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

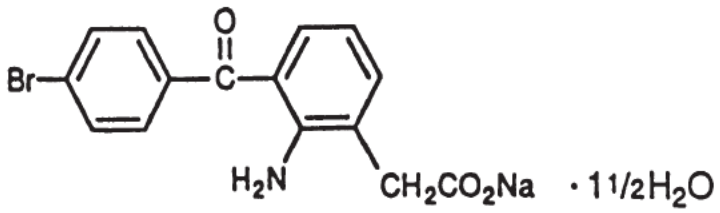
1. Introduction

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.

INSPECTIONS:

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

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 203168/000	**Sponsor:**	ISTA PHARMS INC
Org. Code:	590		50 TECHNOLOGY DR
Priority:	5		IRVINE, CA 92618
Stamp Date:	07-JUN-2012	**Brand Name:**	BROMFENAC
PDUFA Date:	07-APR-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	06-FEB-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; SOLUTION; BROMFENAC SODIUM; .0805%

FDA Contacts:	A. CUFF	Project Manager	(HF-01)	3017964061
	R. KAMBHAMPATI	Review Chemist	(HFD-830)	3017961382
	B. SHANMUGAM	Team Leader		3017961457

Overall Recommendation:	ACCEPTABLE	on 27-JUL-2012	by A. ALEXANDROW	(HFD-001)	3017965363
	PENDING	on 24-JUL-2012	by EES_PROD		
	PENDING	on 29-JUN-2012	by EES_PROD		

Establishment:	**CFN:** 1052807 **FEI:** 1000113778 BAUSCH AND LOMB PHARMACEUTICALS INC TAMPA, , UNITED STATES 336371014		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	STERILE LIQUID (EXCLUDE SUSPENSIONS & EMULSIONS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	03-JUL-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORIES "ALSO" (DRUGS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	03-JUL-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:	(b) (4)	**AADA:**	
Responsibilities:	(b) (4)		
Profile:		**OAI Status:**	NONE
Last Milestone:	NO FURTHER EVALUATION		
Milestone Date:	06-JUL-2012		

Establishment:	**CFN:** 1416120 **FEI:** 1416120 REGIS TECHNOLOGIES, INC. MORTON GROVE, , UNITED STATES 600533205		
DMF No:	16414	**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE STABILITY TESTER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-JUL-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORIES "ALSO" (DRUGS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	02-JUL-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

4. 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. 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).

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review dated 2/29/2013:

No new clinical pharmacology data was presented in this supplement. Thus, no review is needed for this NDA submission.

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.

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

6. Sterility Assurance

From the original drug substance Product Quality Microbiology Review dated 1/22/2013:

NDA 203168/N-000 is recommended for approval from the standpoint of product quality microbiology.

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.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 3/22/2013:

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

Table 8. Subjects, N (%), with SOIS of Grade 0 *by* Each Visit (LOCF Analysis; ITT Population)

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

Source: Table 14.2.1.1 and Table 14.2.1.5.3

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

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.

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

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

Table 8. Subjects, N (%), with SOIS of Grade 0 by Each Visit (LOCF Analysis; ITT Population)

	Bromfenac ophthalmic solution 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]

Source: Table 14.2.1.1 and Table 14.2.1.5.3

1 Cleared ocular inflammation by each visit was defined as a SOIS of Grade 0 at or prior to each visit.

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.

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

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.

Summary Efficacy Statement

Adequate and well controlled studies (S00124-ER and S00124-WR) support the efficacy of Prolensa (bromfenac ophthalmic solution) 0.07% for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

The proportion of subjects who had cleared ocular inflammation (SOIS Grade 0) by Day 8 and by Day 15 (specified primary endpoint) was significantly higher in the bromfenac 0.07% group compared with the placebo group in both Phase 3 trials.

