CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203168Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review
BLA Number	NDA 203168
Related IND	IND 60295
Related NDA	NDA 21664, NDA 20535
Review type	Standard
Applicant Name	Bausch & Lomb, previously ISTA
Date of Submission **Date of Receipt**	June 5, 2012 June 7, 2012
PDUFA Goal Date	April 7, 2013
Proprietary Name / **Established (USAN) Name**	Prolensa bromfenac
Formulation **Concentration** **Dosing Regimen**	Topical ophthalmic solution 0.07% One drop in the affected eye one time daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the post-operative period.
Therapeutic Class **Proposed Indication**	Nonsteroidal anti-inflammatory agent For the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery
Action for NME	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Bill Boyd 3/20/2013
CDTL Review	Bill Boyd 4/5/2013
Deputy Director Review	Wiley Chambers 4/5/2013
Statistical Review Team Leader Review	Abel Eshete, Yan Wang 3/4/2013 Yan Wang, Daphne Lin 4/4/2013
Pharmacology/Toxicology Review	Robeena Aziz, Lori Kotch 3/4/2013
Clinical Pharmacology Review	Yoriko Hayigaya, Philip Colangelo 2/19/2013
ONDQA CMC Review	Rao Kambhampati, Rapti Madurawe 2/26/2013, 4/4/2013 Rapti Madurawe 4/5/2013
Quality Microbiology Review	Stephen Langille, Bryan Riley 1/22/2013
OSI/DGCPC	Kassa Ayalew, Susan Leibenhaut, Susan Thompson 2/4/2013, 2/20/2013
OSE/DMEPA Proprietary Name Letter Final Review	Jung Lee, Zachary Oleszczuk, Carol Holquist 11/7/2012 Carol Holquist 11/9/2012 Jung Lee, Jamie Wilkins Parker 3/4/2013
OSE/DMEPA Label, Labeling and Packaging Review	Jung Lee, Jamie Wilkins Parker, Carol Holquist 2/8/2013
OPDP/DPDP Review	Christine Corser 3/20/2013
Pediatric Review Committee	This application did not trigger PREA

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
ONDQA=Office of New Drug Quality Assessment
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OSE=Office of Surveillance and Epidemiology
OMEPARM=Office of Medication Error Prevention and Risk Management
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication

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1. Summary and Recommendations

Bromfenac ophthalmic solution, 0.07% has been shown to be effective and safe for the treatment of pain and inflammation associated with cataract surgery based on two Phase 3 trials showing superiority of the product to vehicle. The treatment regimen evaluated in these trials and recommended for approval is one drop in the affected eye one time daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the post-operative period.

Key Efficacy Results of Phase 3 Studies in Prolensa NDA (ITT Population)
Proportion of Subjects with Cleared Ocular Inflammation (0 cell and no flare)

Study	Visit	Bromfenac 0.07%	Vehicle	Difference (%) (Asymptotic 95% CI)
Study 1	Day 8	27/112 (24.1%)	7/108 (6.5%)	17.6 (8.4, 26.8)
	Day 15	51/112 (45.5%)	14/108 (13.0%)	32.5 (21.4, 43.8)
Study 2	Day 8	33/110 (30.0%)	14/110 (12.7%)	17.3 (6.7, 27.9)
	Day 15	50/ 110 (45.4%)	30/ 110 (27.3%)	18.2 (5.7, 30.7)
		Proportion of Subjects Who Were Pain Free		
Study 1	Day 1	91/112 (81.3%)	47/108 (43.5%)	37.7 (25.9, 49.6)
Study 2	Day 1	84/110 (76.4%)	61/110 (55.5%)	20.9 (8.7, 33.1)

The safety of the 0.07% bromfenac formulation was evaluated in 222 patients treated with this product and compared to 218 patients who received vehicle. This represents a new concentration of bromfenac. The safety of bromfenac 0.09% given twice daily (Xibrom) and once daily (Bromday) was evaluated in NDA 21-664 for the same indication(s).

