John Lonsdale, M.D. Central Maine Eye Care 181 Russell St. Lewiston, ME 04240	1118-KCS- 200/ 12/ 80	20-24 Apr 2015	NAI
Robert Smyth-Medina, M.D. North Valley Eye Medical Group 11550 Indian Hills Rd, Suite 341 Mission Hills, CA 91345	1118-DRY-300/ 65/ 49	20, 21 Apr 2015	NAI
Kelly Nichols, O.D. University of Houston 505 J. Davis Armistead Building Houston, TX 77204	1118-DRY-400/ 41/ 30	11-20 May 2015	NAI

Key to Classifications

NAI = No deviation from regulations.  
 VAI = Deviation(s) from regulations.  
 OAI = Significant deviations from regulations. Data unreliable.  
 Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. John Lonsdale, M.D.  
Central Maine Eye Care  
181 Russell St.  
Lewiston, ME 04240

- a. **What was inspected:** At this site for Protocol 1118-KCS- 200, 131 subjects were screened, 80 subjects were enrolled, and 77 subjects completed the study. The study records of 30 enrolled subjects and five subjects who failed screening were reviewed. Records reviewed included, but were not limited to, source documents, informed consent, inclusion/exclusion criteria, monitoring logs, delegation logs, enrollment logs, IRB and sponsor correspondence, co-primary endpoints (fluorescein staining and dry eye score), adverse events, and drug accountability records.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Robert Smyth-Medina, M.D.  
North Valley Eye Medical Group  
11550 Indian Hills Rd, Suite 341  
Mission Hills, CA 91345

- a. **What was inspected:** At this site for Protocol 1118-DRY-300, 95 subjects were screened, and 49 subjects were randomized to the study. The study records of 31 randomized subjects were reviewed. Records reviewed included, but were not limited to, source documents, informed consent, financial disclosure forms, licensures, inclusion/exclusion criteria, the co-primary efficacy endpoints (fluorescein staining and eye dryness score), sponsor, monitor, and IRB correspondence, protocol deviations, and test article accountability.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Kelly Nichols, O.D.  
University of Houston  
505 J. Davis Armistead Building  
Houston, TX 77204

- a. **What was inspected:** At this site for Protocol 1118-DRY-400, 55 subjects were screened, 30 subjects were enrolled in the study, and 17 subjects completed the study. The source records for all screened subjects were reviewed. Records reviewed

included, but were not limited to, informed consent, training documentation, sponsor, monitoring, and IRB correspondence, inclusion/exclusion criteria, case histories, physician’s notes, case report forms (CRFs), laboratory records, adverse event reporting, concomitant therapies, financial disclosure forms, and test article accountability and storage.

- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Lonsdale, Smyth-Medina, and Nichols were inspected in support of this NDA. None of these sites were issued a Form FDA 483, and the final classification of the inspections of each of these sites was No Action Indicated (NAI). The studies appear to have been conducted adequately, and the data generated by each of each of these sites appear acceptable in support of the respective indication.

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

*{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigation

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/s/  
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ROY A BLAY  
06/26/2015

JANICE K POHLMAN  
06/26/2015

KASSA AYALEW  
06/26/2015

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**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** May 29, 2015  
**Requesting Office or Division:** Division of Transplant and Ophthalmology Products (DTOP)  
**Application Type and Number:** NDA 208073  
**Product Name and Strength:** Xiidra (Lifitegrast) ophthalmic solution, 5%  
**Product Type:** Single Ingredient  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Shire  
**Submission Date:** February 25, 2015  
**OSE RCM #:** 2015-593  
**DMEPA Primary Reviewer:** Sarah K. Vee, PharmD  
**DMEPA Team Leader:** Yelena Maslov, PharmD

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## 1 REASON FOR REVIEW

This review evaluates the proposed foil label, carton labeling, and prescribing information for Xiidra (lifitegrast) ophthalmic solution, 5%, NDA 208073, for areas of vulnerability that could lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	N/A

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA reviewed the proposed labels and labeling and determined that there are no significant concerns. Thus, Section 4.1 contains recommendations on increasing readability and prominence of important information on the proposed labels and labeling.

## 4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

#### A. Package Insert

1. Highlights: Dosage and Administration: Revise the statement to read "One drop in each eye in the morning and evening".
2. Dosage and Administration: Revise the statement to read "Instill one drop of Xiidra in each eye in the morning and evening using a single (b) (4) ."

## 4.2 RECOMMENDATIONS FOR BOEHRINGER INGELHEIM

Based on this review, DMEPA recommends the following be implemented prior to the approval of this NDA:

- A. Foil label and carton labeling
  - 1. Unbold the statements “Rx Only” and “5 Single-Use [REDACTED] (b) (4) mL each)”.
  - 2. We recommend that you revise the usual dosage statement to read: “One drop in each eye in the morning and evening” to simplify the language.
  - 3. We recommend that the company name “Shire” be revised to be less prominent than other important information such as the proprietary name.<sup>1</sup>

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<sup>1</sup> <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Xiidra that Shire submitted on February 25, 2015.

