CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203168Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203168
Priority or Standard	Standard
Submit Date(s)	June 6, 2012
Received Date(s)	June 7, 2012
PDUFA Goal Date	April 7, 2013
Division / Office	OAP/DTOP
Reviewer Name(s)	William M. Boyd, M.D.
Review Completion Date	March 20, 2013
Established Name	bromfenac ophthalmic solution 0.07%
(Proposed) Trade Name	Prolensa
Therapeutic Class	nonsteroidal anti-inflammatory
Applicant	Bausch & Lomb, Inc.
Formulation(s)	bromfenac ophthalmic solution 0.07%
Dosing Regimen	one drop into the affected eye once daily
Indication(s)	treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery
Intended Population(s)	patients who have undergone cataract surgery

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on 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.

1.2 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, and foreign body sensation.

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

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Risk evaluation and mitigation strategies are not recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarket requirements/commitments are not recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Proprietary Name:	Prolensa
Established Name:	bromfenac ophthalmic solution 0.07%
Applicant:	Bausch & Lomb, Inc.
Chemical Class:	5S
Pharmacologic Category:	non-steroidal anti-inflammatory
Proposed Indication:	The treatment of ocular inflammation and pain following cataract surgery
Dosage Form and Route of Administration:	topical drops

2.2 Tables of Currently Available Treatments for Proposed Indications

There are multiple ophthalmic topical drugs approved for inflammation and pain following cataract extraction (i.e. surgery) including:

Ketorolac tromethamine ophthalmic solution 0.45%, (i.e. Acuvail)
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).

2.3 Availability of Proposed Active Ingredient in the United States

Bromfenac ophthalmic solution 0.09% is currently marketed and is available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

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.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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.

2.6 Other Relevant Background Information

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.

NDA 21-664 Xibrom (bromfenac ophthalmic sodium) 0.09% BID 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.

ISTA Pharmaceuticals, Inc. (ISTA) initiated development of bromfenac ophthalmic solution (b) (4) as a once-daily alternative to the currently marketed product. Data from this clinical development program demonstrated that the 0.09% (b) (4) QD dosing formulations were equivalent in terms of safety and efficacy. ISTA subsequently performed simultaneous Phase 3 studies comparing bromfenac ophthalmic solution 0.09% QD to placebo (CL-S&E-0415081-P-ER [QD-ER] and CL-S&E-0415081-P-WR [QD-WR]). QD-WR showed statistical significance for the primary efficacy endpoint; however, QD-ER failed to show a statistically significant treatment effect in either the primary or secondary endpoints. ISTA initiated a third placebo-controlled Phase 3 study with bromfenac ophthalmic solution 0.09% QD (CL-S&E-1205081-P [QDII]) to confirm that bromfenac ophthalmic solution 0.09% QD was safe and effective in the subject population enrolled.

Bromday (bromfenac ophthalmic sodium) 0.09% was approved on 10/16/2010 (SE2 S-13).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of sufficient quality to allow for a substantive review.

3.2 Compliance with Good Clinical Practices

All completed clinical studies in this submission were conducted in compliance with the Declaration of Helsinki, the International Conference on harmonization (ICH Good Clinical Practice (GCP) guidelines and the applicable governmental regulatory requirements.

Two clinical investigator sites were inspected by the Office of Scientific Investigations (OSI) for this application. The data derived from both inspected sites are considered reliable.

3.3 Financial Disclosures

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)	S00124-WR
		S00124-ER

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Table 1. Bromfenac Ophthalmic Solution 0.07% Quantitative Composition

Component	Function	Bromfenac 0.07% Formulation (%w/v)	Amount /mL (mg/mL)	(b) (4) Batch Composition (b) (4)
Bromfenac sodium sesquihydrate	Active ingredient	0.0805[1]	0.805	
Boric acid				(b) (4)
Sodium borate				
Sodium sulfite				
Edetate disodium (EDTA)				
Tyloxapol				
Benzalkonium chloride	Preservative	0.005	0.05	(b) (4)
Povidone (b) (4)				(b) (4)
Sodium hydroxide[2]	pH adjuster	q.s. to pH 7.8	q.s. to pH 7.8	q.s. to pH 7.8
Water for Injection (b) (4)				(b) (4)

[1] Equivalent to 0.07% bromfenac free acid.
[2] Only if necessary to adjust pH to 7.8.

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 proposed trade sizes for the drug product are 1.6 mL and 3 mL per bottle. In addition, the applicant has proposed sample sizes of 0.6 mL and 0.8 mL per bottle.

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).

Reviewer's Comments:

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.

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)	

4.2 Clinical Microbiology

Not applicable to this review.

4.3 Preclinical Pharmacology/Toxicology

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 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 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 labeling, the multiple would be approximately 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 labeling, the multiple would be approximately 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).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Bromfenac is a non-steroidal 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.

4.4.2 Pharmacodynamics/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.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The double-masked, placebo controlled clinical trials utilizing bromfenac ophthalmic solution 0.7% dosed once daily in subjects undergoing cataract surgery (S00124-ER and S00124-WR) form the primary efficacy and safety databases for this new drug product. These trials utilized the same protocol administered in the eastern and western regions of the United States, respectively.

Following is the applicant's table of all bromfenac ophthalmic solution PK and safety and efficacy trials. This table includes all formulations and concentrations of bromfenac and their study report locations.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
(b) (4)									

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
(b) (4)									

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	ISTA-BR-CS001-ER	NDA 21-664, Mod. 5, Vols 2-15 CRFs in Vols 36-54	Efficacy and safety (US Phase 3)	Double-masked, placebo-controlled	Bromfenac ophthalmic solution 0.09%, 1 drop BID	296	Subjects with postoperative inflammation after IOL implant	2 weeks	Completed Full Report
Efficacy and Safety	ISTA-BR-CS001-WR	NDA 21-664, Mod. 5, Vol 16-27 CRFs in Vols 55-66	Efficacy and safety (US Phase 3)	Double-masked, placebo-controlled	Bromfenac ophthalmic solution 0.09%, 1 drop BID	231	Subjects with postoperative inflammation after IOL implant	2 weeks	Completed Full Report
(b) (4)									

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
[redacted] (b) (4)									
Efficacy and Safety	S00124-ER		Efficacy and safety (US Phase 3)	Double-masked, placebo-controlled	Bromfenac ophthalmic solution 0.07% 1 drop QD	220	Subjects undergoing cataract surgery	16 days	Completed Full Report
Efficacy and Safety	S00124-WR		Efficacy and safety (US Phase 3)	Double-masked, placebo-controlled	Bromfenac ophthalmic solution 0.07% 1 drop QD	220	Subjects undergoing cataract surgery	16 days	Completed Full Report

PK = pharmacokinetics; QID = four times daily; BID = two times daily; QD = one time daily; IOL = intraocular lens

5.2 Review Strategy

The June 6, 2012, submission was submitted electronically. Subsequent amendments were also submitted in electronically. All study reports were reviewed. The included clinical study reports, literature review, and package insert formed the basis for the review of efficacy and safety for the proposed indications.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Bausch & Lomb, Inc. in this application for this indication.

5.3 Discussion of Individual Studies/Clinical Trials

The 2 Phase 3 studies, S00124-ER and S00124-WR utilized the same protocol administered in the eastern and western regions of the United States, respectively.