The labeling will include information on adverse reactions in these trials, and other safety information. The Warnings and Precautions includes information that the product contains sodium sulfite and may cause allergic reactions in susceptible people, NSAIDs may slow or delay healing, there is a potential cross-sensitivity with aspirin, increase bleeding time, and potential for keratitis and corneal erosion, ulceration and perforation. Common adverse reactions after cataract surgery associated with Prolensa use included anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision. These adverse reactions were reported in 3 to 8% of patients.

All reviewers recommend approval. OSI recommends that clinical site data are considered reliable. As summarized in the CMC review, OC recommends that manufacturing facilities are

recommended acceptable. DMEPA considered the trade name Prolensa acceptable. Product labeling has been reviewed and is acceptable. The package insert is in PLR format.

The application will be issued an *Approval* letter.

1.1 Deficiencies
None

1.2 Post-Marketing Studies:
None

1.3 Other Issues
(b) (4)
(CMC reviews April 4 and 5, 2013).

2. Background

Bromfenac is a non-steroidal anti-inflammatory drug (NSAID). The active ingredient was first approved March 24, 2005 as Xibrom (bromfenac ophthalmic solution) 0.09% under NDA 21664 for the treatment of inflammation following cataract surgery. The sponsor was ISTA Pharmaceuticals, Inc. The recommended treatment regimen of Xibrom is one drop of XIBROM ophthalmic solution applied to the affected eye two times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period. Bromday was approved October 16, 2010 as Supplement 13 to NDA 21664, and established that one drop (instead of two drops) of Bromday ophthalmic solution 0.09% was safe and effective. The current product provides a lower concentration (0.07%) of bromfenac.

There are currently a number of NSAIDs and corticosteroids approved for the treatment of postoperative inflammation (and pain for some):

- bromfenac sodium ophthalmic solution 0.09% (Xibrom, Bromday)
- nepafenac ophthalmic solution 0.1% (Nevanac), nepafenac 0.3% (Ilevro)
- ketorolac tromethamine ophthalmic solution 0.5% (Acular)
- diclofenac sodium ophthalmic solution 0.1% (Voltaren)
- loteprednol etabonate ophthalmic solution, suspension and gel, each 0.5% (Lotemax)
- difluprednate ophthalmic solution 0.05% (Durezol)
- rimexolone ophthalmic suspension 1% (Vexol)

2.1 Application History

IND 60295 for bromfenac was originally submitted as a pre-IND on October 12, 2001 and as an IND for a 0.1% solution by ISTA on March 8, 2003 for the study of ophthalmic bromfenac. The 0.09% formulation was approved under NDA 21664 in 2005. (b) (4) the division recommended a 0.09% solution instead, due to concerns about *corneal toxicity issues and the*

class labeling of NSAIDs. (b) (4)

On May 29, 2008 a proposal to study the bromfenac 0.09% QD regimen was submitted and after the company conducted three trials, two of which showed the product was safe and effective, this regimen was approved in 2010 under NDA 21664/supplement 13.

On February 28, 2011, a SPA was submitted for bromfenac 0.07% for treatment of ocular inflammation and pain associated with cataract surgery – no agreement on the protocol was reached with the Division. A No Agreement letter was issued April 14, 2011.

The rationale for developing the 0.07% formulation was included in the Integrated Summary of Safety of this application (NDA 203168):

(b) (4) The net effects of the changes led to a formulation that maintains both safety and efficacy."

(b) (4)

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.

On August 20, 2012, ISTA notified the FDA they had been acquired by Bausch & Lomb Incorporated.

3. CMC/Product Quality Microbiology

For complete details, see the reviews by the product quality and quality microbiology reviewers. The following summary is excerpted from these reviews:

The CMC reviewer noted that the manufacturer and supplier, manufacturing process, test methods, specifications, and all other parameters are the same for the 0.07% concentration as those used for the drug substance in NDA 21664, bromfenac ophthalmic solution, 0.09% (Bausch & Lomb, formerly ISTA).

