CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-664/S013

Trade Name: Bromday (bromfenac ophthalmic solution) 0.09%

Generic Name: Bromfenac sodium

Sponsor: ISTA Pharmaceuticals Inc.

Approval Date: 10/16/2010

Indication: Bromday is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction/surgery.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

CONTENTS

Reviews / Information Included in this NDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021664/S-013 **SUPPLEMENT APPROVAL**

ISTA Pharmaceuticals, Inc.
Attention: Paul Nowacki
Director, Regulatory Affairs
15295 Alton Parkway
Irvine, CA 92618

Dear Mr. Nowacki:

Please refer to your Supplemental New Drug Application (sNDA) dated December 16, 2009, received December 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for bromfenac sodium ophthalmic solution, 0.09%.

We acknowledge receipt of your amendments dated February 24, March 2, April 8, May 21 and 25, July 9, 12, 23 and 30, and September 7, 9 and 15, and October 8, 2010.

This Prior Approval supplemental new drug application proposes a change in dosing regimen from twice-a-day (BID) dosing following cataract extraction surgery to once-a-day (QD) dosing beginning one day prior to surgery, continuing on the day of surgery and for 14 days after surgery.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

We acknowledge your September 9, 2010, submission containing final printed carton and container labels.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for this application because this product does not represent a meaningful therapeutic benefit over existing therapies (topical corticosteroids) for pediatric patients **and** is not likely to be used in a substantial number of pediatric patients.

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

WILEY A CHAMBERS
10/16/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Bromday (bromfenac ophthalmic solution) 0.09% safely and effectively. See full prescribing information for Bromday.

Bromday (bromfenac ophthalmic solution) 0.09%
Initial U.S. Approval: 1997

----------**INDICATIONS AND USAGE**---------

Bromday is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction **(1)**.

---------**DOSAGE AND ADMINISTRATION**---

Instill one drop into the affected eye(s) once daily beginning 1 day prior to surgery, continued on the day of surgery and through the first 14 days post-surgery **(2.1).**

------**DOSAGE FORMS AND STRENGTHS**--

Topical ophthalmic solution: bromfenac 0.09% **(3)**

-------**WARNINGS AND PRECAUTIONS**-----

- Sulfite Allergic Reactions **(5.1)**
- Slow or Delayed Healing **(5.2)**
- Potential for cross-sensitivity **(5.3)**
- Increase bleeding of ocular tissues **(5.4)**
- Corneal effects including keratitis **(5.5)**
- Contact Lens Wear **(5.6)**

----------**ADVERSE REACTIONS**----------

The most commonly reported adverse reactions in 2-7% of patients were abnormal sensation in eye, conjunctival hyperemia and eye irritation (including burning/stinging) **(6.1)**.

To report SUSPECTED ADVERSE REACTIONS, contact ISTA Pharmaceuticals, Inc. at 1-877-788-2020, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Bromday (bromfenac ophthalmic solution) 0.09% is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of Bromday ophthalmic solution should be applied to the affected eye(s) once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

2.2 Use with Other Topical Ophthalmic Medications

Bromday ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Topical ophthalmic solution: bromfenac 0.09%.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

5.2 Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

5.3 Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

5.4 Increased Bleeding Time

With some NSAIDs, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that Bromday ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

5.5 Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for the occurrence and severity of corneal adverse events.

5.6 Contact Lens Wear

Bromday should not be administered while wearing contact lenses

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

The most commonly reported adverse experiences reported following use of bromfenac after cataract surgery include: abnormal sensation in eye, conjunctival hyperemia, eye irritation (including burning/stinging), eye pain, eye pruritus, eye redness, headache, and iritis. These events were reported in 2-7% of patients.

6.2 Post-Marketing Experience

The following events have been identified during post-marketing use of bromfenac ophthalmic solution 0.09% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical bromfenac ophthalmic solution 0.09% or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown. [*see Warnings and Precautions* (5)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. Reproduction studies performed in rats at oral doses up to 0.9 mg/kg/day (1300 times the recommended human ophthalmic dose [RHOD]) and in rabbits at oral doses up to 7.5 mg/kg/day (11,000 times RHOD) revealed no evidence of teratogenicity due to bromfenac. However, 0.9 mg/kg/day in rats caused embryo-fetal lethality, increased neonatal mortality, and reduced postnatal growth. Pregnant rabbits treated with 7.5 mg/kg/day caused increased post-implantation loss.

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.

Nonteratogenic Effects:

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of Bromday ophthalmic solution during late pregnancy should be avoided.

8.3 Nursing Mothers

Caution should be exercised when Bromday is administered to a nursing woman.

8.4 Pediatric Use

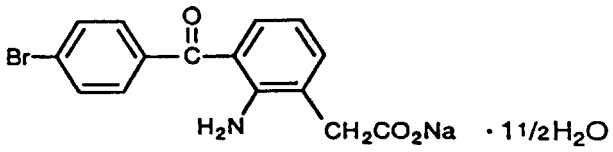
Safety and efficacy in pediatric patients below the age of 18 have not been established.

8.5 Geriatric Use

There is no evidence that the efficacy or safety profiles for Bromday differ in patients 65 years of age and older compared to younger adult patients.

11 DESCRIPTION

Bromday (bromfenac ophthalmic solution) 0.09% is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each mL of Bromday contains 1.035 mg bromfenac sodium (equivalent to 0.9 mg bromfenac free acid). Bromfenac sodium is designated chemically as sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate, with an empirical formula of $C_{15}H_{11}BrNNaO_3 \bullet 1½H_2O$. The structural structure for bromfenac sodium is:



Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. Bromday ophthalmic solution is supplied as a sterile aqueous 0.09% solution, with a pH of 8.3. The osmolality of Bromday ophthalmic solution is approximately 300 mOsmol/kg.

Each mL of Bromday ophthalmic solution contains:
Active: bromfenac sodium hydrate 0.1035%
Preservative: benzalkonium chloride (0.05 mg/mL)
Inactives: boric acid, disodium edetate (0.2 mg/mL), polysorbate 80 (1.5 mg/mL), povidone (20 mg/mL), sodium borate, sodium sulfite anhydrous (2 mg/mL), sodium hydroxide to adjust pH and water for injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 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.

12.3 Pharmacokinetics

The plasma concentration of bromfenac following ocular administration of 0.09% Bromday (bromfenac ophthalmic solution) in humans is unknown. Based on the maximum proposed dose of one drop to the eye (0.045 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (900 times the recommended human ophthalmic dose [RHOD] of 1.67 mcg/kg in 60 kg person on a mg/kg/basis, assuming 100% absorbed) and 5 mg/kg/day (7500 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 (1300 and 450 times RHOD, respectively).

14 CLINICAL STUDIES

14.1 Ocular inflammation and pain following cataract surgery

Clinical efficacy was evaluated in three randomized, double-masked, placebo-controlled trials in which subjects requiring cataract surgery were assigned to Bromday or placebo. Patients were dosed with one drop per eye starting the day before surgery and continuing for 14 days. The primary endpoint was clearing of ocular inflammation by day 15. An additional efficacy endpoint was the number of patients who were pain free on day 1 after cataract surgery.

In 2 of the 3 studies, Bromday ophthalmic solution had statistically significant higher incidence of completely clearing inflammation (46-47% vs. 25-29%) and also had a statistically significant higher incidence of subjects that were pain free at day 1 post cataract surgery (83-89% vs. 51-71%).

16 HOW SUPPLIED/STORAGE AND HANDLING

Bromday (bromfenac ophthalmic solution) 0.09% is supplied in a white LDPE plastic squeeze bottle with a 15 mm LDPE white dropper-tip and 15 mm polypropylene gray cap as follows:

1.7 mL in 7.5 mL container (NDC 67425-999-17)

STORAGE

Store at 15º – 25ºC (59º – 77ºF).

17 PATIENT COUNSELING INFORMATION

17.1 Slowed or Delayed Healing

Patients should be advised of the possibility that slow or delayed healing may occur while using NSAIDs.

17.2 Sterility of Dropper Tip

Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.3 Concomitant Use of Contact Lenses

Contact lenses should not be worn during the use of this product.

17.4 Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart

Rx Only

Manufactured for: ISTA Pharmaceuticals, Inc.
Irvine, CA 92618

By: Bausch & Lomb Incorporated
Tampa, FL 33637

Under license from:
Senju Pharmaceuticals Co., Ltd.
Osaka, Japan 541-0046

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

OFFICER/EMPLOYEE LIST

Officer/Employee List
NDA 21-664/S-013

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Ayalew, Kassa
Bergman, Kimberly
Bonapace, Charles
Boyd, William
Chambers, Wiley
Dean, Jane
Dillon-Parker, Maureen
Ocheltree, Terrance
Rodriguez, Libaniel
Schmidt, Wendelyn

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

OFFICE DIRECTOR MEMO

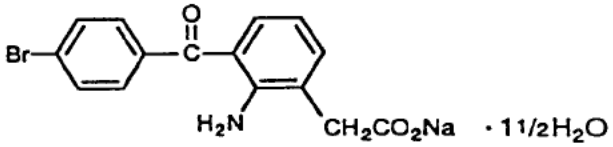
Division Director Review for NDA 21-664/S-13

Date	October 14, 2010
From	Wiley A. Chambers, M.D.
NDA #	NDA 21-664 / Supplement 13
Applicant	ISTA Pharmaceuticals
Date of Submission	December 16, 2009
PDUFA Goal Date	October 16, 2010
Type of Application	505(b)(1) efficacy supplement
Name	Bromday (bromfenac ophthalmic solution) 0.09%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction
Action:	Approval

1. Introduction/Background

Bromfenac ophthalmic solution is a non-steroidal anti-inflammatory drug (NSAID) studied for the treatment of postoperative inflammation and the reduction of pain in subjects who have undergone cataract extraction. The currently marketed product, Xibrom (bromfenac ophthalmic solution) 0.09%, administered twice daily (BID), is indicated for the treatment of postoperative inflammation and the reduction of pain in subjects who have undergone cataract extraction. Xibrom (bromfenac ophthalmic solution) 0.09% was approved in March of 2005 for the treatment of post-operative ocular inflammation and in January of 2006 for the treatment of post-operative pain when dosed twice daily.

The chemical structure for bromfenac sodium (b) (4) is:



This efficacy supplement (S-013), proposes to change the dosing regimen to "instill one drop into the affected eye(s) once daily beginning one day prior to surgery, continued on the day of surgery and through the first 14 days post-surgery." This proposal represents a change from the currently approved BID dosing regimen to QD dosing.