8. Safety

From the original Medical Officer Review dated 3/22/2013:

Exposure

Table 4. Treatment Compliance in Studies of Bromfenac 0.07% QD (Safety Population, S00124 Pooled Studies)

	Bromfenac 0.07% QD Studies	
	Pooled Bromfenac 0.07% QD n (%)	Pooled Placebo QD n (%)
Safety Population, N	212	204
Subjects Completing Treatment		
n (%)	143 (67.5%)	100 (49.0%)
p-value	0.0002[1]	
Number of Doses Received		
Mean	14.6	12.2
SD	3.32	4.75
Median	16.0	15.0
Min, Max	1, 16	2, 16
p-value	<0.0001[2]	
Percent Compliance		
Mean	91.21	75.98
SD	20.729	29.677
Median	100.00	93.75
Min, Max	6.3, 100.0	12.5, 100.0
p-value	<0.0001[2]	
≥75% Compliance		
n (%)	187 (88.2%)	121 (59.3%)
p-value	<0.0001[1]	

Source: **Appendix 1, Table 2**.

Note: Treatment was complete if at least 16 doses were received.

Note: Percent compliance=100 x number of doses received/16.

[1] p-value for bromfenac 0.07% versus placebo was from a Fisher's exact test.

[2] p-value for bromfenac 0.07% versus placebo was from a t-test.

Subjects participating in studies S00124-ER and S00-124-WR were assigned to receive bromfenac 0.07% QD for a maximum of 16 days. The mean number of doses received in a pooled analysis was 14.6 (1.0 to 16.0).

Disposition of Subjects

Table C: Subjects Discontinuing IP Early in S00124 (ER vs WR)

BROMFENAC GROUP			
S00124-ER	#	**S00124-WR**	#
AE	4	AE	7
Disallowed Concurrent Med	0	Disallowed Concurrent Med	2
Lack of Efficacy	2	Lack of Efficacy	5
"Other" Category (5 subjects; 4 sites)	5	**"Other" Category (9 subjects; 7 sites)**	9
Surgery cancelled		Withdrew consent; drug not dispensed (2)	
Never used IP		Withdrew consent (2)	
Non-compliance with IP dosing frequency		Ran out of IP	
Withdrawal of consent		Surgery cancelled	
Withdrew consent on randomization day; did not administer IP		Surgery not scheduled in protocol timeframe	
		Lost IP	
		Patient misunderstood directions; discontinued IP instead of antibiotic	
Total:	**11**	**Total:**	**23**
PLACEBO GROUP			
S00124-ER	#	**S00124-WR**	#
AE	3	AE	26
Disallowed Concurrent Med	0	Disallowed concurrent med	2
Lack of Efficacy	37	Lack of efficacy	15
"Other" Category (7 subjects; 5 sites)	7	**"Other" Category (6 subjects; 5 sites)**	6
No administration of IP (4)		Surgery cancelled (2)	
Screening period not respected; no administration of IP		Disallowed concurrent med (2)	
Surgery cancelled		Did not show up for surgery	
Visit was out of window		Withdrew consent; noncompliance	
Total:	**47**	**Total:**	**49**

The definition of "study completion" as defined in Table 4 (Section 10.1 of the CSRs) for S00124-ER and S00124-WR in the original NDA submission was not acceptable. Subjects who discontinued investigational product early and completed the final study visit should not be considered to have completed the study. Revised tables for study disposition were provided to the application S00124-ER and S00124-WR on March 13, 2013. See the following tables.

S00124-ER

Table 3.1: Summary of Subject Disposition (ITT Population) in Study S00124-ER

	Bromfenac 0.07% n (%)	Placebo n (%)	P-value[2]
Number of Subjects Randomized	112 (100%)	108 (100.0%)	
Subjects who Completed the Study [1]	101 (90.2%)	61 (56.5%)	
Subjects who Discontinued the Study Early	11 (9.8%)	47 (43.5%)	
Primary Reason for Early Termination:			
Withdrawal of Consent/Non-compliance	2 (1.8%)	3 (2.8%)	>0.9999
Lost to Follow-up	0	0	
Death	0	0	
Other [3]	1 (0.9%)	3 (2.8%)	

Source: Table 14.1.1.4.1

[1] A subject was considered to have completed the study if the subject took all study drug and completed all study visits thru at least Day 15.

