CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203168Orig1s000

OFFICE DIRECTOR MEMO

Deputy Division Director Review of NDA 203168

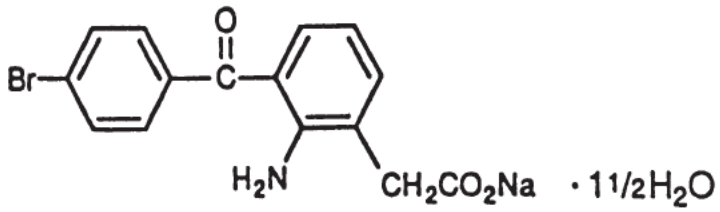
Date	April 4, 2013
From	Wiley A. Chambers, M.D.
NDA	203168
Applicant	Bausch & Lomb, Inc.
Date of Submission	June 6, 2012
PDUFA Goal Date	April 7, 2013
Name	Prolensa (bromfenac ophthalmic solution) 0.07%
Dosage forms / Strength	Topical ophthalmic solution, 0.07%
Proposed Indication(s)	Treatment of postoperative 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

mean anterior chamber cells score and anterior flare score. All analyses of efficacy were conducted on the ITT Population. The primary analyses were based on the ITT Population with the LOCF data.

Analysis of Primary Endpoint(s)

S00124-ER (LOCF; ITT Population)

	Bromfenac 0.07% N = 112	**Placebo N = 108**	**P-value**
Cleared Ocular Inflammation			
Day 1	2 (1.8%)	0 (0.0%)	0.4979
Day 3	7 (6.3%)	1 (0.9%)	0.1314
Day 8	30 (26.8%)	8 (7.4%)	0.0006
Day 15 (Primary Endpoint)	54 (48.2%)	18 (16.7%)	<0.0001
Day 22	74 (66.1%)	57 (52.8%)	0.1314

p-value was for bromfenac 0.07% versus placebo and was from the Fisher's exact test adjusted for multiple comparisons using Hochberg's method.

The proportion of subjects who had cleared ocular inflammation (SOIS Grade 0) by Day 8 and by Day 15 were significantly higher ($p<0.001$) in the bromfenac 0.07% group (27-48%) compared with the placebo group (7-17%).

S00124-WR (LOCF; ITT Population)

	Bromfenac 0.07% N = 110	**Placebo N = 110**	**P-value**
Cleared Ocular Inflammation [1]			
Day 1	3 (2.7%)	4 (3.6%)	>0.9999[2]
Day 3	8 (7.3%)	7 (6.4%)	>0.9999[2]
Day 8	36 (32.7%)	18 (16.4%)	0.0370[2]
Day 15 (Primary Endpoint)	54 (49.1%)	35 (31.8%)	0.0132[3]
Day 22	81 (73.6%)	63 (57.3%)	0.0470[2]

p-value was for bromfenac 0.07% versus placebo and was from the Fisher's exact test adjusted for multiple comparisons using Hochberg's method.

The proportion of subjects who had cleared ocular inflammation by Day 8 and by Day 15 was significantly higher ($p<0.05$) in the bromfenac 0.07% group (33-49%) compared with the placebo group (16-32%).

Analysis of Secondary Endpoints(s)

For both Phase 3 studies, the secondary efficacy outcome was the proportion of subjects who were free of ocular pain at Day 1.

S00124-ER

Table 22. Subjects, N (%), Pain Free *at* Each Visit (LOCF Analysis, ITT Population)

	Bromfenac 0.07% N = 112	Placebo N = 108	P-value [1]
Day 1 (Secondary Endpoint)	91 (81.3%)	47 (43.5%)	<0.0001
Day 3	97 (86.6%)	57 (52.8%)	<0.0001
Day 8	105 (93.8%)	64 (59.3%)	<0.0001
Day 15 [2]	104 (92.9%)	73 (67.6%)	<0.0001

Source: Table 14.2.3.1 and Table 14.2.3.3.1

Note: A subject was considered to be pain free *at* a particular visit if there was a score of "None" on the pain scale of the OCGA in the subject diary at that visit.