(b) (4) (b) (4) The current application (NDA 21-664 SE 2 S-013) presents data from a dose-ranging Phase 2 study comparing bromfenac ophthalmic solution 0.18% QD with bromfenac ophthalmic solution 0.09% QD (Study CL-S&E-0802071-P) which demonstrated no difference between the concentrations and three Phase 3 studies comparing bromfenac ophthalmic solution 0.09% QD to placebo (Studies CL-S&E-0415081-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081- P) to support once daily use of bromfenac ophthalmic solution 0.09%. There has not been a head to head comparison between qd and bid dosing.

The applicant (b) (4) the acid, bromfenac ophthalmic solution, 0.09%. The acid is the active moiety and therefore the labeling refers to the product as a 0.09% concentration.

2. CMC/Sterility Assurance

There are no changes either for drug substance or drug product to the currently approved Xibrom drug product. All the CMC information remains as referenced to the currently approved NDA 21-664.

3. Nonclinical Pharmacology/Toxicology

No new non-clinical studies are submitted. From a Pharmacology/Toxicology prospective, the studies supporting the bid dosing also support the qd dosing.

4. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data was presented in this supplement. Based on the assessment of dose-response information from the Phase 2 and 3 studies, no clear dose-response for the primary efficacy endpoint nor for safety was observed between bromfenac ophthalmic solution 0.18% QD versus bromfenac ophthalmic solution 0.09% QD, nor for bromfenac ophthalmic solution 0.09% QD versus Xibrom 0.09% BID.

5. Clinical/Statistical - Efficacy

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 a Summed Ocular Inflammation Score **(**SOIS) of zero (i.e., zero cells and absence of flare) by Day 15.

Studies 0415081-P-ER (QD-ER) and 0415081-P-WR (QD-WR)

Study 0415081-P-ER (QD-ER) and Study 0415081-P-WR (QD-WR) were performed under a common (identical) protocol.

Cleared Ocular Inflammation by Each Visit (LOCF Analysis; ITT Population) - QD-ER

	Bromfenac N=63	Vehicle N=63	p-value
Day 1	3 (5%)	3 (5%)	1
Day 3	6 (10%)	7 (11%)	.77
Day 8	20 (32%)	15 (24%)	.32
Day 15	28 (44%)	20 (32%)	.14

Cleared Ocular Inflammation by Each Visit (LOCF Analysis; ITT Population) - QD-WR

	Bromfenac N=78	Vehicle N=78	p-value
Day 1	5 (6%)	9 (12%)	.26
Day 3	9 (12%)	10 (13%)	.80
Day 8	20 (26%)	14 (18%)	.24
Day 15	36 (46%)	23 (30%)	.03

Study 1205081-P (QDII)

Cleared Ocular Inflammation by Each Visit (LOCF Analysis; ITT Population) - Study QDII

	Bromfenac N=152	Vehicle N=147	p-value
Day 1	12 (8%)	9 (6%)	.55
Day 3	17 (11%)	12 (8%)	.38
Day 8	36 (24%)	23 (16%)	.08
Day 15	70 (46%)	36 (25%)	<.001

Studies WR and QDII demonstrate that bromfenac QD is statistically superior to placebo in the clearance of ocular inflammation on day 15. However, based cross study comparisons, the efficacy of qd dosing is inferior to bid dosing and equivalent to vehicle given once a day. As described in the labeling for the bid administration, clinical efficacy was evaluated in two randomized, double-masked, vehicle-controlled U.S. trials with the same primary endpoint as listed above. In the intent-to-treat analyses of both studies, a significant effect of XIBROM on ocular inflammation after cataract surgery was demonstrated (62-66% vs. 40-48%).

Analyses of Secondary Endpoints

A subject was considered to be pain free by a particular visit if there was a score of 'None' on the pain scale of the Ocular Comfort Grading Assessment in the subject diary at or prior to that visit.

The secondary efficacy endpoints for all three studies were also the same – defined as the proportion of subjects who had an ocular pain response of "None" in the study eye at Day 1.

Pain Free at Each Visit (LOCF Analysis; ITT Population) - QD-ER

	Bromfenac N=63	Vehicle N=63	p-value
Day 1	51 (81%)	46 (73%)	.29
Day 3	59 (94%)	53 (84%)	.09
Day 8	60 (95%)	57 (91%)	.49
Day 15	60 (95%)	59 (94%)	1

Pain Free at Each Visit (LOCF Analysis; ITT Population) - QD-WR

	Bromfenac N=78	Vehicle N=78	p-value
Day 1	65 (83%)	40 (52%)	<.001
Day 3	74 (95%)	51 (66%)	<.001
Day 8	75 (96%)	54 (70%)	<.001
Day 15	76 (97%)	57 (74%)	<.001

Pain Free at Each Visit (LOCF Analysis; ITT Population) – Study 1205081-P

	Bromfenac N=152	Vehicle N=147	p-value
Day 1	135 (89%)	105 (71%)	<.001
Day 3	139 (91%)	105 (71%)	<.001
Day 8	142 (93%)	106 (72%)	<.001
Day 15	145 (95%)	106 (73%)	<.001

Efficacy Summary Statement

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Bromday (bromfenac ophthalmic solution) 0.09% is statistically superior to placebo in the proportion of subjects who had cleared ocular inflammation in the study eye by Day 15 and is statistically superior to placebo for the absence of pain in the first day post-op. (b) (4)

(b) (4)

6. Safety

The Applicant utilized four studies in support of the safety of QD dosing of bromfenac ophthalmic solution 0.09% for this supplement: Study CL-S&E- 0802071-P [BromCom], Study CL-S&E-0415081-P-ER [QD-ER], CL-S&E-0415081- P-WR [QD-WR], and CL-S&E-1205081-P [QDII].

Study CL-S&E-0802071-P was a multi-center, randomized, double-masked, active-control study comparing bromfenac ophthalmic solution 0.18% once daily versus 0.09% once daily. The non-inferiority margin for study CL-S&E-0802071-P could not be justified clinically, and this study was not evaluated for efficacy purposes.

The safety is also supported by the studies which support the bid dosing and all of the class Warnings and Precautions are relevant to the qd dosing.

The most commonly reported adverse reactions in 2-7% of patients were eye inflammation, conjunctival hyperemia, and abnormal/foreign body sensation.

7. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application.

8. Pediatrics

PREA is triggered for this supplement because it is adding a new dosing regimen (QD dosing) to an approved product. 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 Bromday (bromfenac ophthalmic solution) 0.09% in pediatric patients have not been established.

9. Other Relevant Regulatory Issues

Pharmacology/Toxicology, Clinical Pharmacology, Clinical, CMC, and Biostatistics recommend approval of this supplemental new drug application.

DSI
A Division of Scientific Investigations (DSI) audit was requested; DSI completed their review on October 12, 2010. One domestic clinical investigator site was inspected in support of the NDA. In general, the studies at this site appear to have been conducted adequately and the data in support of the NDA appear reliable. Dr Sall's site was selected for inspection, mainly due to concerns with possible falsification of data by an individual previously in his employ. With respect to the concern raised by Dr. Sall regarding a prior employee's participation in the studies, it appears that this employee did not

have extensive involvement in the conduct of these studies. It appears that this employee was involved with the studies, but not to an extent where she could have adversely affected the studies and no evidence was noted that this employee's participation negatively impacted the conduct of the study. Further, there was no evidence to suggest falsification or record manipulation by her or any other study staff.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment evaluated "XiDay" as the proposed proprietary name for bromfenac ophthalmic solution. DMEPA found the name "Xiday" unacceptable in a letter dated April 23, 2010, and linked to the IND 60,295. This naming approach is confusing and misleading because it implies that XiDay (Bromfenac Sodium (b) (4) Ophthalmic Solution (b) (4) Xibrom (Bromfenac) Ophthalmic Solution, 0.09%, (b) (4) DMEPA also find the proposed proprietary name XiDay vulnerable to confusion with the medical abbreviation for "times one day" (*i.e.,* x 1 day). The proposed proprietary name XiDay may be misinterpreted as "times one day" when written on the same prescription/physician order with another medication (*i.e.,* another eye drop), medication errors can occur. ISTA proposed another proprietary name, Bromday (bromfenac sodium (b) (4) ophthalmic solution) (b) (4) in a subsequent submission dated May 25, 2010. In an amendment dated July 9, 2010, ISTA clarified: Once Bromday (bromfenac sodium (b) (4) ophthalmic solution) (b) (4) is approved, it will replace Xibrom (bromfenac ophthalmic solution) 0.09% as rapidly as the market will allow. (b) (4)

DMEPA granted the proprietary name "Bromday" for bromfenac sodium ophthalmic solution, 0.09% in a correspondence inked to the NDA dated August 23, 2010.

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Bromday (bromfenac ophthalmic solution) 0.09% and provided a separate review dated September 29, 2010.

10. Labeling

The labeling found below matches the currently approved Xibrom labeling except for the change in dosing frequency and is acceptable.

Proposed Trade Carton Label

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

11. Action

NDA 21-664 S-013, Bromday (bromfenac ophthalmic solution) 0.09% will be approved for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction. There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

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

/s/

WILEY A CHAMBERS
10/19/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

CROSS DISCIPLINE TEAM LEADER REVIEW

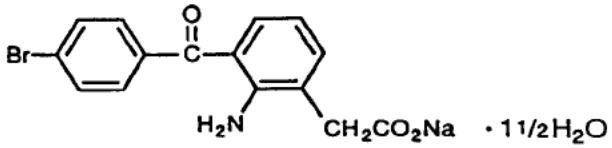
Cross-Discipline Team Leader Review for NDA 21-664 SE2 S-13

Date	October 8, 2010
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	21-664
Applicant	ISTA Pharmaceuticals
Date of Submission	December 16, 2009
PDUFA Goal Date	October 16, 2010
Type of Application	505(b)(1) efficacy supplement
Name	Bromday (bromfenac ophthalmic solution) 0.09%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction
Recommended:	Recommended for Approval

1. Introduction

Bromfenac ophthalmic solution is a non-steroidal anti-inflammatory drug (NSAID) studied for the treatment of postoperative inflammation and the reduction of pain in subjects who have undergone cataract extraction. The currently marketed product, Xibrom (bromfenac ophthalmic solution) 0.09%, administered twice daily (BID), is indicated for the treatment of postoperative inflammation and the reduction of pain in subjects who have undergone cataract extraction. Xibrom (bromfenac ophthalmic solution) 0.09% was approved by the US Food and Drug Administration (FDA) in March 2005 for the treatment of post-operative ocular inflammation and in January of 2006 for the treatment of post-operative pain when dosed twice daily.

The chemical structure for bromfenac sodium (b) (4) is:



Bromday (bromfenac ophthalmic solution) 0.09% may alternately be referred to by various review disciplines as XiDay (bromfenac sodium (b) (4) ophthalmic solution) (b) (4) throughout this review.

2. Background

This is a 505(b)(1) supplemental application.