The drug product is manufactured by Bausch & Lomb Pharmaceuticals, Inc. (B&L) in Tampa, FL and the process is summarized in the CMC review. The solution is (b) (4)

(b) (4)

Bromfenac ophthalmic solution 0.07% is (b) (4) filled into 7.5 mL size (b) (4) low-density polyethylene (LDPE) white round bottles into which a (b) (4) controlled dropper tip is then inserted. It is capped and a tamper-evident (b) (4) seal is shrink-sealed over the cap and the neck of the bottle. Labels coded with lot number and expiry date are affixed to the 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%.

QC sampling and inspection is performed throughout the packaging operation. The product is then released for final distribution. The trade sizes for the drug product are 1.6 mL and 3 mL fill volume per bottle. In addition, the applicant has submitted professional sample sizes of 0.6 mL and 0.8 mL per 7.5 mL bottle. The applicant was asked why a 3mL bottle size was needed for the 16 drops of the treatment regimen and responded on March 4, 2013 that, "the 3-mL fill size of Prolensa™ takes into account the documented wastage in the elderly population to ensure every patient is able to complete the labeled dosing regimen without compromising safety and efficacy." Publications to support this rationale are summarized and included in the submission.

The composition of the product is provided in the table below (applicant table from section 3.2.P.1)

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 revised product specifications from the CMC review are listed in the following table

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)	

Based on 12 months of real-time data, the expiration period granted is 12 months for the 0.8 and 0.6 mL fill sizes. Based on 18 months of real-time data, the expiration dating period granted is 22 months for the 1.6 and 3 mL fill sizes. The recommended label storage condition is 15°C-25°C (59°F-77°F).

The applicant's request for exemption from environmental assessment was considered acceptable (21 CFR 25.31(b)).

Comments:
The Product Quality and Microbiology Sterility reviewers recommend approval of the application from the CMC perspective. They conclude there is sufficient information to assure the identity, strength, purity, and quality of the drug product. The labels have adequate CMC information as required, (b) (4)

(b) (4) *The establishment evaluation of the manufacturing and testing facilities was complete and the Office of Compliance issued an Overall Acceptable Recommendation. There are no post-marketing studies requested.*

4. Nonclinical Pharmacology/Toxicology

For detailed information, see Pharmacology/Toxicology (P/T) reviews.

There are no new pharmacology/toxicology (P/T) studies submitted in this application, the applicant refers to their applications, NDA 21664 (Xibrom and Bromday) and NDA 20535 (Duract, bromfenac sodium capsules) for nonclinical information. The P/T reviewer recommended using mg/m^2 exposure to calculate safety margins in patients receiving the topical solution in the labeling because AUC data were not provided. This approach showed that animal findings of embryolethality, maternal toxicity, delayed parturition, and delayed growth were seen at 80 to 4000 times the anticipated human exposure.

The Deputy Director located tables of Cmax data for the oral animal studies in NDA 20535, and also noted the lower limit of detection for the assay was 50 ng/mL for bromfenac, and human testing showed values to be below this limit. Based on this information, he calculated the following:

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

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

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

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

Comment:
Although exposure comparisons are based on AUC, AUC information was not available for animal studies and not available in humans after topical application since values were below level of detection. Therefore, the Cmax comparison was used. As shown above, this approach yielded more conservative margins (30 to 340) compared to the mg/m^2 approach (80 to 4000) and are acceptable for presenting the safety margins in the labeling. Therefore, the application is recommended for approval from a pharmacology/toxicology standpoint. Labeling recommendations have been finalized. The applicant asked for clarification on the animal to human plasma exposure calculations, and these were provided, including an

explanation that calculations were historically based on mg/kg comparison, and then mg/m^2 comparison and more recently based on comparison of exposures.

5. Clinical Pharmacology/Biopharmaceutics

For complete information, see clinical pharmacology review.

There are no new PK studies submitted with this application, and the labeling of Section 12 Clinical Pharmacology has the same information on mechanism of action and pharmacokinetics as NDA 21664. Specifically, based on information from bromfenac ophthalmic solution 0.09%, the company states that systemic absorption is estimated to be below the level of detection at steady state (50 ng/mL).

Comment:
The clinical pharmacolgoy reviewer recommends approval from the clinical pharmacology perspective; labeling is acceptable and no phase 4 studies are requested.