S00124-ER and S00124-WR

Methodology
This was a multi-center (20 site S00124-ER; 19 site S00124-WR), randomized,

double-masked, parallel-group, and placebo-controlled study. Subjects were screened for this study between 1 and 8 days prior to the initiation of dosing with the investigational product (IP). Subjects who signed the informed consent and met all inclusion/exclusion criteria were randomized to receive either bromfenac or placebo (1:1).

Subjects were seen for evaluation on Days 1, 3±1, 8±1, 15±1 following cataract surgery. In addition, subjects were seen for a follow-up visit on Day 22 (+3) following surgery or 7 days (+3) after their last dose of the IP if the subject prematurely discontinued the IP.

Number of Subjects
200 subjects were planned; 211 subjects were analyzed for safety; 220 subjects were analyzed for efficacy. (S00124-ER)

200 subjects were planned; 205 subjects were analyzed for safety; 220 subjects were analyzed for efficacy. (S00124-WR)

Reviewer's Comments:

More subjects were evaluated for efficacy than were evaluated for safety in both S00124-ER and S00124-WR. Safety analyses were to be conducted on the Safety Population, defined as all randomized subjects who received at least 1 dose of IP. All analyses of efficacy were to be conducted on the Intent-to-Treat (ITT) Population, defined as all randomized subjects, where subjects were to be analyzed in the group to which they were randomized.

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.

See Sections 6.1.3, 7.1.3, and 7.4.1 of this review for the results of this reanalysis.

Inclusion Criteria
Each subject had to meet the following criteria to be eligible for the study:

1. Were male or female at least 18 years of age who were scheduled for unilateral cataract surgery (phacoemulsification or extracapsular) with PCIOL implantation and for whom no other ophthalmic surgical procedures (eg, relaxing incisions, iridectomy, conjunctival excisions, etc.) were to be conducted during the cataract surgery.
2. Agreed not to have any other ocular surgical procedures in the study or fellow (non-study) eye within 15 days prior to the initiation of dosing with the IP and throughout the duration of the study.
3. Had VA logMAR of 0.6 (ETDRS) or better in the fellow (non-study) eye.

4. Were willing and able to return for all required study visits.
5. Were willing and able to follow instructions from the study investigator and his/her staff.
6. Had IOP ≥5 mmHg and ≤22 mmHg (in study eye) with or without anti-glaucoma therapy at the pre-operative screening visit (if >22 mmHg, adjust, if necessary, following documented pachymetry).
7. Were willing and able to self administer the IP (or had a caregiver available to instill all doses of the IP).
8. If a woman capable of becoming pregnant, agreed to have urine pregnancy testing performed at screening (must be negative) and agreed to use a medically acceptable form of birth control throughout the study duration and for at least 1 week prior to and after completion of the study. Women considered capable of becoming pregnant included all females who have experienced menarche and who had not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
9. Had signed informed consent approved by Institutional Review Board or Independent Ethics Committee.

Exclusion Criteria
Subjects who met any of the following criteria were excluded from the study:

1. Had known hypersensitivity to bromfenac or to any component of the IP (including "procedural" medications such as anesthetic and/or fluorescein drops, dilating drops, etc.).
2. Used anterior capsule staining for capsulorhexis (i.e., trypan blue).
3. Had a known hypersensitivity to the class of salicylates (i.e., acetylsalicylic acid or Aspirin) or to other NSAIDs.
4. Had a known hypersensitivity to sulfites.
5. Had intraocular inflammation (ie, any cells or flare in the anterior chamber as measured on slit lamp examination) or had ocular pain (greater than "None") on the pain scale of the OCGA in either eye at the screening visit.
6. Had any active or chronic/recurrent ocular or systemic disease that was uncontrolled and likely to affect wound healing (ie, diabetes mellitus, systemic connective tissue disease, severe atopic disease, etc.). Note: An uncontrolled disease was described by a change in disease severity or by a clinically significant change assessed by the investigator within the past 30 days prior to screening.
7. Had a known uncontrolled systemic disease including bleeding disorder.
8. Had taken any anticoagulants (i.e., Coumadin, Plavix, etc.) within 7 days of initiating dosing with the IP, or needed to take anticoagulant therapy (including aspirin at doses of more than 165 mg/day) during the study, or had any known or suspected bleeding tendencies.
9. Had used within 7 days prior to initiation of dosing with the IP or throughout the duration of the study:

• Ocular, topical, or systemic NSAIDs,
• Ocular, topical, or systemic gentamicin,
• Any form of opioid, narcotic, or any other pain relieving medication that could have interfered with the interpretation of the study results, eg, gabapentin, pregabalin, COX-2 inhibitors. Note: Use of acetaminophen (up to 4,000 mg/day) during the study and/or an opioid during surgery (i.e., fentanyl) were allowed,
• Immunomodulators (i.e., Restasis).

10. Had used ocular, topical, inhaled, or oral corticosteroids within 15 days prior to the initiation of dosing with the IP or depo-corticosteroids within 45 days prior to initiation of dosing with the IP or throughout the duration of the study.
11. Had used:
• tamsulosin (Flomax),
• silodosin (Rapaflo),
• afluzoxin (Uroxatral), or
• finasteride (Proscar or Propecia).

12. Had used any ocular, topical, or systemic medication that could have interfered with normal lacrimation, wound healing, the IP, or the interpretation of study results, within 7 days prior to initiation of dosing with the IP or throughout the duration of the study. Examples:
• Ocular prostaglandins,
• Daily use of preserved artificial tears.

13. Had active corneal pathology noted in either eye at the screening visit. Active corneal pathology was defined as corneal pathology that is non-stable, or greater than mild, or would compromise assessment of the safety or efficacy of treatment. Superficial punctate keratitis in the study eye was a criterion for exclusion.
14. Had any extraocular/intraocular inflammation in either eye noted at the screening visit (blepharitis was allowed if mild only, and no concurrent conjunctivitis or lid erythema/edema) or ongoing, unresolved uveitis.
15. Had corneal transplant (i.e., DSEK), or corneal refractive surgery (radial keratometry, PRK, LASIK) in the study eye within the last 2 years.
16. Had a history of abuse of alcohol/drugs within 6 months prior to the screening visit.
17. Were pregnant or nursing/lactating.
18. Had participated in any other study of an investigational drug or device within 30 days.

Treatments Administered
Subjects self-instilled 1 drop of IP, either bromfenac or placebo, QD into the study eye for a total of 16 days (Day -1 to 14). Dosing began 1 day prior to surgery (Day -1), and continued on the day of surgery (Day 0) and for 14 days after surgery (Days 1 to 14). Each dose was instilled into the lower cul de sac of the study eye.

Investigational Products
Bromfenac ophthalmic solution 0.07% (Lot 138681)
Manufacturer: Bausch & Lomb, Tampa, FL

Active ingredient: bromfenac sodium (0.81) mg/mL
Inactive ingredients: boric acid, sodium borate, sodium sulfite, edetate disodium, povidone, tyloxapol, benzalkonium chloride, pH adjust with sodium hydroxide, and water for injection.