In this efficacy supplement (S-013), bromfenac ophthalmic solution 0.09% is proposed for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction with the following dosing: instill one drop into the affected eye(s) once daily beginning one day prior to surgery, continued on the day of surgery and through the first 14 days post-surgery. This proposal represents a change from the currently approved BID dosing regimen to QD dosing.

(b) (4) The current application (NDA 21-664 SE 2 S-013) presents data from a dose-ranging Phase 2 study comparing bromfenac ophthalmic solution 0.18% QD with bromfenac ophthalmic solution 0.09% QD (Study CL-S&E-0802071-P) and three Phase 3 studies comparing bromfenac ophthalmic solution 0.09% QD to placebo (Studies CL-S&E-0415081-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081- P) to support once daily use of bromfenac ophthalmic solution 0.09%.

The applicant (b) (4) the acid, bromfenac ophthalmic solution, 0.09%.

3. CMC

From the CMC Reviews finalized 7/22/2010 and 9/10/2010:

This supplement provides for the change in dosing regime from the currently approved twice-a-day following cataract extraction surgery to once-a-day (QD) dosing beginning one day prior to surgery; continuing on the day of surgery and for 14 days after surgery.

ISTA originally intended to rename the already approved Xibrom (bromfenac ophthalmic solution) 0.09% drug product with the name XiDay (bromfenac sodium (b) (4) ophthalmic solution) (b) (4) %.

There are no changes either for drug substance or drug product to the currently approved Xibrom drug product. All the CMC information remains as referenced to the currently approved NDA 21-664.

Labeling was revised according to the suggestions made by the Agency. From the CMC point of view, this supplement is recommended for approval.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 7/7/2010:

No new non-clinical studies are submitted. The review of non-clinical studies contained in the initial submission of NDA 21-664 will not be repeated here.

The proposed labeling is similar to that of Xibrom which is currently marketed. The calculation of ratio of animal dose vs. human dose in the labeling is based on average human body weight of 60 kg. Since the recommended human daily dose of XiDay is one-half of Xibrom, the ratio of animal dose vs. human dose in the labeling should be recalculated.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 7/12/2010:

The approved product Xibrom (bromfenac ophthalmic solution) 0.09% is equivalent to the proposed bromfenac [sodium (b) (4) ophthalmic solution (b) (4) drug product formulation.

Specific clinical pharmacology findings from review of this efficacy supplement are summarized as follows:

- A comparison of proportion of subjects who had cleared ocular inflammation by Day 15 between bromfenac ophthalmic solution 0.09% QD and bromfenac 0.18% QD did not demonstrate dose-response relationship, i.e. there was no significant difference between bromfenac ophthalmic solution 0.09% QD data compared to that of bromfenac 0.18% QD. Pooled data from the Xibrom 0.09% BID treatment showed a greater proportion of subjects achieving the primary efficacy outcome compared to the pooled bromfenac ophthalmic solution 0.09% QD subjects, suggesting a dose-response when considering frequency of administration (i.e. total daily dose).
- No clear dose-response relationship for safety was observed for adverse events between bromfenac ophthalmic solution 0.18% QD versus bromfenac ophthalmic solution 0.09% QD, nor for bromfenac ophthalmic solution 0.09% QD versus Xibrom 0.09% BID.

No new clinical pharmacology data was presented in this supplement. Based on the assessment of dose-response information from the Phase 2 and 3 studies, no clear dose-response for the primary efficacy endpoint nor for safety was observed between bromfenac ophthalmic solution 0.18% QD versus bromfenac ophthalmic solution 0.09% QD, nor for bromfenac ophthalmic solution 0.09% QD versus Xibrom 0.09% BID.

6. Sterility Assurance

From the CMC Reviews finalized 7/22/2010 and 9/10/2010:

There are no changes either for drug substance or drug product to the currently approved Xibrom drug product. All the CMC information remains as referenced to the currently approved NDA 21-664.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 7/19/2010:

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 a Summed Ocular Inflammation Score **(**SOIS) of zero (i.e., zero 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.

Analyses of Primary Endpoints

Studies 0415081-P-ER (QD-ER) and 0415081-P-WR (QD-WR)

Study 0415081-P-ER (QD-ER) and Study 0415081-P-WR (QD-WR) were performed under a common (identical) protocol.

Subjects, N (%), with Cleared Ocular Inflammation by Each Visit (LOCF Analysis; ITT Population) - QD-ER

	Bromfenac ophthalmic solution 0.09% N = 63	Placebo N = 63	P-value
Cleared Ocular Inflammation [a]			
Day 1	3 (4.8%)	3 (4.8%)	1.0000 [b]
Day 3	6 (9.5%)	7 (11.1%)	0.7696 [c]
Day 8	20 (31.7%)	15 (23.8%)	0.3200 [c]
Day 15 (Primary Endpoint)	28 (44.4%)	20 (31.7%)	0.1422 [d]

Source: **Table 14.2.1.5**

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

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0167.

[c] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0167.

[d] Primary Efficacy Endpoint, p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using an alpha level of 0.05.

Summed Ocular Inflammation Score: Mean (SD) at Each Visit (LOCF Analysis, ITT Population) - Study QD-ER

	Bromfenac ophthalmic solution 0.09% N = 63	Placebo N = 63	P-value [a]
Baseline (Screening)	0.0 (0.0)	0.0 (0.0)	N/A
Day 1	2.7 (1.4)	2.7 (1.3)	0.9139
Day 3	2.3 (1.6)	2.6 (1.7)	0.1743
Day 8	1.5 (1.6)	2.6 (2.0)	0.0031
Day 15	1.3 (1.6)	2.5 (2.0)	0.0010
Day 22	1.0 (1.6)	2.2 (1.9)	0.0003

Source: **Table 14.2.1.11**

Note: The anterior chamber cells score component of the SOIS was transformed as follows: 0=0, 0.5=1, 1=2, 2=3, 3=4, and 4=5.

N/A = not applicable.

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Wilcoxon Rank Sum test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.01.

Subjects, N (%), with Cleared Ocular Inflammation by Each Visit (LOCF Analysis; ITT Population) - Study QD-WR

	Bromfenac ophthalmic solution 0.09% N = 78	Placebo N = 78	P-value
Cleared Ocular Inflammation [a]			
Day 1	5 (6.4%)	9 (11.5%)	0.2625 [b]
Day 3	9 (11.5%)	10 (12.8%)	0.8066 [b]
Day 8	20 (25.6%)	14 (17.9%)	0.2446 [b]
Day 15 (Primary Endpoint)	36 (46.2%)	23 (29.5%)	0.0318 [c]

Source: **Table 14.2.1.5**

[a] Cleared ocular inflammation by each visit is defined as a SOIS of Grade 0 at or prior to each visit.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0167.

[c] Primary Efficacy Endpoint, p-value is for bromfenac ophthalmic solution 0.09% versus placebo and is from the Chi-square test. Statistical significance is determined using an alpha level of 0.05.

Summed Ocular Inflammation Score: Mean (SD) at Each Visit (LOCF Analysis, ITT Population) - Study QD-WR

	Bromfenac Ophthalmic Solution 0.09% N = 78	Placebo N = 78	P-value [a]
Baseline (Screening)	0.0 (0.0)	0.0 (0.0)	N/A
Day 1	2.8 (1.4)	3.3 (1.7)	0.0192
Day 3	2.3 (1.4)	3.2 (1.9)	0.0017
Day 8	1.7 (1.6)	3.2 (2.0)	<0.0001
Day 15	1.3 (1.6)	2.8 (2.3)	<0.0001
Day 22	1.0 (1.7)	2.6 (2.4)	<0.0001

Source: Table 14.2.1.11

Note: The anterior chamber cells score component of the Summed Ocular Inflammation Score was transformed as follows: 0=0, 0.5=1, 1=2, 2=3, 3=4, and 4=5

N/A = not applicable.

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Wilcoxon Rank Sum test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.01.

Although Studies QD-ER and QD-WR were conducted under a common protocol, the results between these two trials are inconsistent. Study QD-ER fails to demonstrate efficacy for clearance of ocular inflammation while study QD-WR clearly demonstrates efficacy for this endpoint. Study QD-WR has approximately 30 more patients than QD-ER which may have contributed to this result.

Study 1205081-P (QDII)

Subjects, N (%), with Cleared Ocular Inflammation by Each Visit (LOCF Analysis; ITT Population) - Study QDII

	Bromfenac ophthalmic solution 0.09% N = 152	Placebo N = 147	P-value
Cleared Ocular Inflammation [a]			
Day 1	12 (7.9%)	9 (6.1%)	0.5488[b]
Day 3	17 (11.2%)	12 (8.2%)	0.3775 [b]
Day 8	36 (23.7%)	23 (15.6%)	0.0808 [b]
Day 15 (Primary Endpoint)	70 (46.1%)	36 (24.5%)	<0.0001[c]

Source: Table 14.2.1.1 and Table 14.2.1.5

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

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0167.

[c] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using an alpha level of 0.05.

Summed Ocular Inflammation Score: Mean (SD) at Each Visit (LOCF Analysis, ITT Population) - QDII

	Bromfenac ophthalmic solution 0.09% N = 152	Placebo N = 147	P-value [a]
Baseline (Screening)	0.0 (0.0)	0.0 (0.0)	N/A
Day 1	3.1 (1.6)	3.2 (1.7)	0.6271
Day 3	2.4 (1.5)	3.1 (1.8)	0.0011
Day 8	1.5 (1.4)	3.0 (1.9)	<0.0001
Day 15	1.0 (1.3)	2.8 (2.1)	<0.0001
Day 22	0.8 (1.3)	2.2 (2.2)	<0.0001

Source: Table 14.2.1.7

Note: The anterior chamber cells score component of the SOIS was transformed as follows: 0=0, 0.5=1, 1=2, 2=3, 3=4, and 4=5.

N/A = not applicable.

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Wilcoxon Rank Sum test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.01.

Study QDII demonstrates that bromfenac QD is statistically superior to placebo in the clearance of ocular inflammation on day 15. This study enrolled twice as many patients as the QD-ER and QD-WR trials.

Analyses of Secondary Endpoints

A subject was considered to be pain free by a particular visit if there was a score of 'None' on the pain scale of the Ocular Comfort Grading Assessment in the subject diary at or prior to that visit.

The secondary efficacy endpoints for all three studies were also the same – defined as the proportion of subjects who had an ocular pain response of "None" in the study eye at Day 1.

Studies 0415081-P-ER (QD-ER) and 0415081-P-WR (QD-WR)

Study 0415081-P-ER (QD-ER) and Study 0415081-P-WR (QD-WR) were performed under a common (identical) protocol.