6. Clinical Microbiology/Immunology

Not applicable

7. Clinical/Statistical-Efficacy

For complete details, see clinical and statistical reviews. The summary below is excerpted from these reviews, and additional information is taken from NDA 203168:

7.1 Phase 3 clinical trials

Two randomized, masked, vehicle (placebo) controlled trials, S00124-ER (ER)and S00124-WR (WR), were conducted in the "eastern" and "western" region of the United States, respectively. The same protocols and statistical analysis plan was used in each study. A total of 220 patients were randomized 1:1 in each study; there were 20 sites that participated in Study ER and 19 sites in Study WR.

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, measured on the ocular comfort grading assessment (ODGA). The ODGA rated 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.

The primary efficacy analysis was conducted on the ITT population, defined as all randomized subjects. The Fisher's exact test was used to compare the bromfenac 0.07% and the placebo groups with respect to the primary efficacy endpoint and the key secondary endpoint. Missing

data were imputed using the Last Observation Carried Forward (LOCF) method. The Hochberg's method was used to adjust for multiple comparisons.

Bromfenac ophthalmic solution 0.07% was superior to vehicle in both studies at Day 8 and Day 15, and significant when adjusted for multiple comparisons. More vehicle-treated patients than bromfenac-treated patients received rescue therapy. The applicant considered subjects who received rescue therapy as having missing data but imputed these as "failure" which is considered the appropriate way to categorize these patients.

In addition, the applicant considered subjects who had non-zero cell and/or flare scores as successes at Day 15 if they has a Day 3 or Day 8 visit with zero cell and flare scores. While the ophthalmology reviewers agreed with this approach, the statistical reviewers did not (see Comments below). As summarized in the statistical reviews, patients who had zero scores on Day 3 or 8, but did not have a score of zero on Day 15 were considered as failures. There were a total of 15 patients in the two studies (out of 440), who met this outcome, and were approximately evenly distributed between the two studies and the two arms.

The Tables below presents the FDA results and the applicant's results for cleared ocular inflammation. It can be seen that both analyses lead to the interpretation of efficacy, The applicant's analysis resulted in rates for the "by Day 15" analysis that were approximately 2% to 4% higher than in the FDA "at Day 15" analysis. Both FDA and the applicant agreed on the analysis of pain, which was evaluated on Day 1.

FDA analysis:
Proportion of Subjects with Cleared Ocular Inflammation (0 cells and no flare)

Study	Visit	Bromfenac 0.7%	Vehicle	Difference (%) (Asymptotic 95% CI)
S00124-ER	At Day 8	27/112 (24.1%)	7/108 (6.5%)	17.6 (8.4, 26.8)
	At Day 15	51/112 (45.5%)	14/108 (13.0%)	32.5 (21.4, 43.8)
S00124-WR	At Day 8	33/110 (30.0%)	14/110 (12.7%)	17.3 (6.7, 27.9)
	At Day 15	50/110 (45.5%)	30/110 (27.3%)	18.2 (5.7, 30.7)
Proportion of Subjects who Were Pain Free				
Study	Visit	Bromfenac 0.07%	Vehicle	Difference (%) (Asymptotic 95% CI)
S00124-ER	At Day 1	91/112 (81.3%)	47/108 (43.5%)	37.7 (25.9, 49.6)
S00124-WR	At Day 1	84/110 (76.4%)	61/110 (55.5%)	20.9 (8.7, 33.1)

Applicant's analysis:
Proportion of Subjects with Cleared Ocular Inflammation (0 cells and no flare)

Study	Visit	Bromfenac 0.7%	Placebo	Difference (%) (Asymptotic 95% CI)
S00124-ER	By Day 15	54/112 (48.2%)	18/108 (16.7%)	31.5 (19.9, 43.2)
S00124-WR	By Day 15	54/110 (49.1%)	35/110 (31.8%)	17.3 (4.5, 30.0)