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

[3] Other reasons for early discontinuation of the study in the bromfenac 0.07% group were inappropriate randomization (should have been a screen failure; 1 subject) and for the placebo group were cancelled surgery (1 subject), did not meet exclusion criteria (1 subject), and the screening period was not respected (1 subject): Listing 16.2.1.

S00124-WR

Table 3.2: Summary of Subject Disposition (ITT Population) in Study S00124-WR

	Bromfenac 0.07% n(%)	Placebo n(%)	P-value [2]
Number of Subjects Randomized	110 (100%)	110 (100%)	
Subjects who Completed the Study [1]	87 (79.1%)	59 (53.6 %)	
Subjects who Discontinued the Study Early	23 (20.9%)	51 (46.4%)	
Primary Reason for Early Termination:			
Withdrawal of Consent/Non-compliance	4 (3.6%)	3 (2.7%)	0.3024
Lost to Follow-up	0	0	
Death	0	0	
Other [3]	2 (1.8%)	7 (6.4%)	

Source: Table 14.1.1.4.1

[1] A subject was considered to have completed the study if the subject took all study drug and completed all study visits thru at least Day 15.

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

[3] The Other reasons for early discontinuation in the bromfenac 0.07% group was surgery cancelled (2 subjects) and in the placebo group the Other reasons were surgery cancelled (2 subjects), disallowed medication at enrollment or during the study (2 subjects), experienced a SAE (2 subjects), and inappropriate randomization (1 subject): Listing 16.2.1.

The Agency asked the applicant to comment on the disparity between the S00124-ER (ER) and S00124-WR (WR) in the number of subjects discontinuing IP early due to an adverse event. Per the applicant's submission dated March 2, 2013, it appears that the WR placebo group had a much higher IP-discontinuation rate due to counting signs and symptoms of ocular inflammation and pain as adverse events, whereas the ER placebo group had appeared to count many of these same signs and symptoms as IP discontinuations due to treatment failures.

Per the applicant, these differences might be reflected in the differences in placebo rates for the efficacy endpoint of cleared ocular inflammation (WR 31.8% vs. ER 16.7%). See the Medical Officer's review, Section 7.3.3, for more detail.

The efficacy outcomes for the proportion of subjects with SOIS=0 by Day 15 with the investigational product were nearly identical in both groups (WR 49.1% vs. ER 48.2%). See the Medical Officer's review, Section 7.3.3, for more detail.

Thus, the applicant concluded that these differences in assessing reasons for discontinuing IP early between groups did not affect the overall study conclusions. This conclusion by the applicant is reasonable.

Deaths

There were no deaths in either Study S00124-ER or Study S00124-WR. No deaths were reported during any of the BromCom, QD-ER, QD-WR, and QDII clinical studies with bromfenac 0.09% QD or in the S00007 studies with bromfenac (b) (4) and bromfenac (b) (4) BID.

Common Adverse Events

Incidence of Adverse Events Affecting the Study Eye: Events with an Incidence of ≥ 1.5 % in the Bromfenac 0.07% Group or Placebo Group (ITT Population)

