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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				
<u>General Information About the Submission</u>				
	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			
<u>Clin. Pharm. and Biopharm. Information</u>				
	"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)

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