Proportion of Subjects who Were Pain Free				
Study	Visit	Bromfenac 0.07%	Vehicle	Difference (%) (Asymptotic 95% CI)
S00124-ER	At Day 1	91/112 (81.3%)	47/108 (43.5%)	37.7 (25.9, 49.6)
S00124-WR	At Day 1	84/110 (76.4%)	61/110 (55.5%)	20.9 (8.7, 33.1)

(b) (4) . An agreement had not been reached on the protocol – a No Agreement letter was issued in April 2011 for the SPA. However, the current approach of reporting results based on findings on the day of the visit is consistent with previous FDA approvals, based on examination of NDAs for this indication and comments from various ophthalmology reviews for these products. In the review of the last 7 NDAs for the indication of inflammation after cataract surgery, the analysis was based on the assessment "at" or "on" the day of evaluation in six of these seven NDAs (see below). The one exception had been Bromday (bromfenac 0.09%) approved in 2010, which was also submitted by ISTA. In addition, "by" is defined as "during the course of "or "no later than," so the expectation would be that these patients were successes "during the course of Day 15" or "no later than Day 15" and had zero scores for inflammation.

The approach to using zero scores to determine success has been applied in the last 6 or 7 NDAs for NSAID or steroid products. ISTA had been previously advised of this during the development of their Xibrom product.

Comment:
A detailed summary of the analyses used to support the approval of the last 7 NSAID or steroid products for treatment of inflammation after cataract surgery, and tabular comparisons of the endpoints, the definitions, the timing of evaluations is included in the Statistical Team Leader Review.

List of NDAs Approved in 2005-2012 for post-operative Inflammation after Cataract Surgery

NDA	Submitted	Approved
3.1 NDA021664 Xibrom (bromfenac ophthalmic solution, 0.09% BID)	2004	2005
3.2 NDA021862 Nevanac (nepafenac ophthalmic suspension, 0.1% TID)	2005	2005
3.3 NDA022212 Durezol (difluprednate ophthalmic emulsion, 0.05%)	2007	2008
3.4 NDA021664 Bromday (bromfenac ophthalmic solution, 0.09% QD)	2009	2010
2.5 NDA200738 Lotemax (loteprednol etabonate ophthalmic ointment, 0.5% QID)	2009	2010
3.6 NDA202872 Lotemax (loteprednol etabonate ophthalmic gel, 0.5% QID)	2011	2012
3.7 NDA203491 Ilevro (nepafenac ophthalmic suspension, 0.3% QD)	2011	2012

(b) (4) *the ophthalmology reviewers recommended presenting data "by Day 15" where patients who had non-zero scores on day 15 were considered successes, this approach was inconsistent with 6 of the above 7 NDAs that present study results on or at the Day of the visit when the inflammation score was zero.*

The decision that success is based on a zero inflammation score is also consistent in that labeling for the majority (6 of 7) NDAs reports success as scores of 0 cell and flare, or 0 cell, in approved labeling. In fact, this interpretation was articulated by the MO at the time of the original Xibrom bromfenac 0.09% NDA 21-664 submission and review:

> *The original primary efficacy endpoint for the phase 3 trials proposed by the sponsor was defined as a summed ocular inflammation score (i.e. cell+ flare) ≤ 1 within the 14-day treatment period. This is not considered an acceptable endpoint for the treatment of ocular inflammation since rebound is a common occurrence after anti-inflammatory drugs are discontinued. This endpoint did not address this concern or the sustainability of the effect after the active-treatment period. (MOR 3/14/2005, NDA 21664)*
>
> *The agency requires a more rigorous definition of efficacy which required bromfenac to demonstrate both statistical and clinical significance in the reduction of summed ocular inflammation score, or reduction in anterior cells, as compared to vehicle. A decision was made to redefine the primary efficacy endpoint. The primary efficacy endpoint is defined as the sum of anterior chamber cell and flare equal to zero (based on a five-point scale for each) at Visit 4 (Day 15). (MOR 3/14/2005, NDA 21664)*

Similar comments are found in reviews by other reviewers for NSAID and steroid products for this indication about the cell counts, and interpretation of rescue therapy is also addressed:

> *If a drug product is given on Day 15 to treat ocular inflammation, the drug product may be considered rescue treatment. (MOR, 3/21/2011, IND 60295)*
>
> *I disagree with the statement in the protocol, "Therefore if a subject completes the treatment Phase (i.e., all 16 days of IP treatment) any alternative treatment given to the subject thereafter is NOT a rescue medication." If an alternative treatment is given to a subject at the end of treatment phase because the patient has not cleared his/her inflammation, the alternative treatment can be considered rescue treatment. (MOR 4/14/2011, IND 60295)*

The latter statements indicate that patients who are non-zero scores at the end of treatment (e.g., Day 15) and require rescue therapy are not counted as successes, therefore, to count patients with non-zero scores as successes is inconsistent with past advice.

Although the rates for efficacy provided by the applicant differ by approximately 2-4% in all treatment arms compared to the FDA statistical reviewers, the FDA analysis is consistent with the approach used in the majority of NDAs approved for this indication. Although the ophthalmology reviewers for this application did not agree with the analysis, all ophthalmology and statistical reviewers agree that the product has demonstrated efficacy and can be approved. The labeling will reflect the analyses that count patient who were not cleared at Day 15 as failures. A summary of the efficacy findings is included in Section 14 of the labeling. Although the ophthalmology reviewers do not agree, the level of detail provided in Section 14 is consistent with the guidance provided by the OPDP reviewer and with the Guidance to Industry for the Clinical Studies section of labeling.

8. Safety

The details on the safety evaluation are included in the clinical and statistical reviews.

The applicant's safety population for these trials consisted of 212 patients in the bromfenac arm and 204 in the vehicle arm; the definition of the safety population was patients who received at least one dose of study drug. The table below from section 2.5 Clinical Overview presents an overview of safety data.

Table 1. Summary of Adverse Events (Safety Population, S00124 Pooled Studies)

	Bromfenac 0.07% QD Studies			
Category	**Pooled Bromfenac 0.07% QD n (%)**	**Pooled Placebo QD n (%)**	**Total n (%)**	**P value[1]**
Safety Population, N	212	204	416	
Subjects with any Adverse Event	61 (28.8%)	87 (42.6%)	148 (35.6%)	0.0041
Subjects with an Ocular Adverse Event [2]	52 (24.5%)	82 (40.2%)	134 (32.2%)	0.0008
Affecting the Study Eye	48 (22.6%)	82 (40.2%)	130 (31.3%)	0.0001
Affecting the Non-Study Eye	4 (1.9%)	1 (0.5%)	5 (1.2%)	0.3724
Affecting Both Eyes	3 (1.4%)	1 (0.5%)	4 (1.0%)	0.6235
Subjects with a Systemic Adverse Event	12 (5.7%)	10 (4.9%)	22 (5.3%)	0.8279
Subjects with a Serious Adverse Event	3 (1.4%)	4 (2.0%)	7 (1.7%)	0.7195
Total Number of Serious Adverse Events	3	4	7	
Number of Unique Serious Adverse Events	3	4	7	
Subjects Discontinued IP Due to an Adverse Event [3]	10 (4.7%)	28 (13.7%)	38 (9.1%)	0.0019

Source: **ISS Appendix 1, Table 9.1.**

1 p-value for bromfenac versus placebo was from a Fisher's exact test

2 A subject may be counted in more than 1 category.

3 Subjects withdrawn for an adverse event based on Action Taken from Adverse Event log eCRF.

Furthermore, the application summarized the disposition of all patients (pooled analysis)

Table 3. Disposition of Subjects 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
Number of Subjects Completing[1]		
Day 1	210 (99.1%)	201 (98.5%)
Day 3	204 (96.2%)	197 (96.6%)
Day 8	193 (91.0%)	155 (76.0%)
Day 15	187 (88.2%)	119 (58.3%)
Day 22	212 (100.0%)	201 (98.5%)
Study Completion		
Number of Subjects Completing the Study	212 (100.0%)	201 (98.5%)
Number of Subjects Discontinuing the Study Early	0	3 (1.5%)
Reason for Study Discontinuation		
Withdrawal of Consent/Non-Compliance	0	1 (0.5%)
Lost to Follow-Up	0	0
Death	0	0
Other	0	2 (1.0%)
Subjects Discontinuing IP Early	24 (11.3%)	82 (40.2%)
Reason for Early IP Discontinuation		
Adverse Event	10 (4.7%)	28 (13.7%)
Disallowed Concurrent Medication	2 (0.9%)	0
Lack of Efficacy	7 (3.3%)	52 (25.5%)
Other	5 (2.4%)	2 (1.0%)

