CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203168Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: March 20, 2013

To: Mike Puglisi, Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Christine Corser, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Review
NDA #203168
PROLENSA™ (bromfenac ophthalmic solution) 0.07%

As requested in your consult dated July 23, 2012, the Office of Prescription Drug Promotion (OPDP) has reviewed the draft labeling for PROLENSA™ (bromfenac ophthalmic solution) 0.07%.

Our comments are based on the substantially complete version of the labeling titled, "nda 203168 draft PI 3_20_13.doc" which was received via email from Mike Puglisi on March 20, 2013.

OPDP has reviewed the PI and our comments are attached in the substantially complete clean version of the labeling.

If you have any questions about our comments on the PI, please contact Christine Corser at 6-2653 or at christine.corser@fda.hhs.gov.

Thank you for the opportunity to review this PI.

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

CHRISTINE G CORSER
03/20/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	February 8, 2013
Reviewer:	Jung Lee, RPh Division of Medication Error Prevention and Analysis
Team Leader:	Jamie Wilkins Parker, PharmD Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Prolensa (Bromfenac Ophthalmic Solution), 0.07%
Application Type/Number:	NDA 203168
Applicant:	Bausch & Lomb, Inc
OSE RCM #:	2012-2059

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Prolensa (NDA 203168) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

On March 24, 2005, Xibrom (Bromfenac) ophthalmic solution 0.09% (NDA 021664) was approved for postoperative inflammation following cataract surgery with a twice-a-day dosing regimen. On May 25, 2010, the Applicant submitted a request for a Supplemental New Drug Application (sNDA) for a new proprietary name Bromday (Bromfenac Sodium Hydrate) ophthalmic solution with a new strength, 0.1035% and a once-a-day dosing regimen.

In a cover letter, also dated May 25, 2010, the Applicant stated their intent to discontinue marketing the existing product, Xibrom, in order to alleviate the confusion between proposed product Bromday and marketed product Xibrom. Xibrom was discontinued on May 24, 2011.

On June 27, 2011, the Applicant submitted a request for a proprietary name review of the name Prolensa (Bromfenac Ophthalmic Solution) with a new strength, 0.07% and a similar once-a-day dosing regimen to Bromday under IND 060295. During the IND review, the Applicant stated they wanted a new proprietary name for the new formulation as it differs significantly from the Bromday formulation (Prolensa contains (b) (4) less active ingredient, has a more neutral PH, (b) (4) and contains tyloxapol (b) (4)); therefore, this product will have a dual proprietary name upon initial launch of the product. (b) (4)

1.2 PRODUCT INFORMATION

The following product information is provided in the August 31, 2012 submission.

- Active Ingredient: Bromfenac
- Indication of Use: Treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction
- Route of Administration: Ophthalmic
- Dosage Form: Solution
- Strength: 0.07%
- Dose and Frequency: One drop into the affected eye once daily beginning 1 day prior to surgery, continued on the day of surgery, and through the first 14 days of post-surgery
- How Supplied: 1.6 mL and 3 mL in a 7.5 mL container

- Storage: Store at -15°C to 25°C (59°F to 77°F)
- Container and Closure System: White LDPE plastic squeeze bottle with a 15 mm (b) (4) dropper-tip and 15 mm (b) (4) gray cap. The gray cap color is consistent with the American Academy of Ophthalmology's policy statement "Color Code for Ocular Medications" which recommends the gray cap color for nonsteroidal anti-inflammatories (NSAIDS).

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA FAERS database for bromfenac medication error reports. We also reviewed the Prolensa container labels, carton labeling, and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1 because Bromfenac ophthalmic solution is currently marketed under the name, Bromday and previous to that under the name Xibrom.