Subjects, N (%), Pain Free by Each Visit (LOCF Analysis, ITT Population) - Study QD-ER

	Bromfenac ophthalmic solution 0.09% N = 63	Placebo N = 63	P-value
Day 1	51 (81.0%)	46 (73.0%)	0.2900 [a]
Day 3	59 (93.7%)	53 (84.1%)	0.0890 [a]
Day 8	60 (95.2%)	57 (90.5%)	0.4915 [b]
Day 15	60 (95.2%)	59 (93.7%)	1.0000 [b]

Source: **Table 14.2.4.3**

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0125.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0125.

Ocular Pain Score, Mean (SD), at Each Visit (LOCF Analysis, ITT Population) - Study QD-ER

	Bromfenac ophthalmic solution 0.09% N =63	Placebo N = 63	P-value [a]
Baseline	0.00 (0.00)	0.00 (0.00)	N/A
Day 1	0.19 (0.40)	0.32 (0.56)	0.2431
Day 3	0.16 (0.48)	0.40 (0.73)	0.0246
Day 8	0.08 (0.37)	0.43 (0.76)	0.0004
Day 15	0.10 (0.39)	0.40 (0.73)	0.0022

Source: **Table 14.2.4.9**

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Wilcoxon Rank Sum test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0125.

Subjects, N (%), Pain Free by Each Visit
(LOCF Analysis, ITT Population) - Study QD-WR

	bromfenac ophthalmic solution 0.09% N = 78	Placebo[c] N = 77	P-value[b]
Day 1	65 (83.3%)	40 (51.9%)	<0.0001
Day 3	74 (94.9%)	51 (66.2%)	<0.0001
Day 8	75 (96.2%)	54 (70.1%)	<0.0001
Day 15	76 (97.4%)	57 (74.0%)	<0.0001

Source: **Table 14.2.4.3**

[a] Grade 0 by each visit is defined as grade 0 on the pain scale of the Ocular Comfort Grading in the subject diary at or prior to each visit

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo, and is from the Chi-square test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0125.

[c] Subject 42-012-143 (placebo) had no pain entries in the diary for any visit; **Listing 16.2.6.2**

Ocular Pain Score, Mean (SD), at Each Visit
(LOCF Analysis, ITT Population) - Study QD-WR

	bromfenac ophthalmic solution 0.09% N = 78	Placebo[b] N = 78	P-value [a]
Subjects with pain scores [b]	n = 78	n = 77	
Baseline	0.00 (0.00)	0.00 (0.00)	N/A
Day 1	0.21 (0.49)	0.69 (0.85)	< 0.0001
Day 3	0.06 (0.29)	0.56 (0.80)	< 0.0001
Day 8	0.06 (0.25)	0.55 (0.80)	< 0.0001
Day 15	0.06 (0.25)	0.49 (0.79)	< 0.0001

Source: **Table 14.2.4.9**

Note: Obtained from the pain scale of the Ocular Comfort Grading in the subject diary.

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from Wilcoxon Rank Sum test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0125.

[b] Subject 42-012-143 (placebo) had no pain entries in the diary for any visit; **Listing 16.2.6.2**.

The ocular pain results were consistent with the primary efficacy endpoint conclusions.

Study QD-ER fails to demonstrate efficacy for pain while study QD-WR demonstrates that bromfenac 0.9% dosed QD is statistically superior to placebo for the absence of pain in the first day post-op.

Reanalysis of Study 0415081-P-WR (QD-WR) - Exclusion of Investigational Site

During the review of the NDA, information was submitted to the FDA noting possible data integrity issues at one of the investigational sites used for this efficacy supplement. Based on this, a for-cause DSI inspection request was made for Sall Research Medical Center (SRMC). ISTA was also asked to resubmit the data for each of the clinical trials omitting any data that was from the SRMC.

Subjects, N (%), with Cleared Ocular Inflammation by Each Visit - Reanalysis of Primary Endpoint – SMRC removed in Study QD-WR

	Bromfenac ophthalmic solution 0.09% N=75	**Placebo N=75**	**p-value**
Cleared ocular Inflammation			
Day 1	5 (6.7%)	9 (12%)	0.2616
Day 3	9 (12%)	10 (13.3%)	0.8061
Day 8	19 (25.3%)	14 (18.7%)	0.3244
Day 15 (primary endpoint)	35 (46.7%)	22 (29.3%)	0.0288

Summed Ocular Inflammation Score: Mean at Each Visit -Reanalysis of Primary Endpoint – SMRC removed in Study QD-WR

	Bromfenac ophthalmic solution 0.09% N=75	**Placebo N=75**	**p-value**
Baseline (Screening)	0	0	N/A
Day 1	2.8	3.2	0.0290
Day 3	2.3	3.1	0.0047
Day 8	1.7	3.3	<0.0001
Day 15	1.3	2.9	<0.0001
Day 22	1.0	2.7	<0.0001

The re-analysis of the data for study QD-WR with data from the SRMC site removed does not change the efficacy results for ocular inflammation for this study.

**Subjects, N (%), Pain Free by Each Visit -
Reanalysis of Secondary Endpoint – SMRC removed in Study QD-WR**

	Bromfenac ophthalmic solution 0.09% N=75	**Placebo N=75**	**p-value**
Day 1	62 (82.7%)	38 (51.4%)	<0.0001
Day 3	71 (94.7%)	48 (64.9%)	<0.0001
Day 8	72 (96%)	51 (68.9%)	<0.0001
Day 15	73 (97.3%)	54 (73%)	<0.0001

**Ocular Pain Score, Mean (SD), at Each Visit -
Reanalysis of Secondary Endpoint – SMRC removed in Study QD-WR**

	Bromfenac ophthalmic solution 0.09% N=75	**Placebo N=75**	**p-value**
Baseline	0	0	N/A
Day 1	0.21	0.70	<0.0001
Day 3	0.07	0.57	<0.0001
Day 8	0.07	0.55	<0.0001
Day 15	0.07	0.49	<0.0001

The re-analysis of the data for study QD-WR with data from the SRMC site removed does not change the efficacy results for absence of pain in the first day post-op for this study.

Efficacy Summary Statement

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Bromday (bromfenac ophthalmic solution) 0.09% (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 in the first day post-op.

8. Safety

The Applicant utilized four studies in support of the safety of QD dosing of bromfenac ophthalmic solution 0.09% for this supplement: Study CL-S&E- 0802071-P [BromCom], Study CL-S&E-0415081-P-ER [QD-ER], CL-S&E-0415081- P-WR [QD-WR], and CL-S&E-1205081-P [QDII].

Study CL-S&E-0802071-P was a multi-center, randomized, double-masked, active-control study comparing bromfenac ophthalmic solution 0.18% once daily versus 0.09% once daily. The non-inferiority margin for study CL-S&E-0802071-P could not be justified clinically, and this study was not evaluated for efficacy purposes.

From the original Medical Officer Review dated 7/19/2010:

Overall Exposure at Appropriate Doses/Durations

Subjects participating in studies QD-ER, QD-WR, QDII, and BromCom were assigned to receive bromfenac 0.09% QD for a maximum of 16 days. The mean number of doses received in the pooled analysis was 14.3 (1.0 to 16.0). There was over an 89% compliance rate in the pooled studies.

Subject Disposition

Study QD-ER

	Bromfenac ophthalmic solution 0.09%	Placebo	P-value
Number of Subjects Randomized	63	63	N/A
Subjects who Completed the Study [a]	61 (96.8%)	61 (96.8%)	1.0000 [b]
Subjects who Terminated the Study prior to Post-surgery Day 22 or prior to 1 Week Follow-up	2 (3.2%)	2 (3.2%)	- -
Primary Reason for Early Termination:			
Withdrawal of Consent/Non-compliance	1 (1.6%)	2 (3.2%)	1.0000 [b]
Lost to Follow-up	0 (0.0%)	0 (0.0%)	N/A
Death	0 (0.0%)	0 (0.0%)	N/A
Other [c]	1 (1.6%)	0 (0.0%)	1.0000 [b]

Source: Table 14.1.1.4

[a] A subject was considered to have completed the study if the subject either completed at or after post-surgery Day 22 or if the subject completed a follow-up visit 1 week (7 +3 days) after discontinuing investigational product.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test.

[c] The Other reason for early termination was cancelled surgery for 1 subject.

N/A: Not Applicable

Study QD-WR

	Bromfenac ophthalmic solution 0.09%	Placebo	P-value
Number of Subjects Randomized	78	78	N/A
Subjects who Completed the Study[a]	73 (93.6%)	72 (92.3%)	0.7545 [b]
Subjects who Terminated the Study prior to Post-surgery Day 22 or prior to 1 Week Follow-up	5 (6.4%)	6 (7.7%)	N/A
Primary Reason for Early Termination:			
Withdrawal of Consent/Non-compliance	2 (2.6%)	0 (0%)	0.4968 [c]
Lost to Follow-up	0 (0%)	0 (0%)	N/A
Death	0 (0%)	0 (0%)	N/A
Other	3 (3.8%)	6 (7.7%)	0.4947 [c]

Source: **Table 14.1.1.4**

[a] A subject was considered to have completed the study if the subject either completed at or after post-surgery Day 22 or if the subject completed a follow-up visit 1 week (7 +3 days) after discontinuing investigational product.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test

[c] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test

N/A: Not Applicable

Study QDII

	Bromfenac ophthalmic solution 0.09%	Placebo	P-value
Number of Subjects Randomized	152	147	- -
Subjects who Completed the Study [a]	146 (96.1 %)	144 (98.0%)	0.5017 [b]
Subjects who Terminated the Study prior to Post-surgery Day 22 or prior to 1 Week Follow-up	6 (3.9%)	3 (2.0%)	- -
Primary Reason for Early Termination:			
Withdrawal of Consent/Non-compliance	2 (1.3%)	1 (0.7%)	1.0000 [b]
Lost to Follow-up	0 (0.0%)	0 (0.0%)	N/A
Death	0 (0.0%)	0 (0.0%)	N/A
Other [c]	4 (2.6%)	2 (1.4%)	0.6846 [b]

Source: **Table 14.1.1.4**

[a] A subject was considered to have completed the study if the subject either completed at or after post-surgery Day 22 or if the subject completed a follow-up visit 1 week (7 +3 days) after discontinuing investigational product.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test.

[c] The "Other" reason for early termination was "cancelled surgery" for 5 subjects and "other – withdrew consent" for 1 subject (**Listing 16.2.1.1**).