[1] p-value was for bromfenac 0.07% versus placebo and was from a Fisher's exact test adjusted for multiple comparisons using Hochberg's method.

[2] Day 15 visit is from diary Day 14.

The proportion of subjects who were pain free was significantly higher in the bromfenac 0.07% than in the placebo group at Day 1 (81.3%, 91/112 versus 43.5%, 47/108; p<0.0001).

S00124-WR

Table 22. Subjects, N (%), Pain Free at Each Visit (LOCF Analysis, ITT Population)

	Bromfenac 0.07% N = 110	Placebo N = 110	P-value [1]
Day 1 (Secondary Endpoint)	84 (76.4%)	61 (55.5%)	0.0017
Day 3	95 (86.4%)	58 (52.7%)	<0.0001
Day 8	99 (90.0%)	68 (61.8%)	<0.0001
Day 15 [2]	100 (90.9%)	74 (67.3%)	<0.0001

Source: Table 14.2.3.1 and Table 14.2.3.3.1

Note: A subject was considered to be pain free *at* a particular visit if there was a score of "None" on the pain scale of the OCGA in the subject diary at that visit.

[1] p-value was for bromfenac 0.07% versus placebo and was from a Fisher's exact test adjusted for multiple comparisons using Hochberg's method.

[2] Day 15 visit is from diary Day 14.

The proportions of subjects who were pain free were significantly higher in the bromfenac 0.07% than in the placebo group at Day 1 (76.4%, 84/110 versus 55.5%, 61/110; p=0.0017).

Additional Efficacy Issues/Analyses: Cleared Cells at Each Visit

The following table shows the proportion of subjects who had cleared inflammation at each visit (LOCF, Summed Ocular Inflammation Score: Grade 0).

S00124-ER

Table 4.1 Subjects, N (%), with SOIS of Grade 0 at Each Visit (LOCF Analysis; ITT Population, S00124-ER)

Cleared Ocular Inflammation[1]	Bromfenac 0.07% N = 112	Placebo N = 108	P-value
Day 1	2 (1.8%)	0 (0.0%)	0.4979[2]
Day 3	6 (5.4%)	1 (0.9%)	0.1194[2]
Day 8	27 (24.1%)	7 (6.5%)	0.0003 [2]
Day 15	51 (45.5%)	14 (13.0%)	<0.0001 [3]
Day 22	65 (58.0%)	52 (48.1%)	0.1765[2]

Source: Table 14.2.1.1.2

1 Cleared ocular inflammation *at* each visit was defined as a SOIS of Grade 0 at a visit.

2 p-value was for bromfenac 0.07% versus placebo and was from the Fisher's exact test .

3 Primary Efficacy Endpoint, p-value was for bromfenac 0.07% versus placebo and was from the Fisher's exact test.

S00124-WR

Table 4.2 Subjects, N (%), with SOIS of Grade 0 at Each Visit (LOCF Analysis; ITT Population, S00124-WR)

Cleared Ocular Inflammation [1]	Bromfenac 0.07% N = 110	Placebo N = 110	P-value
Day 1	3 (2.7%)	4 (3.6%)	>0.9999[2]
Day 3	7 (6.4%)	6 (5.5%)	>0.9999[2]
Day 8	33 (30.0%)	15 (13.6%)	0.0052 [2]
Day 15	50 (45.5%)	31 (28.2%)4	0.0116 [3]
Day 22	76 (69.1%)	58 (52.7%)	0.0186 [2]

Source: Table 14.2.1.1.2

1 Cleared ocular inflammation *at* each visit was defined as a SOIS of Grade 0 at a visit.

2 p-value was for bromfenac 0.07% versus placebo and was from the Fisher's exact test .

3 Primary Efficacy Endpoint, p-value was for bromfenac 0.07% versus placebo and was from the Fisher's exact test.

4 One subject that had cleared and had received a rescue medication is included in this count.

The percentage of patients that clear "at a particular day" is just one of many additional analyses; after adjustment for multiplicity, the differences "at day x" are not statistically significant in both trials.