Bromfenac ophthalmic solution 0.00% Placebo (Lot 138691)
Manufacturer: Bausch & Lomb, Tampa, FL
Active ingredient: none
Inactive ingredients: boric acid, sodium borate, sodium sulfite, edetate disodium, povidone, tyloxapol, benzalkonium chloride, pH adjust with sodium hydroxide, and water for injection.

All the IP was provided in identical polyethylene bottles.

Efficacy Measurements
Summed Ocular Inflammation Score (SOIS)
The primary efficacy outcome was the proportion of subjects who had cleared ocular inflammation by Day 15. A subject was considered to have cleared ocular inflammation if the subject achieved an SOIS grade of 0 (i.e., 0 cells and absence of flare) by Day 15. The SOIS is defined as the sum of the mean anterior chamber cells score and anterior flare score.

Table 2. Ocular Inflammation Score

Anterior Chamber Cells		Anterior Chamber Flare	
Grade	Cell Count	Grade	Flare Count
0	0	0	Complete absence
0.5	1-5 cells (trace)	-	-
1	6-15	1	Very slight (barely detectable)
2	16-25	2	Moderate (iris and lens clear)
3	26-50	3	Marked (iris and lens hazy)
4	>50	4	Intense (fibrin clot)

Ocular Comfort Grading Assessment (OCGA)
The subject rated each of 7 symptoms (eye pain, tearing, itching, foreign body sensation, photophobia [light sensitivity], eye discharge, and haziness) as 0=none, 1=mild, 2=moderate, and 3=severe at Screening and at Days -1 through 14. Subjects were to complete their assessment of the 7 symptoms within an hour after instillation of the IP into their study (operative) eye and record the result in the subject diary.

Primary Efficacy Variable
The primary outcome was the proportion of subjects who were free of ocular inflammation (i.e., 0 cells and absence of flare) by Day 15.

Secondary Efficacy Variable
The secondary efficacy outcome was the proportion of subjects who were pain free (i.e., pain grade of "None" on the Ocular Comfort Grading Assessment) at Day 1.

Analysis Populations
All analyses of efficacy were to be conducted on the Intent-to-Treat (ITT) Population, defined as all randomized subjects, where subjects were to be analyzed in the group to which they were randomized. Four analyses of efficacy were to be performed: an analysis of data based on last observation carried forward (LOCF), the primary efficacy analysis; an analysis of data based on observed cases (OC); an analysis of data based on baseline observation carried forward (BOCF); and an analysis based on multiple imputation.

Safety analyses were to be conducted on the Safety Population, defined as all randomized subjects who received at least 1 dose of IP.

Schedule of Events

Table 3. Schedule of Events

Procedures	Pre Surgery		Surgery		Post Surgery				Study Termination
	Screening Visit 1 Day –8 to –1	Day -1 1st Dose	Visit 2: Day 0		Visit 3: Day 1	Visit 4: Day 3±1	Visit 5: Day 8±1	Visit 6: Day 15±1 or Early D/C of IP[1]	Visit 7: Day 22+3 or 7+3 Days After Last Dose of IP
			Pre Surgery	Post Surgery					
Informed Consent	X								
Medical History/Demographics	X								
Inclusion/Exclusion Criteria	X								
Vital Signs	X								
Visual Acuity (ETDRS)	X[2,8]				X[3,9]	X[3,9]	X[3,9]	X[3,9]	X[2,8]
Pupillary Exam	X[2]								X[2]
Biomicroscopy	X[2]				X[3]	X[3]	X[3]	X[3]	X[2]
Intraocular Pressure[4]	X[2]				X[3]	X[3]	X[3]	X[3]	X[2]
Funduscopic Exam (dilated)	X[2]								X[2]
Urine Pregnancy Test[5]	X								
Dispense IP/Dosing Instructions Diary	X								
Begin IP Dosing[6]		X							
Ocular Comfort Grading Assessment[7]		X	X						
Review Diary			X		X	X	X	X	
Record Concomitant Medications	X		X	X	X	X	X	X	X
Assess AEs			X	X	X	X	X	X	X
Discontinuation from the Study									X

1 Visit must have occurred within 48 hours after the last dose of IP.
2 Ophthalmic examinations were to be conducted in both eyes.
3 Ophthalmic examinations were to be conducted in study (operative) eye **only**.
4 Goldmann tonometry was preferred, recorded in mmHg; adjusted following pachymetry if necessary.
5 Applied only to females capable of becoming pregnant.
6 IP was self-administered by the subjects (or caregiver), 1 drop QD, from Day -1 to 14.

Table 3. Schedule of Events (continued)

7 Beginning on Day -1 (first dosing day), and ending on Day 14, subjects were to complete the Ocular Comfort Grading Assessment in the Diary within 1 hour after each dose of IP was instilled into the study (operative) eye. On Day 0 (day of surgery), subjects were to instill 1 drop of IP into the study (operative) eye upon awakening on the morning of surgery, or at least 1 hour before the surgical incision is made. If it was determined that the subject had not dosed with IP prior to surgery, the subject was then to instill 1 drop that evening.
8 Best corrected visual acuity ETDRS via manifest refraction.
9 Uncorrected visual acuity with pinhole.

Investigators

List of Investigators S00124-ER			
Site	**Investigator**	**Address**	**Subjects Randomized**
50	**John Lim, MD**	Houston Eye Associates 915 Gessner Street, Suite 250 Professional Building #3 Houston, TX 77024	22
51	**Francis W. Price, Jr., MD**	Price Vision Group 9002 North Meridian Street, Suite 100 Indianapolis, IN 46260	4
52	**Eugene Protzko, MD**	Seidenberg-Protzko Eye Associates 2023 Pulaski Highway Havre de Grace, MD 21078	5
53	**W. Colby Stewart, MD**	Houston Eye 2855 Gramercy Street Houston, TX 77025	14
55	**Thomas Walters, MD**	Texan Eye, PA 5717 Balcones Drive Austin, TX 78731	22
56	**Mark Bergmann, MD**	Eye Care Associates of Greater Cincinnati 2859 Boudinot Avenue, Suite 301 Cincinnati, OH 45238	8
57	**Robert Berry, MD**	Eye Care Arkansas, PA 9800 Lile Drive, Suite 301 Little Rock, AR 72205	16
58	**Leonard Cacioppo, MD**	Hernando Eye Institute 14543 Cortez Boulevard Brooksville, FL 34613	22
60	**David Cooke, MD**	Great Lakes Eye Care 2848 Niles Road St. Joseph, MI 49085	6
61	**William Flynn, MD**	R and R Eye Research 5430 Fredericksburg Road, Suite 100 San Antonio, TX 78229	14
62	**Ronald Frenkel, MD**	East Florida Eye Institute 509 SE Riverside Drive, Suite 302 Stuart, FL 34994	9
63	**Marvin Greenberg, MD**	Marvin E. Greenberg, MD, PA 7421 North University Drive, Suite 109 Tamarac, FL 33321	14
64	**Brennan Greene, MD**	The Eye Care Institute 1536 Story Avenue Louisville, KY 40206	9
65	**Lawrence Katzen, MD**	Katzen Eye Care and Laser Center, 901 North Congress Avenue, Suite 104-B Boynton Beach, FL 33426	2