Discontinued Investigational Product – Study QD-ER

	Bromfenac ophthalmic solution 0.09% N = 63	Placebo N = 63	P-value[a, b]
Subjects who discontinued investigational product	14 (22.2%)	31 (49.2%)	0.0016[b]
Primary reason for early discontinuation:			
AE	5 (7.9%)	9 (14.3%)	0.2568[b]
Disallowed concurrent medication	1 (1.6%)	0 (0.0%)	1.0000[a]
Lack of efficacy	6 (9.5%)	20 (31.7%)	0.0021[b]
Other [c]	2 (3.2%)	2 (3.2%)	1.0000[a]

Discontinued Investigational Product – Study QD-WR

	bromfenac ophthalmic solution 0.09% N = 78	Placebo N = 78	P-value
Subjects who discontinued investigational product	16 (20.5%)	47 (60.3%)	<0.0001 [a]
Primary reason for early discontinuation:			
AE	5 (6.4%)	12 (15.4%)	0.0721 [a]
Disallowed concurrent medication	1 (1.3%)	2 (2.6%)	1.0000 [b]
Lack of efficacy	2 (2.6%)	27 (34.6%)	<0.0001 [a]
Other [c]	8 (10.3%)	6 (7.7%)	0.5753 [a]

Discontinued Investigational Product – Study QDII

	Bromfenac ophthalmic solution 0.09% N = 152	Placebo N = 147	P-value[a, b]
Subjects who discontinued investigational product	29 (19.1%)	84 (57.1%)	<0.0001 [b]
Primary reason for early discontinuation:			
Adverse Event	8 (5.3%)	24 (16.3%)	0.0020[b]
Disallowed concurrent medication	3 (2.0%)	5 (3.4%)	0.4955[a]
Lack of efficacy	5 (3.3%)	47 (32.0%)	<0.0001[b]
Other	13 (8.6%)	8 (5.4%)	0.2927[b]

There were significantly more patients that discontinued the study in the placebo arm in these three trials. The main reason for discontinuing was lack of efficacy.

Adverse Events

Systemic Adverse Events Reported in any Treatment Group – Individual Trial Results

	BromCom		QD-ER		QD-WR		QDII	
	0.09% QD[1]	0.18% QD[1]	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD
Safety Population, N	278	266	61	61	73	73	147	144
Subjects with any Adverse Event, n (%)	83 (29.9)	65 (24.4)	24 (39.3)	36 (59.0)	20 (27.4)	31 (42.5)	69 (46.9)	86 (59.7)
p-value[2]	0.156		0.030		0.056		0.029	
Conjunctival infections, irritations and inflammations, n (%)								
Conjunctival hyperemia	19 (6.8)	13 (4.9)	2 (3.3)	1 (1.6)	0 (0.0)	2 (2.7)	7 (4.8)	9 (6.3)
Conjunctival edema	4 (1.4)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)	1 (0.7)	0 (0.0)
Ocular infections, inflammations and associated manifestions, n (%)								
Eye discharge	0 (0.0)	2 (0.8)	1 (1.6)	3 (4.9)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)
Eye inflammation	10 (3.6)	3 (1.1)*	8 (13.1)	14 (23.0)	4 (5.5)	10 (13.7)	15 (10.2)	21 (14.6)
Eye pruritus	1 (0.4)	1 (0.4)	6 (9.8)	2 (3.3)	0 (0.0)	0 (0.0)	8 (5.4)*	4 (2.8)
Ocular hyperemia	1 (0.4)	0 (0.0)	0 (0.0)	6 (9.8)	2 (2.7)	2 (2.7)	5 (3.4)*	15 (10.4)
Eye irritation	4 (1.4)	2 (0.8)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.4)	4 (2.7)	3 (2.1)*
Corneal infections, edemas and inflammations, n (%)								
Corneal edema	9 (3.2)	8 (3.0)	4 (6.6)	2 (3.3)	0 (0.0)	4 (5.5)	3 (2.0)	4 (2.8)
Conjunctival and corneal bleeding and vascular disorders, n (%)								
Conjunctival hemorrhage	8 (2.9)	7 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Eye and ear procedural complications, n (%)								
Eye operation complications	4 (1.4)	5 (1.9)	1 (1.6)	1 (1.6)	0 (0.0)	2 (2.7)	1 (0.7)	5 (3.5)
Eyelid movement disorders, n (%)								
Eyelid ptosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)*	0 (0.0)	0 (0.0)
Ocular disorders NEC, n (%)								
Eye pain	7 (2.5)	9 (3.4)	5 (8.2)	7 (11.5)	2 (2.7)	5 (6.8)	13 (8.8)	34 (23.6)
Ocular discomfort	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)	1 (1.4)	3 (4.1)	3 (2.0)	4 (2.8)

	BromCom		QD-ER		QD-WR		QDII	
	0.09% QD[1]	0.18% QD[1]	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD
Ocular sensation disorders, n (%)								
Abnormal sensation in eyes	6 (2.2)	5 (1.9)*	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)
Foreign body sensation in eyes	0 (0.0)	0 (0.0)	8 (13.1)	6 (9.8)	2 (2.7)*	1 (1.4)	18 (12.2)	21 (14.6)*
Photophobia	3 (1.1)	1 (0.4)	8 (13.1)	17 (27.9)	0 (0.0)	2 (2.7)	11 (7.5)	26 (18.1)
Iris and uveal tract infections, irritations and inflammations, n (%)								
Iridocyclitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Iritis	9 (3.2)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ciliary hyperemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	4 (2.8)
Lacrimal disorders, n (%)								
Lacrimation increased	1 (0.4)	2 (0.8)	3 (4.9)	6 (9.8)	0 (0.0)	3 (4.1)*	5 (3.4)	11 (7.6)
Lacrimation decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)*	0 (0.0)	0 (0.0)
Dry eye (keratoconjunctivitis sicca)	3 (1.1)*	1 (0.4)	0 (0.0)	0 (0.0)	2 (2.7)*	0 (0.0)	6 (4.1)**	2 (1.4)
Ophthalmic function diagnostic procedures, n (%)								
Intraocular pressure increased	5 (1.8)*	4 (1.5)	1 (1.6)	1 (1.6)	2 (2.7)	1 (1.4)	5 (3.4)	3 (2.1)
Visual disorders NEC, n (%)								
Vision blurred	1 (0.4)	0 (0.0)	4 (6.6)	2 (3.3)	0 (0.0)	0 (0.0)	15 (10.2)	11 (7.6)
Partial vision loss, n (%)								
Visual acuity reduced	2 (0.7)	1 (0.4)	2 (3.3)	1 (1.6)	0 (0.0)	0 (0.0)	2 (1.4)	1 (0.7)

	BromCom		QD-ER		QD-WR		QDII	
	0.09% QD[1]	0.18% QD[1]	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD
Retinal, choroid and vitreous infections and inflammations, n (%)								
Macular edema	1 (0.4)	0 (0.0)	1 (1.6)	2 (3.3)	0 (0.0)	1 (1.4)	2 (1.4)	1 (0.7)
Headaches NEC, n (%)								
Headache	13 (4.7)	5 (1.9)	1 (1.6)	0 (0.0)	1 (1.4)	1 (1.4)	4 (2.7)	2 (1.4)
Nausea and vomiting symptoms, n (%)								
Nausea	2 (0.7)	3 (1.1)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Rashes, eruptions and exanthems NEC, n (%)								
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.1)*	0 (0.0)	0 (0.0)	1 (0.7)

Systemic Adverse Events Reported in any Treatment Group – Pooled Data

	Bromfenac 0.09% QD Studies	
	Pooled 0.09%	Pooled Placebo
Safety Population, N	559	278
Subjects with any Adverse Event, n (%)	196 (35.1)	153 (55.0)
Cataracts (exludes congenital), n (%)		
Posterior capsule opacification	2 (0.4)	0 (0.0)
Conjunctival infections, irritations and inflammations, n (%)		
Conjunctival hyperemia	28 (5.0)	12 (4.3)
Conjunctival edema	5 (0.9)	2 (0.7)
Corneal disorders NEC, n (%)		
Descemet's membrane disorder	1 (0.2)	2 (0.7)
Corneal infections, edemas and inflammations, n (%)		
Corneal edema	16 (2.9)	10 (3.6)
Corneal structural change, deposit and degeneration, n (%)		
Corneal striae	0 (0.0)	1 (0.4)
Headaches, n (%)		
Headache	19 (3.4)	3 (1.1)
Iris and uveal tract infections, irritations and inflammations, n (%)		
Iritis	9 (1.6)	0 (0.0)
Lacrimal disorders, n (%)		
Lacrimation increased	9 (1.6)	19 (6.8)
Lid, lash and lacrimal infections, irritations and inflammations, n (%)		
Eyelid edema	2 (0.4)	1 (0.4)
Ocular disorders NEC, n (%)		
Eye pain	27 (4.8)	46 (16.5)
Ocular discomfort	5 (0.9)	7 (2.5)
Ocular infections, inflammations and associated manifestations, n (%)		
Eye inflammation	37 (6.6)	45 (16.2)
Eye irritation	8 (1.4)	5 (1.8)
Eye pruritus	15 (2.7)	6 (2.2)
Eye redness	4 (0.7)	0 (0.0)
Ocular hyperemia	7 (1.3)	23 (8.3)
Ocular sensation disorders, n (%)		
Abnormal sensation in eye	6 (1.1)	4 (1.4)
Foreign body sensation in eyes	28 (5.0)	28 (10.1)
Photophobia	22 (3.9)	45 (16.2)

	Bromfenac 0.09% QD Studies	
	Pooled 0.09%	Pooled Placebo
Ophthalmic function diagnostic procedures, n (%)		
Intraocular pressure increased	13 (2.3)	5 (1.8)
Partial vision loss, n (%)		
Vision blurred	1 (0.2)	0 (0.0)
Visual acuity reduced	6 (1.1)	2 (0.7)
Retinal, choroid and vitreous infections and inflammations, n (%)		
Macular edema	4 (0.7)	4 (1.4)
Visual disorders NEC, n (%)		
Vision blurred	19 (3.4)	13 (4.7)

The most commonly reported adverse reactions were eye inflammation, conjunctival hyperemia, foreign body sensation, eye pain, photophobia, headache, blurred vision, corneal edema, eye pruritus and increased IOP.

