CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203168Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 4, 2013
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	203168
Applicant	Bausch & Lomb, Inc.
Date of Submission	June 6, 2012
PDUFA Goal Date	April 7, 2013
Proprietary Name / Established (USAN) names	Prolensa (bromfenac ophthalmic solution) 0.07%
Dosage forms / Strength	Topical ophthalmic solution, 0.07%
Proposed Indication(s)	Treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery
Recommended:	Recommended for Approval

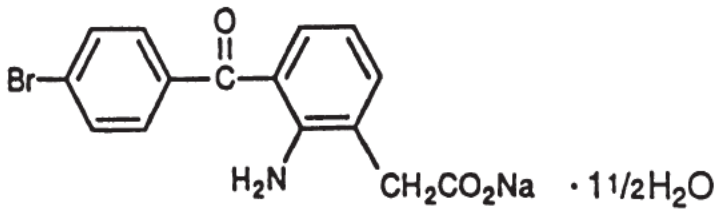
1. Introduction

Bromfenac ophthalmic solution is a non-steroidal anti-inflammatory drug (NSAID) studied for the treatment of postoperative inflammation and the reduction of pain in subjects who have undergone cataract surgery. 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 (COX) 1 and 2.

NDA 21-664 Xibrom (bromfenac ophthalmic sodium) 0.09% was approved in March 2005 (Original) for the treatment of post-operative ocular inflammation and in January of 2006 (SE1 S-01) for the treatment of post-operative pain.

Bromday (bromfenac ophthalmic sodium) 0.09%, the same drug product labeled for the same indication to be dosed once per day was approved on 10/16/2010 (SE2 S-13).

The chemical structure for bromfenac sodium sesquihydrate is:



There are multiple ophthalmic topical drugs approved for inflammation and pain following cataract extraction or ocular surgery including:

Ketorolac tromethamine ophthalmic solution 0.45%, 0.5% (i.e., Acuvail, Acular)
Rimexolone ophthalmic suspension 1% (i.e., Vexol)
Bromfenac ophthalmic solution 0.09% (i.e., Xibrom, Bromday)
Nepafenac ophthalmic suspension 0.1%, 0.3% (i.e., Nevanac, Ilevro)
Loteprednol etabonate ophthalmic suspension 0.5% (i.e., Lotemax)
Loteprednol ophthalmic ointment 0.5% (i.e., Lotemax)
Loteprednol ophthalmic gel 0.5% (i.e., Lotemax)
Difluprednate ophthalmic emulsion 0.05% (i.e., Durezol).

Post-marketing experience with this class of drugs has shown that use of topical NSAIDs for more than 24 hours prior to surgery or use beyond 14 days post surgery may increase the risk for the occurrence and severity of corneal adverse events such as epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration and corneal perforation which are potentially sight threatening. Class labeling addressing this issue has been added to all existing topical NSAID labels and will be contained in the label for this drug product.

2. Background

Clinical studies for this new drug application were conducted under IND 060295.

On April 14, 2011, a Special Protocol Assessment – No Agreement letter was issued for the Phase 3 clinical protocol titled: Efficacy and Safety of Bromfenac Ophthalmic Solution vs. Placebo for the Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery.

On August 29, 2011, a Pre-NDA teleconference meeting was held to discuss bromfenac ophthalmic solution, 0.07% for treatment of ocular inflammation and pain associated with cataract surgery.

In a submission dated August 20, 2012, the Agency was informed that Bausch and Lomb Inc. had acquired ISTA Pharmaceuticals, Inc. The contact information (address and phone numbers) for this NDA remained the same.

3. Product Quality

Each mL of Prolensa (bromfenac ophthalmic solution) 0.07% contains:

Active: Each mL contains bromfenac sodium sesquihydrate 0.0805%, which is equivalent to bromfenac free acid 0.07%.
Preservative: benzalkonium chloride 0.005%
Inactives: boric acid, edetate disodium, povidone, sodium borate, sodium sulfite, tyloxapol, sodium hydroxide to adjust pH and water for injection, USP.

From the original Product Quality Review dated 2/26/2013:

DRUG SUBSTANCE:
The Active Pharmaceutical Ingredient (API) in the drug product is bromfenac sodium drug substance. The same drug substance is used in the manufacture of the currently marketed bromfenac ophthalmic solution 0.09% formulation in this applicant's original NDA 21-664, which was approved on 24 March 2005. The manufacturer and supplier, manufacturing process, test methods, specifications, and all other parameters are the same as those applied to the drug substance for the currently approved Xibrom/Bromday 0.09% formulation.

DRUG PRODUCT:
The drug product is a non-steroidal anti-inflammatory drug (NSAID) for topical ophthalmic use. It is supplied as a clear, yellow, sterile solution containing 0.07% bromfenac free acid and dispensed from a 7.5cc capacity white low density polyethylene (LDPE) bottle with a white linear (b) (4) tip, and grey (b) (4) screw cap. The drug product is supplied in trade sizes of 1.6 mL and 3 mL fill volumes and sample sizes of 0.6 mL and 0.8 mL fill volumes.

Per a March 12, 2013, amendment to the NDA, the applicant states that the 3-mL fill size is necessary to complete the labeled dosing regimen for the elderly population (approximately 45% of the subjects in the Prolensa clinical studies were >70 years of age) as significant wastage of drops has been documented. This is acceptable.

The components of the container closure system used for bromfenac ophthalmic solution 0.07% are identical to the marketed bromfenac ophthalmic solution 0.09% (NDA 21-664).

QUANTITATIVE COMPOSITION:

	Declared Function	%w/v	mg per mL
Bromfenac sodium sesquihydrate	Active	0.0805	0.805
Boric acid	(b) (4)		
Sodium borate			
Sodium sulfite			
Edetate disodium (EDTA)			
Tyloxapol			
Benzalkonium chloride	Preservative	0.005	0.05
Povidone	(b) (4)		
Sodium hydroxide	pH adjuster	q.s. to pH 7.8	q.s. to pH 7.8
Water for Injection	(b) (4)		

REGULATORY SPECIFICATIONS:

Table 1. Specifications for Bromfenac Ophthalmic Solution 0.07%

Test	Specification
Product Appearance	Clear, yellow solution
Description: Container	A white plastic bottle with dropper tip and gray cap, with no significant discoloration or physical distortion
Identification (release only)	(b) (4)
Bromfenac Sodium Assay	
Bromfenac Impurities	
Impurity (b) (4)	
Any Individual Specified Impurity (b) (4)	
Any Individual Unspecified Impurity	
pH	
Osmolality	
Benzalkonium Chloride[1]	
EDTA	
Sodium Sulfite	
Sterility	
Bacterial Endotoxins	
Particulate Matter (Microscopic Evaluation)	
Particulate Matter (Visual)	
Weight Loss (stability only)	
(b) (4)	

In the above specification table, the applicant did not include Leachables testing during shelf-life. The approved 0.09% formulation (NDA 203-168) is also packaged in 7.5 cc plastic bottles (as one of the configurations) and labeled with same labels and adhesive. NDA 21-664/S-017 was recently approved (6/6/12), which allowed the elimination of ongoing leachables testing based on large body of Xibrom-specific historical data.

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