CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203168Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	203,168
Submission Date(s):	June 7, 2012
Brand Name	Prolensa
Generic Name	Bromfenac ophthalmic solution 0.07%
Primary Reviewer	Yoriko Harigaya, Pharm.D.
Team Leader	Philip Colangelo, Pharm.D., Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Transplant and Ophthalmology Products
Applicant	ISTA Pharmaceuticals, Inc.
Relevant IND(s)	60,295
Submission Type	Original Submission: Standard Review
Formulation; Strength(s)	Bromfenac ophthalmic solution 0.07%
Indication	Treatment of inflammation and pain associated with cataract extraction

1. EXECUTIVE SUMMARY

The sponsor submitted an original New Drug Application (NDA) for Prolensa® (bromfenac ophthalmic solution 0.07%) on June 7, 2012. Prolensa®, administered once daily (QD), is a non-steroidal anti-inflammatory drug (NSAID) studied in clinical trials for the treatment of postoperative inflammation and the reduction of ocular pain in subjects who have undergone cataract surgery. The proposed dosage and route of administration for Prolensa® for this indication is as follows: instill one drop of bromfenac ophthalmic solution 0.07% into the affected eye once daily beginning 1 day prior to surgery, continued on the day of surgery, and through the first 14 days post-surgery.

This Prolensa® formulation (0.07%) differs from the currently marketed bromfenac ophthalmic solution 0.09% product (Bromday®) in the amounts of bromfenac sodium and its target pH. (b) (4) The indication is the same as the currently marketed product, Bromday (bromfenac ophthalmic solution 0.09%), administered QD. sNDA 21,664 for Bromday® was approved by the Agency on October 16, 2010 with a change in dosage regimen from the previously approved (March 24, 2005) twice-a-day (BID) dosing for Xibrom® (bromfenac sodium ophthalmic solution 0.1%) following cataract extraction surgery to QD dosing beginning 1 day prior to cataract surgery, continue on the day of surgery, and for 14 days after cataract surgery.

No new clinical pharmacology data was presented in this supplement. Thus, no review is needed for this NDA submission. For information of the pharmacokinetic (PK) characteristics of Xibrom® (bromfenac sodium ophthalmic solution 0.1% BID), please refer to the Office of Clinical Pharmacology review of the original NDA 21,664 (by Dr. Lei Zhang dated March 8, 2005). For the efficacy study information of Bromday® (formerly XiDay®) (bromfenac ophthalmic solution 0.09% QD), please refer to the Office of Clinical Pharmacology review of the NDA 21,664 / SE2-013 (by Dr. Kimberly L. Bergman dated July 12, 2010).

The sponsor conducted two Phase 3 studies S00124-ER and S00124-WR evaluated the efficacy and safety of Prolensa® vs. placebo for the treatment of ocular inflammation and pain associated with cataract surgery.

1.1 Recommendation
From a Clinical Pharmacology perspective, the application is acceptable. No new clinical pharmacology data was presented in this supplement.

1.2 Labeling Recommendations
Please refer to Section 2 for detailed labeling recommendations.

1.3 Phase 4 Requirements
No Phase IV study recommendation.

1.4 Summary of Important Clinical Pharmacology Findings
No additional pharmacological studies were conducted for this NDA.

2. LABELING RECOMMENDATIONS

In the current submission (NDA 203,162 dated June 7, 2012), the applicant has proposed no changes to the already existing Clinical Pharmacology section in the approved label for Xibrom® and Bromday®. The labeling proposed for this supplement is acceptable from a clinical pharmacology perspective (*see proposed labeling below*), and there are no labeling revisions / edits to be sent to the sponsor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2.

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

12.3 Pharmacokinetics

The plasma concentration of bromfenac following ocular administration of 0.07% Prolensa (bromfenac ophthalmic solution) in humans is unknown. Based on the maximum proposed dose of one drop to the eye (0.035 mg) and PK information from other routes of administration, the systemic concentration of bromfenac is estimated to be below the limit of quantification (50 ng/mL) at steady-state in humans.

3. OCP Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**203,168**	**Brand Name**	**Prolensa**
OCP Division (I, II, III, IV, V)	**IV**	**Generic Name**	**Bromfenac**
Medical Division	**DTOP**	**Drug Class**	**NSAID**
OCP Reviewer	**Yoriko Harigaya, Pharm.D.**	**Indication(s)**	**Treatment of inflammation and pain associated with cataract extraction**
OCP Team Leader	**Philip M. Colangelo, Pharm.D., Ph.D.**	**Dosage Form**	**Ophthalmic solution**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Once daily dose**
Date of Submission	**June 7, 2012**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review	**March 7, 2012**	**Sponsor**	**ISTA Pharmaceuticals, Inc.**
Medical Division Due Date	**N/A**	**Priority Classification**	**Standard**
PDUFA Due Date	**April 7, 2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:	**X**			**Refer to the OCP review of the original NDA 21,664 by Dr. Lei Zhang (Mar. 8, 2005) and Efficacy Supplement by Dr. Kimberly L. Bergman (July 12, 2010)**
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**			**Refer to the OCP review of the original NDA 21,664 by Dr. Lei Zhang (Mar. 8, 2005) and Efficacy Supplement by Dr. Kimberly L. Bergman (July 12, 2010)**

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**		

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/s/

YORIKO HARIGAYA
02/19/2013

PHILIP M COLANGELO
02/19/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

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Medical Division	**DTOP**	**Drug Class**	**NSAID**
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OCP Team Leader	**Philip M. Colangelo, Pharm.D., Ph.D.**	**Dosage Form**	**Ophthalmic solution**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Once daily dose**
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Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

multiple dose:	X			**Refer to the OCP review of the original NDA 21,664 by Dr. Lei Zhang (Mar. 8, 2005) and Efficacy Supplement by Dr. Kimberly L. Bergman (Dec. 18, 2009)**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
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In-vivo effects of primary drug:				
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Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
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III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			X	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
There are no potential review issues to be forwarded to the applicant for the 74 day letter from a clinical pharmacology perspective.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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/s/

YORIKO HARIGAYA
07/31/2012

PHILIP M COLANGELO
08/01/2012