Table 1: FAERS Search Strategy	
Date	October 2, 2012
Drug Names	Active Ingredient: Bromfenac Product Names: Xibrom, Bromday
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 13 cases. Each case was reviewed for relevancy and duplication. After individual review, all 13 cases were excluded in the final analysis for the following reasons:

- Cases related to Duract (Bromfenac sodium capsules)
- Product quality issues related to generic Xibrom or complaints of burning eyes and itching from a different lot number of Bromday

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 21, 2012 (Appendix B)
- Carton Labeling submitted August 21, 2012 (Appendix C)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Insert Labeling submitted August 21, 2012

3 RECOMMENDATIONS

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

3.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. In section 16 (How Supplied/Storage and Handling), include a space before the unit of measure. For example, "1.6mL in a 7.5mL container" should be revised to read as follows: 1.6 mL in a 7.5 mL container.
2. The Applicant utilizes trailing zeros within the How Supplied/Storage and Handling section of the insert labeling. Trailing zeros may lead to 10-fold errors in dosing. DMEPA recommends removing all trailing zeros with the exception of when it is required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter/tube sizes.
3. Add a unit of measure immediately following all numbers in the storage statement, as appropriate. For example, revise "15° – 25°C (59° -77°F)" to read as follows: 15°C to 25°C (59°F to 77°F).

4.2 COMMENTS TO THE APPLICANT

A. Container Label (0.6 mL Sample, 0.8 mL Sample, 1.6 mL Trade, 3 mL Trade Sizes)

1. Revise the presentation of the proprietary name from all upper case letters "PROLENSA" to title case "Prolensa" to improve readability. Words set in title case form recognizable shapes, making them easier to read.
2. Revise and relocate the statement "Once Daily" printed vertically on the left side of the principal display panel (PDP) to display horizontally below the strength statement to improve readability.
3. Remove the word "Sterile".
4. Debold and relocate the net quantity statement away from the strength statement so it does not have greater prominence than that of the strength statement and the established name.
5. Remove the trailing zero from the 3.0 mL trade size label and revise to read "3 mL".

B. Carton Labeling (0.6 mL Sample, 0.8 mL Sample, 1.6 mL Trade, 3 mL Trade Sizes)

1. See comments A1and A5.

2. Relocate the route of administration statement, “For topical application in the eye” to the PDP directly below the dosage form and strength statements.
3. Debold the net quantity statement so it does not have greater prominence than that of the strength statement and the established name.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Appendix B: Container Labels

Professional Sample Bottle Label for 0.6 mL Fill Size:

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/s/

JUNG E LEE
02/08/2013

JAMIE C WILKINS PARKER
02/08/2013

CAROL A HOLQUIST
02/08/2013

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: February 4, 2013

TO: Michael Puglisi, Project Manager
William M. Boyd, Medical Team leader
Division of Transplant and Ophthalmology Products

FROM: Kassa Ayalew, Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Thompson
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigators

SUBJECT: Evaluation of Clinical Inspections

NDA: 203168

APPLICANT: ISTA Pharmaceuticals, Inc.

DRUG: Prolensa™ (bromfenac ophthalmic solution 0.7%)

NME: No

INDICATION: Treatment of postoperative inflammation and reduction of ocular pain patients who have undergone cataract extraction

THERAPEUTIC CLASSIFICATION:	Standard
CONSULTATION REQUEST DATE:	July 23, 2012
INSPECTION SUMMARY GOAL DATE:	February 7, 2013
ACTION GOAL DATE:	March 7, 2013
PDUFA DATE:	April 7, 2013

I. BACKGROUND:

The Applicant, ISTA Pharmaceuticals, Inc. (ISTA) submitted an original New Drug Application (NDA) for Prolensa™ (bromfenac ophthalmic solution) 0.07% to support an indication for the treatment of inflammation and pain associated with cataract extraction. Bromfenac ophthalmic solution 0.07% is a new formulation with lower concentration of bromfenac and planned to be administered as once daily (QD).