List of Investigators S00124-ER			
Site	**Investigator**	**Address**	**Subjects Randomized**
66	**Parag Majmudar, MD**	Chicago Cornea Consultants 1585 North Barrington Road, Suite 502 Hoffman Estates, IL 60169	4
68	**Bernard Perez, MD**	International Eye Center 4506 Wishart Boulevard Tampa, FL 33603	2
69	**Harvey Reiser, MD**	Eye Care Specialists 703 Rutter Avenue Kingston, PA 18704	22
73	**Stephen Smith, MD**	Eye Associates of Fort Myers 4225 Evans Avenue Ft. Myers, FL 33901	6
74	**Thomas Elmer, MD**	Fichte, Endl & Elmer Eyecare 2400 Pine Avenue Niagara Falls, NY 14301	16
75	**Mitchell Jackson, MD**	Jacksoneye 300 North Milwaukee Avenue, Suite L Lake Villa, IL 60046	3

List of Investigators S00124-WR			
Site	**Investigator**	**Address**	**Subjects Randomized**
02	**Kenneth Sall, MD**	Sall Research Medical Center 11423 187th Street, Suite 200 Artesia, CA 90701	12
03	**Robert Smyth-Medina, MD**	North Valley Eye Medical Group 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345	6
04	**Jon-Marc Weston, MD**	Roseburg Research Associates, LLC 2435 NW Kline Street Roseburg, OR 97471	15
05	**Jason Bacharach, MD**	North Bay Eye Associates 104 Lynch Creek Way, Suite 12 Petaluma, CA 94954	4
06	**Donald E. Beahm, MD**	3923 Broadway Great Bend, KS 67530	11
07	**James D. Boyce, MD**	Orange County Ophthalmology Medical Group 12665 Garden Grove Boulevard Suite 401 Garden Grove, CA 92843	22
08	**E. Randy Craven, MD**	Glaucoma Consultants of Colorado 11960 Lioness Way, Suite 190 Parker, CO 80134	10

List of Investigators S00124-WR			
Site	**Investigator**	**Address**	**Subjects Randomized**
09	**Jung Dao, MD**	Cornea Consultants of Arizona 3815 East Bell Road, Suite 2500 Phoenix, AZ 85032	18
10	**Eran Duzman, MD**	4605 Barranca Parkway, Suite 100 Irvine, CA 92604	9
12	**Joseph Gira, MD**	Ophthalmology Consultants, Ltd. 12990 Manchester Road, Suite 201 St. Louis, MO 63131	13
13	**Kerry B. Hagen, MD**	Eye Health Northwest 1955 NW Northrup Avenue Portland, OR 97209	12
15	**Michael S. Korenfeld, MD**	Comprehensive Eye Care, Ltd. 901 East 3rd Street Washington, MO 63090	9
16	**David L. Schwartz, MD**	D. L. Schwartz, MD, PC 2000 South Wheeling, Suite 401 Tulsa, OK 74114	8
17	**Ryan McKinnon, MD**	Saltzer Medical Group 215 East Hawaii Avenue Nampa, ID 83686	9
18	**Karl Olsen, MD**	Eye Center of Northern Colorado 1725 East Prospect Road Fort Collins, CO 80525	8
19	**James Peace, MD**	United Medical Research Institute 431 North Prairie Avenue Inglewood, CA 90301	18
21	**Steven Silverstein, MD**	Silverstein Eye Centers 4240 Blue Ridge Boulevard, Suite 1000 Kansas City, MO 64133	4
22	**Michael Depenbusch, MD**	Arizona Eye Center 604 West Warner Road, Suite B6 Chandler, AZ 85225	10
23	**Damien Goldberg, MD**	Wolstan Eye Associates 23600 Telo Avenue, Suite 100 Torrance, CA 90505	22

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The 2 Phase 3 studies, S00124-ER and S00124-WR, in support of bromfenac ophthalmic solution 0.07% QD for the treatment of ocular inflammation and pain associated with cataract surgery were placebo-controlled, randomized, double-masked, multi-center studies designed to evaluate the efficacy of bromfenac 0.07% QD relative to placebo in this subject population.

6.1.1 Methods

See Section 5.3 for specific trial study design.

6.1.2 Demographics

Table 5. Demographics of Subjects in Bromfenac 0.07% QD Studies (Safety Population, S00124 Pooled Studies)

Category	Bromfenac 0.07% QD Studies		
	Pooled Bromfenac 0.07% QD n (%)	Pooled Placebo QD n (%)	P value
Safety Population, N	212	204	
Age (years)			0.9126[1]
Mean	68.3	68.4	
Std Dev	10.71	9.58	
Median	69.0	69.0	
Min, Max	18, 93	40, 90	
Age Category (years)			0.9604[2]
18-30	1 (0.5%)	0	
31-50	13 (6.1%)	11 (5.4%)	
51-70	105 (49.5%)	101 (49.5%)	
> 70	93 (43.9%)	92 (45.1%)	
Gender			0.3551[2]
Male	78 (36.8%)	66 (32.4%)	
Female	134 (63.2%)	138 (67.6%)	
Race			0.3218[2]
American Indian or Alaska Native	1 (0.5%)	0	
Asian	3 (1.4%)	8 (3.9%)	
Black or African American	21 (9.9%)	15 (7.4%)	
Native Hawaiian or Other Pacific Islander	0	0	
White	161 (75.9%)	152 (74.5%)	
Other	26 (12.3%)	29 (14.2%)	
Iris Color – Study Eye			0.3781[2]
Black	0	0	
Blue	55 (25.9%)	61 (29.9%)	
Brown	103 (48.6%)	88 (43.1%)	
Gray	1 (0.5%)	5 (2.5%)	
Green	24 (11.3%)	20 (9.8%)	
Hazel	29 (13.7%)	29 (14.2%)	
Other	0	1 (0.5%)	
Iris Color Category – Study Eye[3]			0.1666[2]
Light Iris	85 (40.1%)	96 (47.1%)	
Dark Iris	127 (59.9%)	108 (52.9%)	

Source: **Appendix 1, Table 3**.
1 p-value for bromfenac versus placebo was from a t-test.
2 p-value for bromfenac versus placebo was from a Fisher's exact test
3 Light Irides – Blue, Gray, Hazel, Other. Dark Irides – Black, Brown, Green.

Demographic and other baseline characteristics were similar across the 2 treatment groups in the pooled safety population for the phase 3 studies.

Demographic and other baseline characteristics were also similar across the 2 treatment groups in the unpooled safety population for the phase 3 studies.

6.1.3 Subject Disposition

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.

Reviewer's Comments:

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 (above) were provided to the application S00124-ER and S00124-WR on March 13, 2013.

See Section 7.3.3 of this review for Dropouts and Discontinuations and further discussion.

6.1.4 Analysis of Primary Endpoint(s)

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.

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.

Reviewer's Comments:

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.

Reviewer's Comments:

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%).

6.1.5 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.

Reviewer's Comments:

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.

Reviewer's Comments:

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).

6.1.6 Other Endpoints

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.

Reviewer's Comments:

This analysis is the proportion of subjects in the LOCF analysis of the ITT Population who had cleared ocular inflammation (SOIS Grade 0) at each visit day. A subject was considered to have cleared ocular inflammation if the subject achieved an SOIS grade of 0 (i.e., 0 cells and absence of flare) at a particular visit day.