Adverse Events Leading to Discontinuation - QD-ER, QD-WR, QDII

Study QD-ER			
	Subject ID	**Treatment**	**Reason for Discontinuation**
	12-012-700	Bromfenac	Pain and photophobia
	14-008-604	Bromfenac	Dizziness, nausea, vomiting, neck pain
	47-004-560	Bromfenac	Conjunctival erythema, increased cell and flare, decreased vision
	48-001-629	Bromfenac	Intraoperative capsular tear
	12-06-650	Placebo	Photophobia
	12-010-698	Placebo	Photophobia, decreased vision
	17-001-529	Placebo	Pain, photophobia
	17-002-530	Placebo	Pain, photophobia, foreign body sensation, increased inflammation, blurred vision
	17-005-577	Placebo	Pain, redness, eyelid swelling, sensation of pressure
	17-009-665	Placebo	Pain, photophobia,
	34-006-573	Placebo	Iritis
	34-014-624	Placebo	Uveitis
	47-002-558	Placebo	Post-op inflammation, posterior capsule rupture
Study QD-WR			
	20-003-015	Bromfenac	Erythema
	46-003-035	Bromfenac	Increased post-op inflammation
	46-016-152	Bromfenac	Increased post-op inflammation
	52-007-139	Bromfenac	Facial rash
	54-006-178	Bromfenac	Eye surgery (pupil stretch)
	13-001-041	Placebo	Worsening inflammation
	13-006-074	Placebo	Ocular inflammation
	13-009-101	Placebo	photophobia
	30-009-113	Placebo	Posterior capsule opacification

	36-001-021	Placebo	Iritis
	42-003-047	Placebo	Iritis
	42-012-143	Placebo	Posterior capsule rupture
	43-006-097	Placebo	Iritis
	52-004-120	Placebo	Pain, photophobia
	52-005-137	Placebo	Pain, inflammation
	52-006-138	Placebo	Conjunctival edema, eye discomfort
	53-002-130	Placebo	Increased inflammation
Study QDII			
	15-20-191	Bromfenac	Constipation
	15-21-192	Bromfenac	Descemet's fold
	20-08-104	Bromfenac	Gout
	21-05-040	Bromfenac	Headache
	24-03-111	Bromfenac	Increased inflammation
	35-04-188	Bromfenac	Cataract wound leakage
	45-02-306	Bromfenac	Ocular hypertension
	52-01-353	Bromfenac	Pain, discharge, itching, foreign body sensation, photophobia
	01-02-034	placebo	Refractive surgery
	05-12-172	placebo	Foreign body sensation, soreness
	05-17-261	placebo	Posterior capsule rupture
	05-19-263	placebo	IOL dislocation
	10-03-031	placebo	Edema
	10-10-213	placebo	Corneal edema
	12-08-096	placebo	Erythema
	12-09-121	placebo	Conjunctival redness, ciliary flush
	20-04-068	placebo	Increased inflammation
	20-06-102	placebo	Inflammation
	20-07-103	placebo	Inflammation, foreign body sensation
	20-12-108	placebo	Pain, photophobia, conjunctival erythema, tearing
	22-03-079	placebo	Inflammation
	31-07-250	placebo	Brow ache
	35-01-185	placebo	Inflammation
	35-14-382	placebo	Inflammation
	37-03-147	placebo	Eyelid pain
	37-07-211	placebo	Inflammation
	42-03-219	placebo	Uveitis
	42-06-309	placebo	Uveitis
	50-03-299	placebo	Eye pain
	50-07-303	placebo	Cataract operation complication
	50-15-402	placebo	Pain, photophobia, foreign body sensation
	53-05-293	placebo	Redness, eye ache

The types of adverse events related to dropouts in each of the trials are similar between the drug and placebo groups. The adverse events reported are consistent with those expected following cataract surgery.

Deaths

No deaths were reported in the studies evaluating bromfenac ophthalmic solution 0.09% or 0.18% QD.

Safety Summary Statement

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Bromday (bromfenac ophthalmic solution) 0.09%, dosed one drop into the affected eye(s) once daily beginning 1 day prior to surgery, continued on the day of surgery and through the first 14 days post-surgery, is safe in the treatment of postoperative inflammation and pain associated with cataract surgery.

The most commonly reported adverse reactions in 2-7% of patients were eye inflammation, conjunctival hyperemia, and abnormal/foreign body sensation.

9. Advisory Committee Meeting

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

10. Pediatrics

PREA is triggered for this supplement because it is adding a new dosing regimen (QD dosing) to an approved product. 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 Bromday (bromfenac ophthalmic solution) 0.09% in pediatric patients have not been established.

11. Other Relevant Regulatory Issues

Pharmacology/Toxicology, Clinical Pharmacology, Clinical, CMC, and Biostatistics recommend approval of this supplemental new drug application.

DSI
A Division of Scientific Investigations (DSI) audit was requested; DSI completed their review on October 12, 2010.

Per the DSI review:

One domestic clinical investigator site was inspected in support of the NDA. In general, the studies at this site appear to have been conducted adequately and the data in support of the NDA appear reliable.

The preliminary classification of Clinical Investigator inspection of Dr. Sall is No Action Indicated (NAI).

Dr Sall's site was selected for inspection, mainly due to concerns with possible falsification of data by an individual previously in his employ. This inspection was a PDUFA/For-Cause inspection.

With respect to the concern raised by Dr. Sall regarding a prior employee's participation in the studies, it appears that this employee did not have extensive involvement in the conduct of these pivotal studies. It appears that this employee was involved with the studies, but not to an extent where she could have adversely affected the studies and no evidence was noted that this employee's participation negatively impacted the conduct of the study. Further, there was no evidence to suggest falsification or record manipulation by her or any other study staff.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment evaluated "XiDay" as the proposed proprietary name for bromfenac ophthalmic solution. DMEPA found the name "Xiday" unacceptable in a letter dated April 23, 2010, and linked to the IND 60,295:

1) We find the proposal to use a different proprietary and established name for the same product confusing and misleading. In your December 18, 2009 cover letter for the supplemental NDA, you stated that you intend to express the established name (b) (4) (b) (4) he active moiety itself, to "alleviate any confusion" created by marketing the same product under two different proprietary names. However, DMEPA believes that this naming approach actually increases the potential for confusion.

This naming approach is confusing and misleading because it implies that XiDay (Bromfenac Sodium (b) (4) Ophthalmic Solution, (b) (4) Xibrom (Bromfenac) Ophthalmic Solution, 0.09%, (b) (4)

2) We also find the proposed proprietary name XiDay vulnerable to confusion with the medical abbreviation for "times one day" (*i.e.,* x 1 day). The proposed proprietary name XiDay

> may be misinterpreted as "times one day" when written on the same prescription/physician order with another medication (*i.e.,* another eye drop), medication errors can occur.

ISTA proposed another proprietary name, Bromday (bromfenac sodium (b) (4) ophthalmic solution) (b) (4) in a subsequent submission dated May 25, 2010. In an amendment dated July 9, 2010, ISTA clarified:

> Once Bromday (bromfenac sodium (b) (4) ophthalmic solution) (b) (4) is approved, it will replace Xibrom (bromfenac ophthalmic solution) 0.09% as rapidly as the market will allow. (b) (4)

DMEPA granted the proprietary name "Bromday" for bromfenac sodium ophthalmic solution, 0.09% in a correspondence inked to the NDA dated August 23, 2010.

DMEPA provided recommendations on the packaging configuration in a separate review dated August 27, 2010.

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the draft product labeling, including the package insert (PI), draft carton label, and draft container label for Bromday (bromfenac ophthalmic solution) 0.09% and provided a separate review dated September 29, 2010.

BIOSTATISTICS

Per the Biostatistics consultative review finalized 8/10/2010:

The Applicant conducted four studies in support of the approval of this supplement. Study CL-S&E-0802071-P was a multi-center, randomized, double-masked, active-control study comparing bromfenac ophthalmic solution 0.18% once daily versus 0.09% once daily. The non-inferiority margin for study CL-S&E-0802071-P can not be justified clinically, and this study will not be evaluated for efficacy purposes. Studies CL-S&E-0415081-P-ER, CL-S&E-0415081- P-WR, and CL-S&E-1205081-P were all randomized, double-masked, multi-center, placebo controlled superiority studies; and they will be the focus of this statistical review for evaluating efficacy.

For studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P, the primary efficacy endpoints were the same – defined as the proportion of subjects who had cleared ocular inflammation in the study eye by Day 15. The secondary efficacy endpoints for all three studies were also the same – defined as the proportion of subjects who had an ocular pain response of "None" in the study eye at Day 1.

For study CL-S&E-0415081-P-ER, there was no statistically significance difference between the bromfenac group 44.4% (28/63) and the placebo group 31.7% (20/63) in the proportion of subjects who had cleared ocular inflammation by Day 15. The treatment difference was 12.7% with 95% CI of (-4.1%, 29.5%), and the p-value was 0.14.

Both studies CL-S&E-0415081-P-WR and CL-S&E-1205081-P showed a statistically significant difference between the bromfenac group and the placebo group in the proportion of subjects who had cleared ocular inflammation by Day 15.

For study CL-S&E-0415081-P-WR, the proportion of subjects who had cleared ocular inflammation by Day 15 was 46.2% (36/78) for the bromfenac group and 29.5% (23/78) for the placebo group. The treatment difference was 16.7% with 95% CI of (1.7%, 31.7%), and the p-value was 0.032.

For study CL-S&E-1205081-P, the proportion of subjects who had cleared ocular inflammation by Day 15 was 46.1% (70/152) for the bromfenac group and 24.5% (36/147) for the placebo group. The treatment difference was 21.6% with 95% CI of (11.0%, 32.1%), and the p-value was <0.0001.

For study CL-S&E-0415081-P-ER, there was no statistically significance difference between the bromfenac group 81.0% (51/63) and the placebo group 73.0% (46/63) in the proportion of subjects who had ocular pain response of "None" at Day 1. The treatment difference was 7.9% 95% CI of (-6.7%, 22.6%), and the p-value was 0.29.

Both studies CL-S&E-0415081-P-WR and CL-S&E-1205081-P showed statistically significant difference between the bromfenac group and the placebo group in the proportion of subjects who had ocular pain response of "None" at Day 1.

For study CL-S&E-0415081-P-WR, the proportion of subjects who had ocular pain response of "None" at Day 1 was 83.3% (65/78) for the bromfenac group and 51.9% (40/78) for the placebo group. The treatment difference was 31.4% with 95% CI of (17.5%, 45.3%), and the p-value was <0.0001.

For study CL-S&E-1205081-P, the proportion of subjects who had cleared ocular inflammation by Day 15 was 88.8% (135/152) for the bromfenac group and 71.4% (105/147) for the placebo group. The treatment difference is 17.4% with 95% CI of (8.5%, 26.2%), and the p-value was 0.0002.

12. Labeling

NDA 21-664 SE2 S-013, Bromday (bromfenac ophthalmic solution) 0.09% is recommended for approval for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.

The labeling found in the Appendix at the end of this CDTL review (submitted by ISTA Pharmaceuticals, Inc. on 10/8/10) is acceptable.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 21-664 SE2 S-013, Bromday (bromfenac ophthalmic solution) 0.09% is recommended for approval for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.

RISK BENEFIT ASSESSMENT:
There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Bromday (bromfenac ophthalmic solution) 0.09% (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 in the first day post-op.

The most commonly reported adverse reactions in 2-7% of patients were eye inflammation, conjunctival hyperemia, and abnormal/foreign body sensation.