The Office of Scientific Investigation received a consult from Division of Transplant and Ophthalmology Products to conduct clinical inspections of the following two identical studies:

> **S00124-ER (East Region)** entitled **"**Efficacy and Safety of Bromfenac Ophthalmic Solution vs. Placebo for the Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery"
>
> **S00124-WR (West Region)** entitled "Efficacy and Safety of Bromfenac Ophthalmic Solution vs. Placebo for the Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery".

The studies were multi-center, randomized, double-masked, parallel-group, and placebo-controlled studies to evaluate the efficacy of bromfenac for the treatment of ocular inflammation and pain associated with cataract surgery with PCIOL (posterior chamber intraocular lens). For both studies, subjects were to be randomized to receive either bromfenac or placebo in a ratio of 1:1. The primary endpoint of efficacy was the proportion of subjects who had cleared ocular inflammation by Day 15. Approximately 220 subjects were to be randomized to receive either bromfenac or placebo in a ratio of 1:1 in each study (Study S00124-WR and Study S00124-ER **).**

One site from each study was chosen for inspection based on enrollment, number of INDs in the OSI database, and previous inspectional history.

II. RESULTS (by Site):

Name of CI	Protocol # /Site #/ # of Subjects Enrolled:	Inspection Date	Classification
Leonard Cacioppo, MD Hernando Eye Institute 14543 Cortez Boulevard Brooksville, FL 34613	**S00124-ER** Site #58 21 subjects	September 10 to 14, 2012	NAI
Damien Goldberg, MD Wolstan & Goldberg Eye Associates 23600 Telo Ave, Suite 100 Torrance, CA 90505	**S00124-WR** Site #23 22 subjects	August 24 to September 6, 2012	VAI

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 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Leonard Cacioppo, MD

Hernando Eye Institute
14543 Cortez Boulevard, Brooksville, FL 34613

a. What was inspected: This inspection was performed a data audit for Protocol # S00124-ER. There are (b) (4) associated with the inspected entity in CDER's database, and the CI had one prior inspection in November, 2003 that was classified NAI.

At this site, a total of 22 study subjects were screened for Protocol # S00124-ER. Twenty one (21) subjects were enrolled, randomized, and completed the study. Of the twenty one (21) subjects who completed Visit Seven (Day 22+3 or 7 + 3 Days after last dose of investigational product, ten (10) subjects discontinued investigational product prior to visit 7. Eight (8) of the 10 subjects who discontinued were in the placebo arm and two were on the investigational product arm. The source documents revealed that the above subjects were discontinued secondary to lack of efficacy and were placed on rescue medication.

An in depth audit of the study records for all 22 subjects was conducted. There were no limitations to the inspection. Records reviewed included, but were not limited to, source documents, protocol specified blinding/randomization procedures, inclusion/exclusion criteria, adverse events, primary efficacy endpoints, protocol deviations, concomitant therapies, and test article accountability. In addition, IRB correspondence, monitoring logs and correspondence, and financial disclosure documentation were reviewed.

b. General observations/commentary: The investigator's source documents were organized, complete and legible. The primary endpoint data were verifiable. There were two instances of unreported adverse events (AE). Those adverse events were non-ocular episode of syncope, ecchymosis of left upper eyelid (Subject 5812) and floater in the left study eye (Subject 5807). The above adverse events were reported as not serious and not related. They were considered isolated instances. No significant regulatory violations were noted and no Form FDA 483 was issued. The study appears to have been executed appropriately at this site.

c. Assessment of data integrity: Based on inspectional findings and the observations noted, efficacy and safety data obtained from this site are considered reliable.

2. Damien Goldberg, MD
Wolstan & Goldberg Eye Associates
23600 Telo Ave, Suite 100, Torrance, CA 90505

a. What was inspected: This inspection was conducted in accordance with Compliance Program 7348.811. There were (b) (4) associated with the inspected entity in CDER's database, and the CI had no prior inspection.

This inspection was performed as a data audit for Protocol S00124-WR. At this site, 22 subjects were screened. Twenty two (22) subjects were enrolled and randomized into the study. A total of 20 subjects completed the study. An audit of 22 subjects' records was conducted. There was no evidence of under reporting of adverse events. The primary efficacy endpoint data was verifiable.