Preferred Term	Bromfenac 0.07% N = 112 (ER)	Bromfenac 0.07% N = 110 (WR)	Placebo N = 108 (ER)	Placebo N = 110 (WR)
Anterior chamber inflammation	0 (0%)	8 (7.3%)	0 (0%)	18 (16.4%)
Vitreous floaters	0 (0%)	0 (0%)	3 (2.8%)	2 (1.8%)
Conjunctival hyperemia	1 (0.9%)	2 (1.8%)	2 (1.9%)	13 (11.8%)
Conjunctival edema	0 (0%)	1 (0.9%)	0 (0%)	2 (1.8%)
Corneal edema	1 (0.9%)	1 (0.9%)	2 (1.9%)	8 (7.3%)
Punctate keratitis	0 (0%)	0 (0%)	0 (0%)	2 (1.8%)
Iritis	0 (0%)	1 (0.9%)	0 (0%)	3 (2.7%)
Lacrimation increased	0 (0%)	0 (0%)	6 (5.6%)	0 (0%)
Eye pain	3 (2.7%)	9 (8.2%)	6 (5.6%)	14 (12.7%)
Eye pruritis	1 (0.9%)	2 (1.8%)	2 (1.9%)	2 (1.8%)
Ocular hyperemia	0 (0%)	0 (0%)	2 (1.9%)	4 (3.6%)
Foreign body sensation in eyes	3 (2.7%)	4 (3.6%)	5 (4.6%)	3 (2.7%)
Photophobia	1 (0.9%)	3 (2.7%)	6 (5.6%)	5 (4.5%)
Intraocular pressure increased	0 (0%)	2 (1.8%)	0 (0%)	3 (2.7%)
Visual acuity reduced	0 (0%)	0 (0%)	0 (0%)	2 (1.8%)

Preferred Term	Bromfenac 0.07% N = 112 (ER)	Bromfenac 0.07% N = 110 (WR)	Placebo N = 108 (ER)	Placebo N = 110 (WR)
Cystoid macular edema	0 (0%)	0 (0%)	0 (0%)	2 (1.8%)
Diplopia	0 (0%)	0 (0%)	0 (0%)	2 (1.8%)
Vision blurred	0 (0%)	4 (3.6%)	2 (1.9%)	2 (1.8%)

More subjects were evaluated for efficacy than were evaluated for safety in both S00124-ER and S00124-WR.

A reanalysis of the study data for S00124-ER and S00124-WR with the Safety Population defined as least as loosely as the Intent-to-Treat (ITT) Population (i.e. all randomized subjects, where subjects were to be analyzed in the group to which they were randomized) was requested by the Agency.

The most commonly reported adverse reactions in seen 3-8% of bromfenac ophthalmic solution 0.7% treated patients were: anterior chamber inflammation, eye pain, foreign body sensation, photophobia, and vision blurred.

Safety Summary Statement

Adequate and well controlled studies have been previously conducted with higher concentrations of bromfenac ophthalmic solution (0.09%) under NDA 21-664, and these studies also support the support the safety of bromfenac ophthalmic solution 0.07% for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

Adequate and well controlled studies (S00124-ER and S00124-WR) support the safety of Prolensa (bromfenac ophthalmic solution) 0.07% for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

A 120 Day Safety Update was submitted on 10/9/2012. No new safety issues relating to Prolensa (bromfenac ophthalmic solution) 0.07% have been found.

9. 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.

10. Pediatrics

PREA was not triggered for this application, and thus this application was not presented at the Pediatric Review Committee (PeRC). 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.

11. Other Relevant Regulatory Issues

BIOSTATISTICS
Per the original Biostatistics review dated 3/4/2013:

The efficacy and safety data from two Phase 3 studies, S00124-WR and S00124-ER, were included in this NDA. The two studies shared a common protocol and a statistical analysis plan. Both studies were double-masked, placebo-controlled, and randomized (with a 1:1 ratio) studies conducted in the United States, with S00124-WR including study sites in the west region and S00124-ER in the east region.

A total of 220 subjects were randomized in each study. The primary efficacy endpoint was the proportion of subjects with 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. The key secondary efficacy endpoint was the proportion of subjects who were pain free at Day 1.

Compared to the placebo group, the bromfenac 0.07% group had a significantly higher proportion of subjects with cleared ocular inflammation by Day 15, defined as no cells and no flare, and a significantly higher proportion of subjects who were pain free at Day 1.