6. Safety

The primary basis for establishing relative safety in this application comes from the clinical trials supporting the bromfenac ophthalmic solution, 0.9%. The trials conducted with the bromfenac ophthalmic solution 0.7% are consistent with the results of those earlier trials.

The most commonly reported adverse reactions in seen clinical trials conducted with bromfenac ophthalmic solution, 0.7%, occurred in 3-8% of patients and included anterior chamber inflammation, eye pain, foreign body sensation, photophobia, and vision blurred.

7. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

8. Pediatrics

PREA was not triggered for this application. Studies were waived for all pediatric age groups; cataract surgery is not performed on a substantial number of pediatric patients, and the use of topical NSAIDS in pediatric patients does not represent a meaningful therapeutic benefit over topical corticosteroids. Safety and effectiveness of Prolensa (bromfenac ophthalmic solution) 0.07% in pediatric patients have not been established.

9. Other Relevant Regulatory Issues

a. The Statistical Group has proposed to change the labeling to reflect one of the additional endpoints and not include the primary endpoint. The Ophthalmology Clinical Group, including myself, does not agree with the proposed revision of the primary endpoint. Cleared ocular inflammation by Day 15, which was defined as the summed ocular inflammation score (SOIS) of Grade 0 (0 cells and absence of flare) at any post surgery visit prior to and including Day 15, is a precise and well-defined endpoint. We do not agree that the 15 subjects (treated as successes in the applicant's primary efficacy analysis despite a non-zero score at Day15) represent treatment failure as defined by the protocol or by clinical practice.

b. Office of Prescription Drug Promotion (OPDP) completed a formal review of the package insert based on the substantially complete labeling from 3/20/13. OPDP's suggestion to add "including Prolensa" at any mention of a general NSAID-risk in Section 5 of the package insert is not recommended. Section 5, as currently proposed in the substantially complete labeling, is clear that all topical NSAIDS carry the specified risks. OPDP's suggestion to remove the statement regarding prostaglandins in animal models in Section 12.1 is not recommended. The statement in question is not speculative; this statement and its implications are clinically relevant and supported by substantial evidence for humans. OPDP's suggestion to expand upon the primary efficacy endpoint in Section 14.1 is not recommended. The endpoint, proportion of subjects clearing ocular inflammation, is understood by prescribing ophthalmologists who would be performing cataract surgery and performing postoperative evaluations. OPDP's suggestion to separate the efficacy results of the two trials in Section 14.1 is not recommended. 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. Identical protocols were not necessarily utilized in other NSAIDS, Phase 3 trials and thus their Clinical Studies Sections differ in format.

c. The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Prolensa, on 3/4/2013. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

d. Financial disclosure information has been provided by the applicant for the covered clinical studies in this application. A review of the financial disclosure data does not indicate a potential impact on the clinical study results.

e. A routine Office of Scientific Investigations (OSI) audit was requested. 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).

10. Labeling

NDA 203168, Prolensa (bromfenac ophthalmic solution) 0.07%, is recommended for approval for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

Carton and container labeling submitted on 3/18/13 and found in the Appendix of this review is acceptable. With the next scheduled printing, the cartons should be revised to include a more precise description of the active (i.e. bromfenac sodium sesquihydrate 0.0805%).

The package insert submitted by the applicant on 4/2/2013 is found in the Appendix of this review. I do not agree with altering the endpoint from "the proportion of subjects who had complete clearance of ocular inflammation by day 15" to "complete clearance at Day 8 and Day 15." The proportion of subjects who had complete clearance of ocular inflammation by day 15 is an appropriate endpoint and was statistically significant. The percentage of patients who had complete clearance on a particular day, when adjusted for the multiplicity of the multiple additional endpoints was not statistically significant.

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

11. Recommendations/Risk Benefit Assessment

NDA 203168, Prolensa (bromfenac ophthalmic solution) 0.07%, is recommended for approval for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery. It is also recommended that the labeling be revised to remove the references to the outcome "at day 8 and at day 15."

Wiley A. Chambers, MD
Deputy Division Director

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

/s/

WILEY A CHAMBERS
04/05/2013