The inspection included reviews of the following items: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequacy of adverse experience reporting. In addition, drug accountability records, Informed Consents Documents, IRB approval and dates, and sponsor monitoring records were reviewed. All primary efficacy endpoint data were compared with the sponsor supplied line listings and no discrepancies were noted. There were no limitations to the inspection.

b. General observations/commentary: In general, the study was conducted appropriately. However, a Form FDA 483, Inspectional Observations, was issued for failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60]. Specifically,

1. Failure to exclude Subject # 2309 (bromfenac arm) who had eye pain that was rated as mild on the Ocular Comfort Grading at the time of Screening.

   <u>OSI Reviewer Comments</u>: The clinical investigator should have excluded the above subject from participation in this study based on the Exclusion Criterion requiring that subjects have no ocular pain. Dr. Goldberg's written response

(dated September 20, 2012) to the Form FDA 483, acknowledges the findings identified above and stated that he has implemented corrective actions. The above-mentioned protocol deviation was identified and described by the study monitor and is noted in the data listings submitted by the sponsor. This finding was isolated in nature, and it is unlikely that it would affect subject safety or data reliability.

2. Failure to exclude Subject # 2322 (placebo arm) who received prior/ ongoing concomitant medications (tamsulosin and finasteride) from the study.

   OSI Reviewer Comments: The clinical investigator should have excluded the above subject from participation in this study based on Exclusion Criterion listing the above medications as exclusionary. This protocol deviation was identified and described by the study monitor and is noted in the data listings submitted by the sponsor. The CI reported the deviations for Subject # 2322 to the sponsor. In his written response, he acknowledged that he incorrectly included this patient in the study. He plans to correct the problem in the future prior to considering patients for clinical trials. This finding was isolated in nature, and it is unlikely that it would affect subject safety or data reliability.

Dr. Goldberg adequately responded to the inspectional findings in a letter dated September 20, 2012. His response to the FDA Form 483 adequately addresses and explains findings that were initially considered violations by the field investigator in three additional subjects. The three subjects were Subject # 2310 (bromfenac arm) who was suspected to have received artificial tears, Subject # 2301 (placebo arm) suspected to have received heparin and tamsulosin, and Subject # 2312 (bromfenac arm) suspected to have had history of hypersensitivity to salicylates.

c. Assessment of data integrity: Although regulatory violations were noted above, it is unlikely, based on the isolated nature of the violations, that they significantly affect overall reliability of safety and efficacy data from the site. The data derived from Dr. Goldberg's site are considered reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites were inspected for this application. The data derived from both inspected sites are considered reliable. The classification of the Clinical Investigator inspection of Dr. Cacioppo is No Official Action Indicated (NAI). The classification of the Clinical Investigator inspection of Dr. Goldberg is Voluntary Action Indicated (VAI).

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

KASSA AYALEW
02/04/2013

SUSAN D THOMPSON
02/04/2013

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 # 203168 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Prolensa Established/Proper Name: bromfenac Dosage Form: ophthalmic solution Strengths: 0.07%		
Applicant: ISTA Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: June 6, 2012 Date of Receipt: June 7, 2012 Date clock started after UN:		
PDUFA Goal Date: April 7, 2013	Action Goal Date (if different):	
Filing Date: August 6, 2012	Date of Filing Meeting: July 24, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type-5		
Proposed indication: treatment of inflammation and pain associated with cataract extraction		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 60295	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	√			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	√			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	√			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		√		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	√			

User Fee Status ***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.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			√	
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)].**				
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)]?** ***If you answered yes to any of the above 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***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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 will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:***		√		

http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: **3 years** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	√			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		√		
If yes, 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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	√			
Index: Does the submission contain an accurate comprehensive index?	√			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2	√			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

(*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			√	
• If yes, were all of them submitted on time?			√	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			√	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			√	
Forms and Certifications				
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), 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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	√			
Are all establishments and their registration numbers listed on the form/attached to the form?	√			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	√			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	√			

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	√			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&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…"*	√			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			√	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			√	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage 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.*		√		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			√	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			√	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			√	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	√			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		√		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	√			
Is the PI submitted in PLR format?[4]	√			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			√	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	√			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			√	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	√			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined?				