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

Pharmacology/Toxicology, Biostatistics, Clinical, Clinical Pharmacology, and CMC have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

Appendix

The labeling found in this Appendix and submitted by ISTA Pharmaceuticals on 9/15/10 (carton/container) and 10/8/10 (package insert) is acceptable.

9 Page(s) 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
10/13/2010

WILEY A CHAMBERS
10/16/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

MEDICAL REVIEW(S)

Team Leader Memorandum

NDA#	21-664 (SE2-013)
SUBMISSION DATE	December 16, 2009
DRUG NAME	Bromfenac sodium (b) (4)
BRAND NAME	XiDay™
FORMULATION	Ophthalmic solution, (b) (4)
SPONSOR	ISTA Pharmaceuticals, Inc.
REVIEWER	Kimberly L. Bergman, Pharm.D.
TEAM LEADER	Charles R. Bonapace, Pharm.D.

Bromfenac ophthalmic solution 0.09% (Xibrom™) is a non-steroidal anti-inflammatory drug approved for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction. The approved dosage regimen is one drop to the affected eye(s) two times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

In the current submission (SE2-013), bromfenac ophthalmic solution (b) (4) is proposed for the treatment of (b) (4). The proposed dosage regimen of bromfenac ophthalmic solution (b) (4) is one drop to the affected eye(s) once daily beginning one day prior to surgery, continued on the day of surgery and through the first 14 days post-surgery. Since the proposed drug product (bromfenac ophthalmic solution (b) (4)) is equivalent to the approved drug product Xibrom™ (bromfenac ophthalmic solution) 0.09%, it is referred to as bromfenac ophthalmic solution 0.09%.

In support of the new dosage regimen, the sponsor performed a dose-ranging Phase 2 study comparing bromfenac ophthalmic solution 0.18% once daily with bromfenac ophthalmic solution 0.09% once daily and three Phase 3 studies comparing bromfenac ophthalmic solution 0.09% once daily to placebo. The Sponsor's analysis of efficacy also included a cross-study comparison between bromfenac ophthalmic solution 0.09% once daily and Xibrom™ (bromfenac ophthalmic solution) 0.09% two times daily (based on studies previously submitted to NDA 21-664). No new clinical pharmacology data were submitted with this supplement.

I concur with Dr. Bergman's conclusions that no dose-response relationship was observed between bromfenac ophthalmic solution 0.18% once daily versus bromfenac ophthalmic solution 0.09% once daily or bromfenac ophthalmic solution 0.09% once daily versus Xibrom™ 0.09% two times daily. The Sponsor's analyses support the proposed dosage regimen of one drop to the affected eye(s) once daily beginning one day prior to surgery, continued on the day of surgery and through the first 14 days post-surgery for bromfenac ophthalmic solution 0.09%.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

CHARLES R BONAPACE
09/08/2010

CLINICAL REVIEW

Application Type	SE 2
Application Number(s)	NDA 21-664
Priority or Standard	Standard
Submit Date(s)	December 16, 2009
Received Date(s)	December 16, 2009
PDUFA Goal Date	October 16, 2010
Division / Office	DAIOP/OAP
Reviewer Name(s)	Jennifer D. Harris, M.D.
Review Completion Date	June 23, 2010
Established Name	bromfenac sodium ophthalmic solution
(Proposed) Trade Names	Xi Day, Bromday, (b) (4)
Therapeutic Class	Non-steroidal anti-inflammatory
Applicant	ISTA Pharmaceuticals
Formulation(s)	bromfenac ophthalmic solution 0.09%
Dosing Regimen	One drop QD
Indication(s)	Treatment of ocular inflammation and pain following cataract surgery
Intended Population(s)	Patients who have undergone

cataract surgery

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 21-664/S-013 Xibrom (bromfenac ophthalmic solution) 0.09% is recommended for approval for the treatment of inflammation and pain following cataract surgery.

1.2 Risk Benefit Assessment

Xibrom (bromfenac ophthalmic sodium) 0.09% BID is currently marketed for treatment of treatment of post-operative ocular inflammation and pain. Three phase 3 studies comparing bromfenac ophthalmic solution 0.09% QD to placebo (QD-ER, QD-WR and QDII were submitted in this supplement to demonstrate efficacy for once a day dosing of the product. QD-WR and QDII demonstrated 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.

Study QD-ER and QD-WR were conducted under a common protocol; however, the results between these two trials are inconsistent. Study QD-ER failed to demonstrate efficacy for clearance of ocular inflammation and pain while study QD-WR demonstrated efficacy for these endpoint. The third study, study QDII replicated the results of QD-WR and demonstrated that bromfenac QD is statistically superior to placebo in the clearance of ocular inflammation and pain.

Overall, the types of adverse events were similar between the treatment group and vehicle on all three trials. The adverse events reported were consistent with those expected following cataract surgery. The most commonly reported adverse reactions were eye inflammation, conjunctival hyperemia, foreign body sensation, eye pain, photophobia, headache, blurred vision, corneal edema, eye pruritus and increased IOP.

The safety profile for the QD dosing regimen of bromfenac is consistent with other products in the class of topical non-steroidal anti-inflammatory drugs, and the efficacy of this product has been replicated on two phase 3 trials.

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:	Xibrom
Xibrom:	bromfenac ophthalmic solution 0.09%
Sponsor:	ISTA Pharmaceuticals 15279 Alton Parkway, Suite 100 Irvine, CA 92618
Chemical Class:	3S
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 currently two topical drugs approved for inflammation and pain following cataract surgery:

Bromfenac ophthalmic solution 0.09%
Nepafenac ophthalmic solution 0.1%

2.3 Availability of Proposed Active Ingredient in the United States

Bromfenac ophthalmic solution 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

Xibrom (bromfenac ophthalmic sodium) 0.09% BID was approved in March 2005 for the treatment of post-operative ocular inflammation and in January of 2006 for the treatment of post-operative pain (b) (4) Data from this clinical development program demonstrated that the 0.09% and 0.18% 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.

2.6 Other Relevant Background Information

N/A – see section 2.5

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of sufficient quality to allow for a substantive review. During the review of the NDA information was submitted to the FDA noting data integrity issues at one of the investigational sites used for this efficacy supplement. These issues involved an ophthalmic technician. It is unknown at this time whether the problem extended to this study. Based on this, a for cause inspection request was conducted at Sall Research Medical Center (SRMC). The sponsor was also asked to resubmit the data for each of the clinical trials omitting any data that was from the SRMC.

3.2 Compliance with Good Clinical Practices

During the review of the NDA information was submitted to the FDA noting data integrity issues at one of the investigational sites used for this efficacy supplement. Based on this, a for cause DSI inspection request was requested fort Sall Research Medical

Center (SRMC). The sponsor was also asked to resubmit the data for each of the clinical trials omitting any data that was from the SRMC.

3.3 Financial Disclosures

Financial disclosure information has been provided by ISTA, Inc. for the covered clinical studies in this supplement. A review of this data does not indicate a potential impact on the clinical study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The overview of chemistry manufacturing and controls has been previously submitted in original NDA. This drug product is unchanged from the originally approved product.

4.2 Clinical Microbiology

The overview of product microbiology has been previously submitted in original NDA.

4.3 Preclinical Pharmacology/Toxicology

No new biopharmaceutics studies were performed for this supplemental NDA submission.

4.4 Clinical Pharmacology

No new clinical pharmacology studies were performed for this supplemental NDA submission.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study	Study Design	Test product	Number of Subjects	Duration of Treatment
CL-S&E-	Phase 3 double-	Bromfenac	126	16 days

0415081-P-ER	masked, placebo controlled	0.09% 1 drop QD		
CL-S&E-0415081-P-WR	Phase 3 double-masked, placebo controlled	Bromfenac 0.09% 1 drop QD	156	16 days
CL-S&E-1205081-P	Phase 3 double-masked, placebo controlled	Bromfenac 0.09% 1 drop QD	299	16 days

5.2 Review Strategy

Each of the phase 3 trials described in these sections were reviewed independently for the demonstration of efficacy. The results of these trials were each weighted equally in the determination of the overall efficacy for this product.

5.3 Discussion of Individual Studies/Clinical Trials

Study 0415081-P-ER (QD-ER) and Study 0415081-P-WR (QD-WR) were performed under a common protocol.

Efficacy and Safety of Xibrom™ (Bromfenac Ophthalmic Solution) 0.09% QD vs. Placebo QD for Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery

Objectives:
Primary Objective: To investigate the efficacy of bromfenac ophthalmic solution 0.09% QD for the treatment of ocular inflammation associated with cataract surgery in subjects who have undergone cataract extraction with posterior chamber intraocular lens implantation.

Secondary Objective: To investigate the efficacy of bromfenac ophthalmic solution 0.09% QD for the treatment of ocular pain associated with cataract surgery in subjects who have undergone cataract extraction with posterior chamber intraocular lens implantation.

Other Objective: The safety of bromfenac ophthalmic solution 0.09% administered once daily (QD) was evaluated.

Methodology:

This was a multi-center, randomized, double masked, parallel group, and placebo (vehicle) controlled study. The data for the study was collected under a common protocol conducted as two individual studies and analyzed as two separate studies.

Subjects were screened between 1 and 8 days prior to the initiation of dosing with the investigational product. Subjects who signed the informed consent form and met all inclusion/exclusion criteria were randomized to receive either bromfenac ophthalmic solution 0.09% or placebo, in a ratio of 1:1.

Subjects instilled 1 drop of investigational product into the study (operative) eye once daily for a maximum of 16 days. Dosing with investigational product began 1 day prior to surgery (Day -1), and continued on the day of surgery and for 14 days after cataract surgery.

Subjects were evaluated for ocular inflammation, pain and photophobia on Days 1, 3±1, 8±1, and 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 investigational product if subjects discontinued prematurely the investigational product.

Schedule of Events

Table 3: Schedule of Events

	Pre-Surgery		Surgery		Post-Surgery				Study Termination
			Visit 1 Day 0						
Procedures	Screening Visit Day –8 to –1	1st Dose Day -1	Pre-Surgery	Post-Surgery	Visit 2 Day 1	Visit 3 Day 3±1	Visit 4 Day 8 ±1	Visit 5 Day 15±1 or Early D/C of investigational product[a]	Visit 6 Day 22+3 or 7+3 days after last dose of investigational product
Informed Consent	X								
Medical History/Demographics	X								
Inclusion/Exclusion Criteria	X								
Vital Signs	X								
Visual Acuity	X[b,h]				X[c,i]	X[c,i]	X[c,i]	X[c,i]	X[b,h]
Pupillary Exam	X[b]								X[b]
Biomicroscopy	X[b]				X[c]	X[c]	X[c]	X[c]	X[b]
Intraocular Pressure[d]	X[b]				X[c]	X[c]	X[c]	X[c]	X[b]
Funduscopic Exam (dilated)	X[b]								X[b]
Urine Pregnancy Test[e]	X								
Dispense Investigational Product/Dosing Instructions Diary	X								
Begin Investigational Product Dosing[f]		X							
Ocular Comfort Grading Assessment	X	X[g]							
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

[a] Visit must have occurred within 48 hours after the last dose of investigational product.
[b] Ophthalmic examinations were conducted in both eyes.
[c] Ophthalmic examinations were conducted in study (operative) eye only.
[d] Goldmann tonometry was preferred; adjusted following pachymetry if necessary.
[e] Applied only to females capable of becoming pregnant.
[f] Investigational product was self-administered by subjects, 1 drop once daily, from Study Days 1 to 14.
[g] Beginning on Day 1, subjects completed the Ocular Comfort Grading Assessment in the Diary within 1 hour after each dose of investigational product was instilled into the study (operative) eye.
[h] Best corrected visual acuity.
[i] Uncorrected visual acuity.