The proportions of subjects who had cleared ocular inflammation (SOIS Grade 0) in study S00124-ER was significantly higher in the bromfenac 0.07% group compared with the placebo group at Day 8 and Day 15. The proportions of subjects who had cleared ocular inflammation at Days 1, 3 and 22 were each higher but not statistically different for bromfenac 0.07% as compared to the placebo group.

The proportions of subjects who had cleared ocular inflammation (SOIS Grade 0) in study S00124-WR was significantly higher in the bromfenac 0.07% group compared with the placebo group at Days 8, 15 and 22. The proportions of subjects who had cleared ocular inflammation at Days 1 and 3 were not statistically different for bromfenac 0.07% as compared to the placebo group.

6.1.7 Subpopulations

Pooled S00124-ER and S00124-WR: Gender and Age

Analyses of SOIS of grade 0 by each visit for the demographic sub-groups of gender and age (≤70 years and >70 years) where consistent with the overall population studied. For the subgroups by gender and age, the proportion of subjects reaching the primary efficacy endpoint (SOIS grade 0 by Day 15) was greater for bromfenac 0.07% QD populations compared to placebo in the pooled data. The differences in the proportions of subjects with a SOIS grade of 0 by Day 15 in the bromfenac 0.07% QD group and placebo group were statistically significant for each gender and age subgroup analyzed.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Successful development of bromfenac 0.09% BID and 0.09% QD, as well as studies conducted with bromfenac (b) (4) showing similar safety and efficacy results suggested that bromfenac in a lower concentration with QD dosing may also be safe.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There are no persistence of efficacy or tolerance effects related to the use of this drug. The intended use of bromfenac ophthalmic solution 0.07% QD is for the treatment of post-surgical inflammation and pain in individuals undergoing unilateral cataract surgery. Treatment is expected to be limited to a maximum of 16-day, once-daily dosing.

6.1.10 Additional Efficacy Issues/Analyses

N/A – There are no additional efficacy issues.

7 Review of Safety

Safety Summary

7.1 Methods

See Section 5.3 for specific trial study design.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The 2 Phase 3 studies, S00124-ER and S00124-WR, in support of the safety of bromfenac ophthalmic solution 0.07% QD for the treatment of ocular inflammation and pain associated with cataract surgery were placebo-controlled, randomized, double-masked, multi-center studies designed to evaluate the efficacy of bromfenac 0.07% QD relative to placebo in this subject population. Prior studies of higher concentrations of bromfenac ophthalmic solution also support the safet6y of the drug product (see Section 5.1 of this review).

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) higher level terms and preferred terms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

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%)
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%)

Reviewer's Comments:

As discussed in Section 5.3 of this review, 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.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

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 the pooled analysis was 14.6 (1.0 to 16.0). There was over a 90% compliance rate in the pooled studies.

See Section 6.1.2 of this review for Demographics.

7.2.2 Explorations for Dose Response

Successful development of bromfenac 0.09% BID and 0.09% QD, as well as studies conducted with bromfenac (b) (4) showing similar safety and efficacy results suggested that bromfenac in a lower concentration with QD dosing may also be safe and efficacious.

7.2.3 Special Animal and/or In Vitro Testing

Special animal or in vitro testing was not conducted.

7.2.4 Routine Clinical Testing

Laboratory and vital signs were not evaluated as part of this supplement.

There was adequate monitoring of the anterior and posterior segments of the eye, intraocular pressure, and visual acuity.

7.2.5 Metabolic, Clearance, and Interaction Workup

A metabolic work-up was not conducted as part of this application.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

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.

No special evaluations beyond routine adverse event monitoring were conducted as part of this application.

7.3 Major Safety Results

7.3.1 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)

7.3.2 Nonfatal Serious Adverse Events

Table 15. Summary of SAEs (Safety Population, S00124 Pooled Studies)

Preferred Term	Bromfenac 0.07% QD Studies	
	Pooled Bromfenac 0.07% QD N = 212 n (%)	Pooled Placebo QD N = 204 n (%)
Subjects reporting a Serious Adverse Event	3 (1.4%)	4 (2.0%)
Asthenic conditions		
Asthenia	0	1 (0.5%)
Eye and ear procedural complications		
Eye operation complication	1 (0.5%)	0
Ischaemic coronary artery disorders		
Angina pectoris	1 (0.5%)	0
Myocardial infarction	0	1 (0.5%)
Lower limb fractures and dislocations		
Hip fracture	1 (0.5%)	0
Lower limb fractures and dislocations		
Deep vein thrombosis	0	1 (0.5%)
Vascular hypertensive disorders NEC		
Hypertension	0	1 (0.5%)

Source: **Appendix 1, Table 15.**
Note: Subjects who reported the same event more than once were counted once for each higher level or preferred term. Incidence was defined as the number of subjects reporting an adverse event per the number of subjects in the safety population.
Note: MedDRA dictionary version 14.0.

In the S00124 studies, 3/212 (1.4%) subjects in the pooled bromfenac 0.07% QD and 4/204 (2.0%) subjects in the pooled placebo group experienced a total of 7 SAEs.

In the pooled bromfenac 0.07% QD group, Subject 1505 experienced an SAE of angina pectoris (subject recovered and the AE resolved), Subject 2302 experienced a hip fracture (the AE stabilized), and Subject 2313 experienced an eye operation complication, i.e. posterior capsule rupture with vitreous loss (subject recovered with sequelae).

In the pooled placebo group, Subject 1007 experienced an SAE of deep vein thrombosis (the AE stabilized), Subject 1203 experienced hypertension (the AE stabilized), Subject 2301 experienced an SAE of asthenia (the AE did not resolve), and Subject 6401 experienced an SAE of myocardial infarction (subject recovered and AE resolved).

7.3.3 Dropouts and/or Discontinuations

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**

Reviewer's Comments:

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 Section 6.1.3 of this review.

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 Tables 14.2.1.1 on the next page.

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 Tables 14.2.1.1 on the next page.

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.

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S00124-ER

Table 14.2.1.1
Primary Efficacy Analysis: Summed Ocular Inflammation Score, Subjects with Grade 0 by Day 15
Intent-to-Treat Population

Category	Statistic	Bromfenac N = 112	Placebo N = 108	Total N = 220	P-value [a]
ITT Subjects	n	112	108	220	
SOIS Grade 0 by Day 15 using LOCF [b]	n (%)	54 (48.2)	18 (16.7)	72 (32.7)	< 0.0001
	Treatment Difference [c]			31.5	
	95% Confidence Interval [c]			19.9, 43.2	
ITT Subjects with a Day 15 Score	n	100	59	159	
Observed Cases SOIS Grade 0 by Day 15 [d]	n (%)	50 (50.0)	17 (28.8)	67 (42.1)	0.0124
	Treatment Difference [c]			21.2	
	95% Confidence Interval [c]			6.0, 36.3	

[a] P-value for Bromfenac vs. Placebo is from a Fisher's exact test.
[b] Primary efficacy endpoint, SOIS Grade 0 by Day 15 is defined as grade 0 on or prior to Day 15.
[c] Treatment Difference = Bromfenac percent - Placebo percent. Confidence interval was computed by using the normal approximation method.
[d] SOIS Grade 0 on or prior to Day 15 for subjects with a Day 15 SOIS score.
Table Generation: 15MAR2012 08:22 Confidential Cross-Reference: Listing 16.2.6.1
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S00124-WR