Table 1: Applicant's Results for the Primary and Key Secondary Endpoints (S00124-ER)

Percentage of Subjects with Cleared Ocular Inflammation				
Visit	**Bromfenac 0.07% N=112**	**Placebo N=108**	**% difference (Asymptotic 95% CI)**	**P-value**
Day 1	2 (1.8%)	0 (0.0%)	1.8% (-0.6%, 4.4%)	0.4979
Day 3	7 (6.3%)	1 (0.9%)	5.3 %(0.5%, 10.2%)	0.1314
Day 8	30 (26.8%)	8 (7.4%)	19.4% (9.8%, 28.9%)	0.0006
Day 15 (Primary Endpoint)	54 (48.2%)	18 (16.7%)	31.5% (19.9%, 43.2%)	<0.0001
Day 22	74 (66.1%)	57 (52.8%)	13.3% (0.4%, 26.2%)	0.1314
Percentage of Subjects Who Were Pain Free				
Day 1 (Secondary Endpoint)	91 (81.3%)	47 (43.5%)	37.7 %(25.9%, 49.6%)	<0.0001
Day 3	97 (86.6%)	57 (52.8%)	33.8 %(22.5%, 45.2%)	<0.0001
Day 8	105 (93.8%)	64 (59.3%)	34.5% (24.2%, 44.8%)	<0.0001
Day 15	104 (92.9%)	73 (67.6%)	25.3% (15.2%, 35.3%)	<0.0001

Source: Table 8 and 22 of the applicant's study reports (CI was calculated by the reviewer using normal approximation)

Table 2: Applicant's Results for the Primary and Key Secondary Endpoints (S00124-WR)

Percentage of Subjects with Cleared Ocular Inflammation				
Visit	**Bromfenac 0.07% N=110**	**Placebo N=110**	**% difference (Asymptotic 95% CI)**	**P-value**
Day 1	3 (2.7%)	4 (3.6%)	-0.91% (-5.5%, 3.7%)	>0.9999
Day 3	8 (7.3%)	7 (6.4%)	0.91 %(-5.7%, 7.6%)	>0.9999
Day 8	36 (32.7%)	18 (16.4%)	16.4% (5.2%, 27.5%)	0.0370
Day 15 (Primary Endpoint)	54 (49.1%)	35 (31.8%)	17.3% (4.5%, 30.0%)	0.0132
Day 22	81 (73.6%)	63 (57.3%)	16.4% (4.0%, 28.7%)	0.0470
Percentage of Subjects Who Were Pain Free				
Day 1 (Secondary Endpoint)	84 (76.4%)	61 (55.5%)	20.9% (8.7%, 33.1%)	0.0017
Day 3	95 (86.4%)	58 (52.7%)	33.6 %(22.3%, 45.0%)	<0.0001
Day 8	99 (90.0%)	68 (61.8%)	28.2% (17.5%, 38.9%)	<0.0001
Day 15	100 (90.9%)	74 (67.3%)	23.6% (13.3%, 33.9%)	<0.0001

Source: Table 8 and 22 of the applicant's study reports (CI was calculated by the reviewer using normal approximation)

There were 15 subjects, who were treated as successes in the applicant's primary efficacy analysis despite a non-zero score at Day15. The Biostatistics reviewer believes that the primary efficacy analysis should treat every subject who received a rescue therapy or did not have cleared ocular inflammation at Day 15 as a failure.

Table 3: FDA Reviewer's Results for the Percentage of Subjects with Cleared Ocular Inflammation by Visit