Source: **Appendix 1, Table 1.**
[1] A visit was considered complete if at least 1 procedure was performed.

The applicant reported that adverse reactions affecting the study eye that occurred with an incidence ≥2.0% in the pooled bromfenac 0.07% QD or pooled placebo treatment groups in descending order of incidence are as follows:

- Eye pain (12/212, 5.7% versus 20/204, 9.8%)
- Anterior chamber inflammation (10/212, 4.7% versus 18/204, 8.8%)
- Conjunctival hyperemia (3/212, 1.4% versus 15/204, 7.4%)
- Photophobia (4/212, 1.9% versus 11/204, 5.4%)
- Corneal edema (2/212, 0.9% versus 10/204, 4.9%)
- Foreign body sensation in eyes (7/212, 3.3% versus 8/204, 3.9%)
- Lacrimation increased (2/212, 0.9% versus 7/204, 3.4%)
- Ocular hyperemia (0/212, 0.0% versus 6/204, 2.9%)
- Vitreous floaters (0/212, 0.0% versus 5/204, 2.5%)
- Vision blurred (4/212, 1.9% versus 4/204, 2.0%)
- Eye pruritus (3/212, 1.4% versus 4/204, 2.0%)
- Intraocular pressure increased (3/212, 1.4% versus 4/204, 2.0%)

The tables and information above indicates that more patients in the bromfenac arm, compared to the vehicle arm, completed the investigational product, and more patients in the vehicle arm reported adverse reactions and lack of efficacy. These adverse reactions included reports of "anterior chamber inflammation" and "eye pain" which could represent an adverse reaction to

the drug but could also represents a lack of efficacy. These findings are consistent with the interpretation that the vehicle is less effective than the active treatment.

In the ISS, the applicant also includes the following table of adverse reaction rates:

Table 13. Summary of AEs Affecting the Study Eye and Related to IP with an Incidence ≥2.0% (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 an IP-related adverse event affecting the Study Eye or Both Eyes	14 (6.6%)	43 (21.1%)
Chambers (anterior and posterior) and lens infections and inflammations		
Anterior chamber inflammation	5 (2.4%)	11 (5.4%)
Conjunctival infections, irritations and inflammations		
Conjunctival hyperemia	2 (0.9%)	8 (3.9%)
Corneal infections, oedemas and inflammations		
Corneal edema	1 (0.5%)	5 (2.5%)
Lacrimal disorders		
Lacrimation increased	1 (0.5%)	5 (2.5%)
Ocular disorders NEC		
Eye pain	6 (2.8%)	16 (7.8%)
Ocular infections, inflammations and associated manifestations		
Ocular hyperaemia	0	4 (2.0%)
Ocular sensation disorders		
Foreign body sensation in eyes	0	5 (2.5%)
Photophobia	1 (0.5%)	8 (3.9%)

Source: **Appendix 1, Table 14**.
Note: Subjects who reported the same event more than once were counted once for each higher level or preferred term.
Note: An event was considered related to IP if the relationship to IP was possible, probable, or definite. 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.

The above are rates based on the applicant's safety population ---which includes 212 bromfenac patients and 204 vehicle patients from the pooled S00124 studies, instead of the total 222 bromfenac and 218 vehicle patients evaluated for efficacy. Thus, 10 bromfenac and 14 vehicle patients are not included in the analysis. The MO requested reanalysis of the safety results using randomized patients. The applicant updated the application by providing the safety analysis including all 222 bromfenac 0.07% and 218 vehicle controlled subjects. (Sent March 13, 2013) The adverse reaction rates are reflected in the table below from Dr. Boyd's review.