Table 14.2.1.1
Primary Efficacy Analysis: Summed Ocular Inflammation Score, Subjects with Grade 0 by Day 15
Intent-to-Treat Population

Category	Statistic	Bromfenac N = 110	Placebo N = 110	Total N = 220	P-value [a]
ITT Subjects	n	110	110	220	
SOIS Grade 0 by Day 15 using LOCF [b]	n (%)	54 (49.1)	35 (31.8)	89 (40.5)	0.0132
	Treatment Difference [c]			17.3	
	95% Confidence Interval [c]			4.5, 30.0	
ITT Subjects with a Day 15 Score	n	87	60	147	
Observed Cases SOIS Grade 0 by Day 15 [d]	n (%)	51 (58.6)	32 (53.3)	83 (56.5)	0.6121
	Treatment Difference [c]			5.3	
	95% Confidence Interval [c]			-11.0, 21.6	

[a] P-value for Bromfenac vs. Placebo is from a Fisher's exact test.
[b] Primary efficacy endpoint, SOIS Grade 0 by Day 15 is defined as grade 0 on or prior to Day 15.
[c] Treatment Difference = Bromfenac percent - Placebo percent. Confidence interval was computed by using the normal approximation method.
[d] SOIS Grade 0 on or prior to Day 15 for subjects with a Day 15 SOIS score.
Table Generation: 15MAR2012 08:22 Confidential Cross-Reference: Listing 16.2.6.1
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All Adverse Events for Subjects Who Reported an Adverse Event that Led to Investigational Product Discontinuation – S00124-ER and S00124-WR

Study Number	Sub ID	Treatment	MedDRA Preferred Term	Discontinued Investigational Product	Discontinued Study
S00124-ER	5301	Bromfenac	Hyphema	Yes	No
	5302	Bromfenac	Arrhythmia	Yes	No
	5816	Bromfenac	Erythema of eyelid Edema of eyelid	Yes	No
	6102	Bromfenac	Corneal operation	Yes	No
	5012	Placebo	Headache	Yes	No
	6401	Placebo	Myocardial infarction	Yes	No
	7408	Placebo	Eye pain	Yes	No
S00124-WR	0502	Bromfenac	Uveitis Drug hypersensitivity	Yes	No
	1006	Bromfenac	Gout	Yes	No
	1309	Bromfenac	Conjunctival hyperemia Eyelid edema	Yes	No
	1917	Bromfenac	BP increased	Yes	No
	2203	Bromfenac	Anterior chamber inflammation Eye pain Lacrimation increased Photophobia	Yes	No
	2313	Bromfenac	IOP test abnormal Eye operation complication	Yes	No
	0205	Placebo	Eye pain Ocular hyperemia	Yes	No
	0207	Placebo	Anterior chamber inflammation	Yes	No
	0209	Placebo	Anterior chamber inflammation Eye pain	Yes	No
	0408	Placebo	Iritis Eye pain Headache	Yes	No
	0415	Placebo	Eye pain Iritis Pupillary disorder	Yes	No
	0501	Placebo	Uveitis	Yes	No
	0907	Placebo	Anterior chamber inflammation Eye pain	Yes	No

Study Number	Sub ID	Treatment	MedDRA Preferred Term	Discontinued Investigational Product	Discontinued Study
	0916	Placebo	Anterior chamber inflammation Corneal edema	Yes	No
	1001	Placebo	Foreign body sensation Ocular hyperemia	Yes	No
	1002	Placebo	Conjunctival hyperemia Foreign body sensation	Yes	No
	1203	Placebo	Hypertension Hypoxia	Yes	Yes
	1208	Placebo	Anterior chamber inflammation Ciliary hyperemia Conjunctival hyperemia Eye pain Eye pruritis Ocular hyperemia	Yes	No
	1213	Placebo	Anterior chamber inflammation Conjunctival hyperemia Conjunctival edema Corneal edema Drug hypersensitivity	Yes	No
	1301	Placebo	Conjunctival hyperemia	Yes	No
	1307	Placebo	Anterior chamber inflammation	Yes	No
	1504	Placebo	Anterior chamber inflammation IOP increased Iris hemorrhage Vitreous fibrin	Yes	No
	1506	Placebo	Corneal edema Visual acuity reduced	Yes	No
	1603	Placebo	Posterior capsule rupture	Yes	No
	1607	Placebo	Iritis	Yes	No
	1912	Placebo	Eye pain	Yes	No
	2204	Placebo	Anterior chamber inflammation	Yes	No
	2205	Placebo	Anterior chamber inflammation Eye pain	Yes	No

Study Number	Sub ID	Treatment	MedDRA Preferred Term	Discontinued Investigational Product	Discontinued Study
	2208	Placebo	Anterior chamber inflammation	Yes	No
	2210	Placebo	Anterior chamber inflammation	Yes	No
	2306	Placebo	Anterior chamber inflammation Corneal edema	Yes	No

Source: Table 14.3.2.3 for CSR S00124-ER and S00124-WR, Original Submission

Reviewer's Comments:

Subject S00124-WR 2313 (bromfenac) discontinued investigational product for a reported adverse event "IOP test abnormal." On (b) (6) *19 days after completion of cataract surgery OD of the study eye and 11 days after completion of the study, the subject underwent cataract surgery of the non-study eye OS and was reported to have an SAE of a moderate eye operation complication OS (i.e. retained cortical fragments, vitrectomy).*

Subject S00124-WR 2301(bromfenac) is not included in this table by the applicant. On (b) (6) *14 days after completion of cataract surgery OS, an 80 year old enrolled male subject was reported to have an SAE of mild generalized weakness. The SAE was reported as serious, not related to the investigational product by the applicant, and the SAE was persists as of the last study visit. On* (b) (6)*, the subject was taken to the hospital after calling 911 due to extreme fatigue and difficulty walking and standing. Subject was released from the hospital the same day and transferred and admitted to a skilled nursing facility. The subject did not come in for the Day 22/1 Week Follow up Visit, and therefore did not complete the study. Investigational product was not discontinued early.*

Subject S00124-WR 2302 (bromfenac) is not included in this table by the applicant. On (b) (6)*, 42 days after completion of cataract surgery OS, an 85 year old enrolled female subject was reported to have an SAE of a mild broken hip. The SAE was reported as serious, not related to the investigational product, and the SAE stabilized on* (b) (6) *Investigational product was not discontinued early.*

Subject S00124-WR 1907 (bromfenac) is not included in this table by the applicant. On (b) (6)*, a 64 year old enrolled female subject was reported to have an AE of mild elevated blood pressure. The AE was reported as not serious, not related to investigational product by the Investigator, and the subject recovered without sequelae. The subject was dispensed investigational product but prior to the subject taking any product as indicated per the subject's diary pages, the cataract surgery OS was*

cancelled due to the AE of mild elevated blood pressure. The site indicated that the subject took investigational product; however as the diary pages did not support that investigational product was taken, the subject was not included in the Safety Population.

7.3.4 Significant Adverse Events

See Section 7.3.2 of this review.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission specific safety concerns raised in this review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

For pooled adverse event data, see Section 7.1.3 of this review.