<b>Table 2. Relevant Product Information for Xiidra</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Lifitegrast
<b>Indication</b>	For the treatment of the signs and symptoms of dry eye disease (DED) (b) (4).
<b>Route of Administration</b>	Ophthalmic
<b>Dosage Form</b>	Solution
<b>Strength</b>	5%
<b>Dose and Frequency</b>	One drop twice daily in each eye
<b>How Supplied</b>	Supplied in low density polyethylene (b) (4), packaged in foil pouches (5 (b) (4) per pouch).
<b>Storage</b>	Store at 25°C (77°F), (b) (4) Store (b) (4) in the original foil pouch.
<b>Container Closure</b>	(b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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SARAH K VEE  
05/29/2015

YELENA L MASLOV  
06/04/2015

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 208073	NDA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Xiidra Established/Proper Name: lifitegrast ophthalmic solution Dosage Form: ophthalmic solution Strengths: 5.0%		
Applicant: Shire Development, LLC Agent for Applicant (if applicable):		
Date of Application: February 25, 2015 Date of Receipt: February 25, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: October 25, 2015	Action Goal Date (if different): October 23, 2015	
Filing Date: April 26, 2015	Date of Filing Meeting: March 19, 2015	
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of signs and symptoms of dry eye disease (DED)		
Type of Original NDA: AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<b>The application will be a priority review if:</b>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> <li>• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</li> <li>• The product is a Qualified Infectious Disease Product (QIDP)</li> <li>• A Tropical Disease Priority Review Voucher was submitted</li> <li>• A Pediatric Rare Disease Priority Review Voucher was submitted</li> </ul>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 77885

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). <b>If yes</b> , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>Check the Electronic Orange Book at: <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></i>					
<b>If yes</b> , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>	
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>If yes</b> , # years requested: 5 years					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes,</b> did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission,</b> which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission,</b> does it follow the eCTD guidance? <sup>1</sup> <i>If not, explain (e.g., waiver granted).</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Applicant included even though it is an electronic submission
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
<b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP): July 22, 2014?</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Pediatric studies were no required by the agreed iPSP
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b><u>BPCA:</u></b>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
<b>Prescription Labeling</b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? <b>Date(s):</b> January 10, 2011 under IND 77885  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> June 13, 2014, under IND 77885  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** March 19, 2015

**BACKGROUND:** Shire Development, LLC has submitted NDA 208073 for lifitegrast ophthalmic solution, for the treatment of signs and symptoms of dry eye disease (DED). Lifitegrast is an NME and this NDA will be reviewed under priority timelines. Development of lifitegrast was conducted in the US under IND 77885.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Christina Marshall	Y
	CPMS/TL:	Judit Milstein	Y
Cross-Discipline Team Leader (CDTL)	William Boyd		Y
Division Director/Deputy	Renata Albrecht/ Wiley Chambers		Y/Y
Office Director/Deputy	Edward Cox/ John Farley		Y/Y
Clinical	Reviewer:	Rhea Lloyd	Y
	TL:	William Boyd	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Gerlie Gieser	Y
	TL:	Philip Colangelo	Y
Biostatistics	Reviewer:	Solomon Chefo	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Maria Rivera	Y
	TL:	Lori Kotch	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Edwin Jao	N
	TL:	Anamitro Banerjee	Y
Biopharmaceutics	Reviewer:	Elsbeth Chikhale	Y
	TL:	Angelica Dorantes	N
Quality Microbiology	Reviewer:	Yuansha Chen	N
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Frank Wackes	N
	TL:	Mahesh Ramanadham	N
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Zarna Patel	N
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Carolyn Yancey, Sarah Vee, Ronald Wassel		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIostatistics</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	

<b>IMMUNOGENICITY (protein/peptide products only)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	

<b>PRODUCT QUALITY (CMC)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	

<b>New Molecular Entity (NDAs only)</b>	
<ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b><u>Environmental Assessment</u></b>	
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>If no</b>, was a complete EA submitted?</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	

<b><u>Quality Microbiology</u></b>	<input type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>Nothing arrived after 30 days</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority: Edward Cox</b></p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): May 21, 2015</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter.  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA's completed: September 2014

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHRISTINA D MARSHALL  
04/07/2015

JUDIT R MILSTEIN  
04/28/2015

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** 208073

**Application Type:** NDA

**Name of Drug/Dosage Form:** Xiidra (lifitegrast) ophthalmic solution 5.0%

**Applicant:** Shire Development, LLC

**Receipt Date:** February 25, 2015

**Goal Date:** October 25, 2015

## 1. Regulatory History and Applicant's Main Proposals

Shire Development, LLC has submitted a New Molecular Entity (NME) New Drug Application (NDA) for the treatment of signs and symptoms of dry eye disease (DED).

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

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## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

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## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

**YES**

## Selected Requirements of Prescribing Information

2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

## Selected Requirements of Prescribing Information

### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

*Comment:*

### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

*Comment:*

### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

*Comment:*

### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

*Comment:*

### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

*Comment:*

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

*Comment:*

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

*Comment:*

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

*Comment:*

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

## Selected Requirements of Prescribing Information

### Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

### Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

### Comment:

### Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

### Comment:

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

### Comment:

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

### Comment:

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- "**See 17 for PATIENT COUNSELING INFORMATION**"

If a product **has** FDA-approved patient labeling:

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

## Selected Requirements of Prescribing Information

- “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”

Comment:

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

- YES** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:* *No postmarketing adverse reaction data included*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

APPEARS THIS WAY ON ORIGINAL

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/s/

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CHRISTINA D MARSHALL  
03/24/2015  
NDA 208073 PLR Label Format Review