CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203168Orig1s000

OFFICE DIRECTOR MEMO

Deputy Division Director Review of NDA 203168

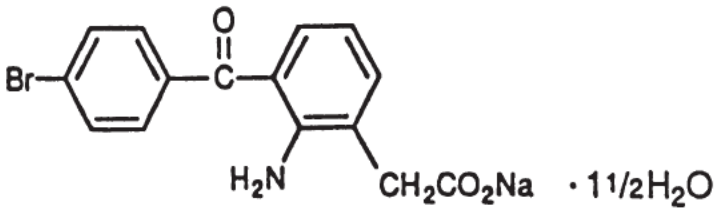
Date	April 4, 2013
From	Wiley A. Chambers, M.D.
NDA	203168
Applicant	Bausch & Lomb, Inc.
Date of Submission	June 6, 2012
PDUFA Goal Date	April 7, 2013
Name	Prolensa (bromfenac ophthalmic solution) 0.07%
Dosage forms / Strength	Topical ophthalmic solution, 0.07%
Proposed Indication(s)	Treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery
Recommendation:	Recommended for Approval

1. Background

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. The mechanism of its action is believed 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. A later supplement added a once a day dosing regimen starting the day before surgery. The product with once a day dosing was relabeled as Bromday (bromfenac ophthalmic sodium) 0.09% and was approved on 10/16/2010 (SE2 S-13).

The chemical structure for bromfenac sodium sesquihydrate is:



There are multiple topical ophthalmic drug products approved for the treatment of 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).

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

2. Product Quality

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. 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 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.

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).

Sterility Assurance
The drug product will be (b) (4) at the Bausch and Lomb Tampa, FL facility. The applicant provided an adequate summary of the microbiological attributes of the drug product. The raw counts for preservative effectiveness testing were requested due to past issues with regard to preservative testing of other bromfenac ophthalmic formulations. The results of preservative testing were adequate. No product quality microbiology deficiencies were identified based upon the information provided.

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:

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)

INSPECTIONS

An “Acceptable” site recommendation from the Office of Compliance has been made.

3. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review of NDA 20-535, Bromfenac tablets, pages 28-30 includes pharmacokinetic parameters of oral administration for mice, rats, rabbits, dogs, cynomologus monkeys, rhesus monkeys and humans. The measured or estimated C_{max} values are listed below. Consistent with this class of products, unlike humans, many of the animals did not tolerate high doses of NSAIDs. The applicant did not attempt to measure systemic absorption from ophthalmic dosing because the limit of the assay detection was 50 ng/mL.

The estimated C_{max} for a 0.9 mg/kg dose to a rat would be 4.4 mcg/mL (4400 ng/mL). Assuming a maximum human C_{max} is the limit of detection or 50 ng/mL as described in the Agency proposed labeling, the multiple would be approximately 90 times.

The estimated C_{max} for a 0.3 mg/kg dose to a rat would be 1.4 mcg/mL (1400 ng/mL). Assuming a maximum human C_{max} is the limit of detection or 50 ng/mL as described in the Agency proposed labeling, the multiple would be approximately 30 times.

For mice, the C_{max} for a 5.0 mg/kg dose was 16.9 mcg/mL (16,900 ng/mL). Assuming a maximum human C_{max} is the limit of detection or 50 ng/mL as described in the Agency proposed labeling, the multiple would be approximately 340 times.

For rabbits, the C_{max} for a 7.5 mg/kg dose was 7.6 mcg/mL (7600 ng/mL). Assuming a maximum human C_{max} is the limit of detection or 50 ng/mL as described in the Agency proposed labeling, the multiple would be approximately 150 times.

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (30 times the recommended human ophthalmic dose [RHOD] assuming the systemic concentration is at the maximum limit of quantification[50 ng/mL]) and 5 mg/kg/day (340 times RHOD), respectively, revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (90 and 30 times RHOD, respectively).

4. Clinical Pharmacology/Biopharmaceutics

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

5. Clinical/Statistical - Efficacy

The two Phase 3 studies, S00124-ER and S00124-WR utilized the same protocol administered in the eastern and western regions of the United States, respectively.

For both Phase 3 studies, the primary efficacy outcome was the proportion of subjects who had cleared ocular inflammation (SOIS of grade 0) by Day 15. The SOIS is defined as the sum of the

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