S00124-ER Ocular Adverse Events

Table 2.1 Incidence of Adverse Events Affecting the Study Eye in S00124-ER: Events with an Incidence ≥ 2.0% in the Bromfenac 0.07% Group or the Placebo group (ITT Population)

Higher Level Term Preferred Term	Bromfenac 0.07% N = 112	Placebo N = 108
Subjects Reporting an AE Affecting the Study Eye	18 (16.1%)	24 (22.2%)
Choroid and vitreous structural change, deposit and Degeneration	0 (0.0%)	4 (3.7%)
Vitreous floaters	0 (0.0%)	3 (2.8%)
Conjunctival infections, irritations, and inflammations	1 (0.9%)	3 (2.8%)
Conjunctival hyperemia	1 (0.9%)	2 (1.9%)*
Corneal infections, oedemas and inflammations	2 (1.8%)	2 (1.9%)*
Corneal oedema	1 (0.9%)	2 (1.9%)*
Lacrimal disorders	0 (0.0%)	6 (5.6 %)
Lacrimation increased	0 (0.0%)	6 (5.6%)
Ocular disorders NEC	4 (3.6%)	6 (5.6%)
Eye pain	3 (2.7%)	6 (5.6%)
Ocular infections, inflammations and associated manifestations	1 (0.9%)	6 (5.6%)
Eye pruritus	1 (0.9%)	2 (1.9%)*
Ocular hyperemia	0 (0.0%)	2 (1.9%)*
Ocular sensation disorders	4 (3.6%)	9 (8.3%)
Foreign body sensation in eyes	3 (2.7%)	5 (4.6%)
Photophobia	1 (0.9%)	6 (5.6%)
Visual disorders NEC	0 (0.0%)	2 (1.9%)*
Vision blurred	0 (0.0%)	2 (1.9%)*

Source: Table 14.3.1.2A
*These percents were ≥ 2.0% in the analysis of the Safety database.

Note: Subjects reporting the same AE more than once were counted only once for each higher level term when calculating the incidence. Incidence was defined as the number of subjects reporting an AE per the number of subjects in the ITT Population. Preferred term included the subjects where the AE was reported for both eyes.

MedDRA dictionary version 14.0 was used for coding.

Reviewer's Comments:

As discussed in Section 5.3 of this review, more subjects were evaluated for efficacy than were evaluated for safety in S00124-ER.

A reanalysis of the study data for S00124-ER 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. This reanalysis, found on the previous page of this review, was submitted on March 12, 2013.

The most frequently reported AEs affecting the study eye in the bromfenac 0.07% group were eye pain and foreign body sensation in eyes (each 3/112 subjects, 2.7%) in the ITT population.

S00124-WR Ocular Adverse Events

Table 2.4 Incidence of Adverse Events Affecting the Study Eye in S00124-WR: Events with an Incidence ≥ 2.0% in the Bromfenac 0.07% Group or the Placebo Group (ITT Population)

Higher Level Term Preferred Term	Bromfenac 0.07% N = 110	Placebo N = 110
Subjects Reporting an AE Affecting the Study Eye	32 (29.1%)	59 (53.6%)
Chambers (anterior and posterior) and lens infections and inflammations)	8 (7.3%)	18 (16.4%)
Anterior chamber inflammation	8 (7.3%)	18 (16.4%)
Choroid and vitreous structural change, deposit and Degeneration	0 (0.0%)	4 (3.6%)
Vitreous floaters	0 (0.0%)	2 (1.8%)*
Conjunctival infections, irritations, and inflammations	4 (3.6%)	14 (12.7%)
Conjunctival hyperemia	2 (1.8%)	13 (11.8%)
Conjunctival oedema	1 (0.9%)	2 (1.8%)*
Corneal infections, edemas and inflammations	2 (1.8%)	9 (8.2%)
Corneal edema	1 (0.9%)	8 (7.3%)
Punctate keratitis	0 (0.0%)	2 (1.8%)*
Iris and uveal tract infections, irritations and inflammations	2 (1.8%)	5 (4.5%)
Iritis	1 (0.9%)	3 (2.7 %)
Ocular disorders NEC	9 (8.2%)	15 (13.6%)
Eye pain	9 (8.2%)	14 (12.7%)
Ocular infections, inflammations and associated manifestations	3 (2.7%)	6 (5.5%)
Eye pruritus	2 (1.8%)	2 (1.8%)*
Ocular hyperemia	0 (0.0%)	4 (3.6%)
Ocular sensation disorders	5 (4.5%)	7 (6.4%)
Foreign body sensation in eyes	4 (3.6%)	3 (2.7%)
Photophobia	3 (2.7%)	5 (4.5%)
Ophthalmic function diagnostic procedures	3 (2.7%)	3 (2.7%)
Intraocular pressure increased	2 (1.8%)	3 (2.7%)
Partial vision loss	0 (0.0%)	2 (1.8%)*
Visual acuity reduced	0 (0.0%)	2 (1.8%)*
Retinal, choroid and vitreous infections and inflammations	0 (0.0%)	3 (2.7%)
Cystoid macular oedema	0 (0.0%)	2 (1.8%)*
Visual disorders NEC	4 (3.6%)	4 (3.6%)
Diplopia	0 (0.0%)	2 (1.8%)*
Vision blurred	4 (3.6%)	2 (1.8%)*

Source: Table 14.3.1.2A
*These percents were ≥ 2.0% in the analysis of the Safety database.

Note: Subjects reporting the same AE more than once were counted only once for each higher level term when calculating the incidence. Incidence was defined as the number of subjects reporting an AE per the number of subjects in the ITT Population. Preferred term included the subjects where the AE was reported for both eyes.

MedDRA dictionary version 14.0 was used for coding.

Reviewer's Comments:

As discussed in Section 5.3 of this review, more subjects were evaluated for efficacy than were evaluated for safety in S00124-WR.

A reanalysis of the study data for 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. This reanalysis, found on the previous page of this review, was submitted on March 12, 2013.

The most frequently reported AEs affecting the study eye in the bromfenac 0.07% group were anterior chamber inflammation (8/110 subjects, 7.3%), eye pain (9/110, 8.2%), foreign body sensation (4/110, 3.6%), and vision blurred (4/110, 3.6%).