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		√		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		√		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s): 8/29/11** ***If yes, distribute minutes before filing meeting***	√			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		√		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 7/24/12

NDA #: 203168

PROPRIETARY NAME: Prolensa

ESTABLISHED/PROPER NAME: bromfenac

DOSAGE FORM/STRENGTH: ophthalmic solution, 0.07%

APPLICANT: ISTA Pharmaceuticals, Inc.

PROPOSED INDICATION: treatment of inflammation and pain associated with cataract extraction

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Puglisi, M.	Y
	CPMS/TL:	Milstein, J.	N
Cross-Discipline Team Leader (CDTL)	Boyd, W.		Y
Clinical	Reviewer:	Boyd, W.	Y
	TL:	n/a	
Clinical Pharmacology	Reviewer:	Harigaya, Y.	Y
	TL:	Colangelo, P.	Y
Biostatistics	Reviewer:	Eshete, A.	N
	TL:	Wang, Y.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Aziz, R.	N
	TL:	Kotch, L.	Y
Product Quality (CMC)	Reviewer:	Kambhampati, R.	Y

	TL:	Shanmugam, B.	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Langille, S.	N
	TL:	Metcalfe, J.	N

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Renata Albrecht, MD, Division Director **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): n/a **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

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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.

/s/

MICHAEL J PUGLISI
08/20/2012

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

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 203-168

Application Type: New NDA

Name of Drug: Prolensa (bromfenac ophthalmic solution) 0.07%

Applicant: ISTA Pharmaceuticals, Inc.

Submission Date: June 5, 2012

Receipt Date: June 7, 2012

1.0 Regulatory History and Applicant's Main Proposals

The applicant has submitted a New Drug Application (NDA) for bromfenac ophthalmic solution 0.07% for the indication of the treatment of inflammation and pain associated with cataract extraction.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the 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).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. The terms, "adverse events" and "adverse experiences" should be avoided in Section 6 Adverse Reactions. The term, "adverse reactions" should be used instead.
2. The "Rx Only" statement that appears at the end of the package insert should be deleted. This statement is only required for container and carton labels.
3. The applicant should submit mock-ups for the carton and container labels for all four presentations (0.6 mL sample, 0.8 mL sample, 1.6 mL trade, and 3 mL trade).

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by **DATE (CHOOSE A DATE WITHIN TWO TO THREE WEEKS OF THE LETTER)**. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

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

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

NO 6. Section headings are presented in the following order in HL:

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

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: *Missing the Contraindications section heading.*

NO 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment: *Horizontal line is present in the SPL, but not the Word/pdf versions*

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

NO 10. Product title in HL must be **bolded.**

Comment: *Established name is not bolded in the Word/pdf versions.*

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Initial US Approval date is not bolded in the Word/pdf versions.*

N/A

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered 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**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. 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

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

NO 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. 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

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

NO 28. A horizontal line must separate TOC from the FPI.

Comment: *Horizontal line is present in the SPL, but not the Word/pdf versions*

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. 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:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

N/A 39. 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 patient labeling must appear at the end of the PI upon approval.

Comment:

N/A 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. 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

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. 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**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

NO 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

NO 46. When clinical trials adverse reactions data is 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 clinical practice."

Comment: *This statement should be added.*

N/A 47. When postmarketing adverse reaction data is 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:

Patient Counseling Information

N/A 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEANNA M KELLY
08/09/2012

JUDIT R MILSTEIN
08/20/2012
NDA 203168-RPM Initial submission-Labeling Review