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%)

The company was also asked to comment on the imbalance in the patients who discontinued from their investigational product (IP). The applicant wrote (March 13, 2013 submission):

> To summarize, 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. 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%). 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%). Thus, it can be concluded that these differences in assessing reasons for discontinuing IP early between groups did not affect the overall study conclusions.

The reviewer 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.

The list of adverse reactions associated with use of the 0.07% formulation were similar to the ones seen with the approved formulations. Because the current trials did not include an arm testing the 0.09% formulation, no direct comparison is available and cross-study comparisons are not appropriate. The labeling for the **ADVERSE REACTIONS** section will address both of these issues:

> Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
>
> The most commonly reported adverse reactions following use of PROLENSA following cataract surgery include: anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and vision blurred. These reactions were reported in 3 to 8% of patients.

There were no deaths in the studies and more patients dropped out of the vehicle arm, mainly due to lack of efficacy.

8.1 Post Marketing Experience

Bromfenac ophthalmic solution 0.09% has been marketed as Xibrom since 2005 and Bromday since 2010. Review of the post-approval information has not identified new toxicities that would warrant inclusion in labeling.

Comment:
The adverse reactions were reviewed. The reviewers concluded that the benefits outweigh the risks and recommend approval of the application. The adverse reaction findings and class labeling was be included in the Warnings and Precautions and Adverse Reactions section of labeling, as appropriate.

9. Advisory Committee Meeting

The application did not raise new scientific issues that needed input from the Advisory Committee.

10. Pediatrics

The application is a new concentration of an approved chemical entity. The application does not provide for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration and therefore the PREA requirement for pediatric assessment is inapplicable.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection - Facilities

The Office of Compliance issued an overall recommendation of "Acceptable" as summarized in the CMC review.

11.2 Office of Scientific Investigation (OSI) Audits

OSI inspected two study sites, and although some regulatory violations were noted at one site, the data derived from both sites were considered to be reliable by OSI.

11.3 Debarment Certification

ISTA (now acquired by B&L) certified that they did not and will not use in any capacity the service of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in the connection of this application.

11.4 Financial Disclosure

The medical officer notes that the applicant provided disclosure of financial arrangements with two clinical investigators who participated in S00124-WR and ER and concluded that these arrangements did not impact the clinical study results.

11.5 Other Regulatory Issues

None identified.

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the Division, DMEPA, OPDP/DPDP, labeling recommendations were discussed and labeling finalized.

- **Package insert (PI):** The PI is written in PLR format. The recommendations made by OPDP were not endorsed by the clinical reviewers; however, these recommendations are based on and consistent with the Guidance to Industry for the Clinical Studies section and other precedents, respectively. They were incorporated into the final package insert.

- **Carton and Container Labels**: The labels have been reviewed by the Division, CMC and DMEPA and agreement reached or any differences in recommendations documented in the CDTL review.

- **Proprietary Name**: The proposed proprietary name Prolensa was reviewed by DMEPA and found acceptable 11/7/2012. A second (final) review 3/4/2013 found the trade name acceptable.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The NDA will be issued an *Approval* letter given that two adequate and well-controlled Phase 3 trials showed the product is safe and effective for the treatment of pain and inflammation associated with cataract surgery. All disciplines recommend approval, the facilities are acceptable and investigator site inspections recommend the clinical trial data are reliable. Labeling has been finalized.

13.2 Risk Benefit Assessment

This application provides for a lower concentration of bromfenac ophthalmic solution 0.07% (currently the 0.09% formulation is marketed). Two randomized, masked vehicle-controlled clinical trials demonstrated that bromfenac ophthalmic solution 0.07% was superior to vehicle, in complete resolution of ocular inflammation and pain following cataract surgery. The safety profile of this drug product is consistent with other products in the topical NSAID class. No new unexpected adverse events associated with the use of this product were observed. The benefits of this drug outweigh the risks.

13.3 Recommendation for other Postmarketing Requirements and Commitments

None

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

/s/

RENATA ALBRECHT
04/05/2013