S00124-ER Non-Ocular Adverse Events

Table 14.3.1.8
Systemic Adverse Events
Safety Population

Higher Level Term Preferred Term [a]	Incidence [b] Bromfenac N = 109 n (%)	 Placebo N = 102 n (%)	 Total N = 211 n (%)	Frequency [c] Bromfenac N = 109 n (%)	 Placebo N = 102 n (%)	 Total N = 211 n (%)
Safety Population	109	102	211			
Subjects Reporting a Systemic Adverse Event	5 (4.6)	4 (3.9)	9 (4.3)			
Total Number of Reported Systemic Adverse Events				5	4	9
Crystal arthropathic disorders	1 (0.9)	0	1 (0.5)	1 (20.0)	0	1 (11.1)
Gout	1 (0.9)	0	1 (0.5)	1 (20.0)	0	1 (11.1)
Disturbances in consciousness NEC	0	1 (1.0)	1 (0.5)	0	1 (25.0)	1 (11.1)
Syncope	0	1 (1.0)	1 (0.5)	0	1 (25.0)	1 (11.1)
Headaches NEC	1 (0.9)	2 (2.0)	3 (1.4)	1 (20.0)	2 (50.0)	3 (33.3)
Headache	1 (0.9)	2 (2.0)	3 (1.4)	1 (20.0)	2 (50.0)	3 (33.3)
Ischaemic coronary artery disorders	0	1 (1.0)	1 (0.5)	0	1 (25.0)	1 (11.1)
Myocardial infarction	0	1 (1.0)	1 (0.5)	0	1 (25.0)	1 (11.1)
Nausea and vomiting symptoms	1 (0.9)	0	1 (0.5)	1 (20.0)	0	1 (11.1)
Nausea	1 (0.9)	0	1 (0.5)	1 (20.0)	0	1 (11.1)
Rate and rhythm disorders NEC	1 (0.9)	0	1 (0.5)	1 (20.0)	0	1 (11.1)
Rate and rhythm disorders NEC (cont.)						
Arrhythmia	1 (0.9)	0	1 (0.5)	1 (20.0)	0	1 (11.1)
Upper respiratory tract signs and symptoms	1 (0.9)	0	1 (0.5)	1 (20.0)	0	1 (11.1)
Oropharyngeal pain	1 (0.9)	0	1 (0.5)	1 (20.0)	0	1 (11.1)

[a] MedDRA dictionary version 14.0
[b] Subjects reporting the same event more than once are counted once for each Higher Level Term or Preferred Term. Incidence is defined as the number of subjects reporting an adverse event per the number of subjects in the safety population.
[c] Frequency is defined as the number of adverse events per the total number of reported adverse events.

Reviewer's Comments:

Two subjects (2.0%, 2/102) in the placebo group experienced headache; this was the only systemic AE that was experienced by more than 1 subject in either treatment group.

S00124-WR Non-Ocular Adverse Events

Table 14.3.1.8
Systemic Adverse Events
Safety Population

Higher Level Term Preferred Term [a]	Incidence [b] Bromfenac N = 103 n (%)	Incidence [b] Placebo N = 102 n (%)	Incidence [b] Total N = 205 n (%)	Frequency [c] Bromfenac N = 103 n (%)	Frequency [c] Placebo N = 102 n (%)	Frequency [c] Total N = 205 n (%)
Safety Population	103	102	205			
Subjects Reporting a Systemic Adverse Event	7 (6.8)	6 (5.9)	13 (6.3)			
Total Number of Reported Systemic Adverse Events				10	9	19
Asthenic conditions	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Asthenia	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Conditions associated with abnormal gas exchange	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Hypoxia	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Crystal arthropathic disorders	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Gout	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Gastric and gastroenteric infections	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Gastroenteritis	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Gastrointestinal atonic and hypomotility disorders NEC	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Constipation	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Headaches NEC	1 (1.0)	1 (1.0)	2 (1.0)	1 (10.0)	1 (11.1)	2 (10.5)
Headache	1 (1.0)	1 (1.0)	2 (1.0)	1 (10.0)	1 (11.1)	2 (10.5)
Ischaemic coronary artery disorders	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Angina pectoris	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Lower limb fractures and dislocations	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Hip fracture	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Muscle weakness conditions	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Muscular weakness	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Nasal congestion and inflammations	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Nasal congestion	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Neurological signs and symptoms NEC	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Dizziness	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Peripheral embolism and thrombosis	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Deep vein thrombosis	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Supraventricular arrhythmias	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Supraventricular arrhythmias (cont.)						
Atrial fibrillation	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Upper respiratory tract signs and symptoms	0	2 (2.0)	2 (1.0)	0	2 (22.2)	2 (10.5)
Paranasal sinus discomfort	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Throat irritation	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Urinary tract infections	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Cystitis	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Vascular hypertensive disorders NEC	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Hypertension	0	1 (1.0)	1 (0.5)	0	1 (11.1)	1 (5.3)
Vascular tests NEC (incl blood pressure)	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)
Blood pressure increased	1 (1.0)	0	1 (0.5)	1 (10.0)	0	1 (5.3)

[a] MedDRA dictionary version 14.0
[b] Subjects reporting the same event more than once are counted once for each Higher Level Term or Preferred Term. Incidence is defined as the number of subjects reporting an adverse event per the number of subjects in the safety population.
[c] Frequency is defined as the number of adverse events per the total number of reported adverse events.

Reviewer's Comments:

No systemic AE was experienced by more than 1 subject in either treatment group.

7.4.2 Laboratory Findings

Laboratory and vital signs were not evaluated as part of this application.

7.4.3 Vital Signs

Laboratory and vital signs were not evaluated as part of this application.

7.4.4 Electrocardiograms (ECGs)

Study of the effects on ECG and QTc interval were not conducted as part of this application.

7.4.5 Special Safety Studies/Clinical Trials

Study of safety in special populations was not conducted as part of this application.

7.4.6 Immunogenicity

Immunogenicity studies were not conducted for this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency was not evaluated for this application.

7.5.2 Time Dependency for Adverse Events

Time to onset of AE's was not presented as part of this submission.

7.5.3 Drug-Demographic Interactions

The review of this application has not revealed any clinically meaningful demographic effects on the safety profile.

7.5.4 Drug-Disease Interactions

Study of potential drug-disease interactions were not conducted as a part of this application. There are no known drug-disease interactions with bromfenac for this indication.

7.5.5 Drug-Drug Interactions

Study of potential drug-drug interactions were not conducted as a part of this application. There are no known drug-drug interactions with bromfenac for this indication.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Because of the low expected absorption of bromfenac in topical preparations, no carcinogenicity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

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.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no drug abuse potential with topical bromfenac ophthalmic solution. No withdrawal effects have been related to the use of bromfenac ophthalmic solution 0.07%.

7.7 Additional Submissions / Safety Issues

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.

8 Postmarket Experience

Prolensa (bromfenac ophthalmic solution) 0.07% is not currently approved in any country.

In the US, since the approval of Xibrom in 2005, Periodic Safety Update Reports (PSURs) have been submitted on a regular basis to the FDA. Since the sNDA of Bromday was submitted in 2009, 2 PSURs were prepared for the periods of 01 January 2009 to 31 December 2009 and 01 January 2010 to 31 December 2010 (2009 PSUR for US and 2010 PSUR for US). These were submitted in the annual reports for NDA #021664. During the reporting period 01 January 2009 to 31 December 2009, 20 AE reports were received by ISTA: 5 serious/unexpected AE reports (3 of which were clinical trial cases for subjects taking placebo), 1 serious/expected report, 10 nonserious/unexpected reports, and 4 nonserious/expected reports (2009 PSUR for US). During the reporting period 01 January 2010 to 31 December 2010), 23 AE reports were received by ISTA: 2 serious/unexpected AE reports, 13 nonserious/unexpected reports, and 8 nonserious/expected reports (2010 PSUR for US). One of these 23 AE reports included an AE that occurred in a patient taking Bronuck which was not reported in the PSUR for Japan.

9 Appendices

9.1 Literature Review/References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Bausch & Lomb, Inc. in this application for this indication.

9.2 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.

9.3 Labeling Recommendations

Following are the carton and container labeling (submitted 3/18/13) and Clinical's recommended changes to the package insert (submitted 8/20/2013).

17 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
03/22/2013

WILEY A CHAMBERS
03/22/2013