Visit	S00124-ER			
	Bromfenac 0.07% N=112	**Placebo N=108**	**% difference (Asymptotic 95% CI)**	**P-value**
Day 1	2 (1.8%)	0 (0.0%)	1.8% (-0.6%, 4.4%)	0.4979
Day 3	6 (5.4%)	1 (0.9%)	4.4 %(-0.1%, 9.0%)	0.2388
Day 8	27 (24.1%)	7 (6.5%)	17.6% (8.4%, 26.8%)	0.0004
Day 15 (Primary Endpoint)	51(45.5%)	14 (13.0%)	32.5% (21.4%, 43.8%)	<0.0001
Day 22	63 (56.2%)	33 (30.6%)	25.7% (13.0%, 38.3%)	<0.0001
S00124-WR				
Visit	**Bromfenac 0.07% N=110**	**Placebo N=110**	**% difference (Asymptotic 95% CI)**	**P-value**
Day 1	3 (2.7%)	4 (3.6%)	1.8% (-0.6%, 4.4%)	>0.9999
Day 3	7 (6.4%)	6 (5.4%)	0.91 %(-5.3%, 7.1%)	>0.9999
Day 8	33 (30.0%)	14 (12.7%)	17.3% (6.7%, 27.9%)	0.0112
Day 15 (Primary Endpoint)	50 (45.4%)	30 (27.3%)	18.2% (5.7%, 30.7%)	0.0076
Day 22	67 (60.9%)	40 (36.4%)	24.5% (11.7%, 37.3%)	<0.0001

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

Note: The Ophthalmology Clinical Group 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. Clinical does 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.

OPDP
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.

DMEPA
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.

DMEPA finalized their review of the Prolensa carton and container labeling on 2/8/2013. Comments regarding suggested changes to the carton and container that were not supported by regulation were not transmitted to the applicant. Agency requested the following revisions to their carton and container labeling submitted by the applicant on 8/21/12:

1) The prominence of "Sample" and "Sample - Not for Resale" should be increased on the 0.6 mL and 0.8 mL carton and container professional sample configurations.

2) The established name should be revised on the carton and container labels to a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2). We suggest you either de-bold the proprietary name or bold the established name.

3) Remove the trailing zero from the 3.0 mL trade size carton and container labeling and revise to read as "3 mL."

FINANCIAL DISCLOSURE

Financial disclosure information has been provided by the applicant for the covered clinical studies in this application.

A Form FDA 3454 certifying the absence of financial interests for primary and subinvestigators who supplied data used in clinical studies that support this application is provided. Table 2 lists those investigators requiring financial disclosure. A Form FDA 3455 for each investigator with financial arrangements requiring financial disclosure is included. A review of the financial disclosure data does not indicate a potential impact on the clinical study results.

Table 2. List of Investigators With Financial Interests Requiring Disclosure

Site	Primary Investigators	Study Number
(b) (6)	(b) (6)	S00124-WR
		S00124-ER

OSI

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

Per the OSI review dated 2/4/2013:

One site from each study was chosen for inspection based on enrollment, number of INDs in the OSI database, and previous inspectional history.

Name of CI	Protocol # /Site #/ # of Subjects Enrolled:	Inspection Date	Classification
Leonard Cacioppo, MD Hernando Eye Institute 14543 Cortez Boulevard Brooksville, FL 34613	**S00124-ER** Site #58 21 subjects	September 10 to 14, 2012	NAI
Damien Goldberg, MD Wolstan & Goldberg Eye Associates 23600 Telo Ave, Suite 100 Torrance, CA 90505	**S00124-WR** Site #23 22 subjects	August 24 to September 6, 2012	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

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).

12. 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. Clinical does not agree with the final edits to Section 14 of the attached package insert which revise the primary 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."

Clinical believes that 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. Clinical does 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.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
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.

RISK BENEFIT ASSESSMENT:
There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Prolensa (bromfenac ophthalmic solution) 0.07% is (1) statistically superior to placebo in the proportion of subjects who had cleared ocular inflammation in the study eye by Day 15 and (2) is statistically superior to placebo for the absence of pain on the first day post-op.

The most commonly reported adverse reactions in seen 3-8% of bromfenac ophthalmic solution 0.7% treated patients were: anterior chamber inflammation, eye pain, foreign body sensation, photophobia, and vision blurred.

The benefits of using this drug product outweigh the risks for the above indication(s).

Clinical, Pharmacology/Toxicology, Clinical Pharmacology, Product Quality Microbiology, and Biostatistics have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

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

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

/s/

WILLIAM M BOYD
04/05/2013

WILEY A CHAMBERS
04/05/2013