Diagnosis and Main Criteria for Inclusion:

Subjects who required unilateral cataract surgery (phacoemulsification or extracapsular) with posterior chamber intraocular lens implantation and who met all other inclusion/exclusion criteria were eligible to enter the study.

Efficacy:

The primary efficacy outcome, cleared ocular inflammation by Day 15 was defined as a summed ocular inflammation score (SOIS) of grade 0 (0 cells and absence of flare) at any visit prior to and including Day 15. The secondary efficacy outcome was the proportion of subjects that were pain free (i.e., pain grading of 'None' on the Ocular Comfort Grading Assessment) at Day 1. The following additional efficacy analyses of SOIS, anterior chamber cells, flare score, and ocular pain were conducted on the ITT population:

- Proportions of subjects with Grade 0 for the SOIS, anterior chamber cells, anterior chamber flare, and grades of "none" for pain by each visit.
- Proportions of subjects with Grade 0 for the SOIS, anterior chamber cells, anterior chamber flare, and grades of "none" for pain at each visit.

- Proportions of subjects with Grade 0 for the SOIS, anterior chamber cells, anterior chamber flare, and grades of "none" for pain at each visit that remained unchanged through Day 15 (i.e., cure).
- Mean values for the SOIS, anterior chamber cells, anterior chamber flare, and pain, at each visit.

Statistical differences between the bromfenac ophthalmic solution 0.09% and placebo subjects was determined using the chi square or Fisher's Exact Test.

Study 1205081-P (QDII)

Efficacy and Safety of Bromfenac Ophthalmic Solution QD vs. Placebo QD for Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery

Objective:
The primary objective of this study was to investigate the efficacy of bromfenac ophthalmic solution 0.09% QD for the treatment of ocular inflammation associated with cataract surgery in subjects who had undergone cataract extraction with posterior chamber intraocular lens implantation.

Safety measured:

- Adverse Events (reports, elicited, and observed)
- Visual Acuity
- Slit Lamp Biomicroscopy
- Intraocular pressure
- Funduscopic examination (dilated)
- Ocular Comfort Grading Assessment (recorded in the subject diary)

The secondary objective was to investigate the efficacy of bromfencac 0.09 % QD for the treatment of ocular pain.

Methodology:
This was a multi-center (44 sites), randomized, double-masked, parallel-group, and placebo-controlled study. Subjects were screened between 1 and 8 days prior to initiation of dosing with the investigational product. Subjects who signed the informed consent and met all inclusion/exclusion criteria were randomized to receive either bromfenac ophthalmic solution 0.09% or placebo (1:1)

Subjects were seen for evaluation on Days 1, 3 ± 1, and 15 ± 1 following cataract surgery. In addition, subjects were seen for a follow-up visit on Day 22 ± 3 following surgery or 7 ± 3 days after their last dose of the investigational product.

Schedule of Events

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

Diagnosis and Main Criteria for Inclusion:

Subjects who required unilateral cataract surgery (phacoemulsification or extracapsular) with posterior chamber intraocular lens implantation and who met all other inclusion/exclusion criteria were eligible to enter the study.

Efficacy:
The primary efficacy outcome, cleared ocular inflammation by Day 15, was defined as a SOIS of grade 0 (0 cells and absence of flare) at any visit prior to and including Day 15. The secondary efficacy outcome was the proportion of subjects who were pain free (i.e., pain grading of 'None' on the Ocular Comfort Grading Assessment) at Day 1.

Two analyses of efficacy were performed: an analysis of data based on last observation carried forward (LOCF) and an analysis of data based on observed cases (OC). Safety analyses were conducted on the Safety population, defined as all randomized subjects who received at least 1 dose of investigational product. The bromfenac ophthalmic solution 0.09% treatment group and the placebo treatment group were compared using Chi square or Fisher's exact test for dichotomous or categorical measures and t-test or Wilcoxon Rank Sum test for continuous variables.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The indication sought for bromfenac ophthalmic solution 0.09% is the same as the currently market dosage form: the treatment of post-operative ocular inflammation and pain in subjects who have undergone cataract extraction with posterior chamber intraocular lens implantation.

6.1.1 Methods

A list of the clinical trials used to demonstrate efficacy for this indication is located in section 5.1. A description of the trial designs are in section 5.3.

6.1.2 Demographics

Study QD-ER

	Bromfenac ophthalmic solution 0.09% N = 63	Placebo N = 63	Total N = 126	P-value
Age (years)				0.3838 [a]
Mean (SD)	67.1 (10.8)	68.6 (8.6)	67.9 (9.8)	- -
Range	41.0, 86.0	51.0, 87.0	41.0, 87.0	- -
Gender (n, %)				0.7137 [b]
Male	23 (36.5%)	25 (39.7%)	48 (38.1%)	- -
Female	40 (63.5%)	38 (60.3%)	78 (61.9%)	- -
Race (n, %)				1.0000 [c]
Asian	0 (0.0%)	1 (1.6%)	1 (0.8%)	- -
Black	4 (6.3%)	4 (6.3%)	8 (6.3%)	- -
Caucasian	53 (84.1%)	53 (84.1%)	106 (84.1%)	- -
Hispanic	5 (7.9%)	4 (6.3%)	9 (7.1%)	- -
Native American	0 (0.0%)	0 (0.0%)	0 (0.0%)	- -
Other [d]	1 (1.6%)	1 (1.6%)	2 (1.6%)	- -
Iris Color (study eye) (n, %)				0.5152 [b]
Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	- -
Blue	22 (34.9%)	22 (34.9%)	44 (34.9%)	- -
Brown	25 (39.7%)	28 (44.4%)	53 (42.1%)	- -
Gray	0 (0.0%)	2 (3.2%)	2 (1.6%)	- -
Green	6 (9.5%)	5 (7.9%)	11 (8.7%)	- -
Hazel	10 (15.9%)	6 (9.5%)	16 (12.7%)	- -
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	- -
Iris Color (study eye) (n, %)[e]				0.7215 [b]
Light Irides	32 (50.8%)	30 (47.6%)	62 (49.2%)	- -
Dark Irides	31 (49.2%)	33 (52.4%)	64 (50.8%)	- -

Source: **Table 14.1.2.1**

[a] P-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from a t-test.

[b] P-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test.

[c] P-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test.

[d] Other races included: Pakistani (1 subject) and Philipino (1 subject) **(Listing 16.2.4.1)**.

[e] Light Irides: Blue, Gray, Hazel, Other. Dark Irides: Black, Brown, Green

Study QD-WR

	Bromfenac ophthalmic solution 0.09% N = 78	Placebo N = 78	Total N = 156	P-value
Age (years)				0.6456 [a]
Mean (SD)	68.7 (11.1)	68.0 (9.7)	68.4 (10.4)	- -
Range	27.0, 90.0	43.0, 86.0	27.0, 90.0	- -
Gender (n, %)				0.6245 [b]
Male	33 (42.3%)	30 (38.5%)	63 (40.4%)	- -
Female	45 (57.7%)	48 (61.5%)	93 (59.6%)	- -
Race (n, %)				0.3285[c]
Asian	3 (3.8%)	4 (5.1%)	7 (4.5%)	- -
Black	3 (3.8%)	10 (12.8%)	13 (8.3%)	- -
Caucasian	59 (75.6%)	53 (67.9%)	112 (71.8%)	- -
Hispanic	11 (14.1%)	10 (12.8%)	21 (13.5%)	- -
Native American	2 (2.6%)	1 (1.3%)	3 (1.9%)	- -
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	- -
Iris Color (study eye) (n, %)				0.9864 [c]
Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	- -
Blue	24 (30.8%)	23 (29.5%)	47 (30.1%)	- -
Brown	35 (44.9%)	38 (48.7%)	73 (46.8%)	- -
Gray	0 (0.0%)	0 (0.0%)	0 (0.0%)	- -
Green	4 (5.1%)	4 (5.1%)	8 (5.1%)	- -
Hazel	14 (17.9%)	12 (15.4%)	26 (16.7%)	- -
Other	1 (1.3%)	1 (1.3%)	2 (1.3%)	- -
Iris Color (study eye) [d] (n, %)				0.6307 [b]
Light Irides	39 (50.0%)	36 (46.2%)	75 (48.1%)	- -
Dark Irides	39 (50.0%)	42 (53.8%)	81 (51.9%)	- -

Source: **Table 14.1.2.1**

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from a t-test.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test.

[c] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test.

[d] Light Irides: Blue, Gray, Hazel, Other; Dark Irides: Black, Brown, Green

Study QDII

	Bromfenac ophthalmic solution 0.09% N = 152	Placebo N = 147	Total N = 299	P-value
Age (years)				0.2877 [a]
Mean (SD)	70.4 (10.1)	69.1 (10.4)	69.8 (10.2)	- -
Range	34.0, 87.0	40.0, 90.0	34.0, 90.0	- -
Gender (n, %)				0.1156 [b]
Male	63 (41.4%)	48 (32.7%)	111 (37.1%)	- -
Female	89 (58.6%)	99 (67.3%)	188 (62.9%)	- -
Race (n, %)				0.1814 [c]
Asian	5 (3.3%)	3 (2.0%)	8 (2.7%)	- -
Black	13 (8.6%)	10 (6.8%)	23 (7.7%)	- -
Caucasian	113 (74.3%)	109 (74.1%)	222 (74.2%)	- -
Hispanic	17 (11.2%)	25 (17.0%)	42 (14.0%)	- -
Native American	0 (0.0%)	0 (0.0%)	0 (0.0%)	- -
Other [d]	4 (2.6%)	0 (0.0%)	4 (1.3%)	- -
Iris Color (study eye) (n, %)				0.3172 [c]
Black	1 (0.7%)	1 (0.7%)	2 (0.7%)	- -
Blue	46 (30.3%)	33 (22.4%)	79 (26.4%)	- -
Brown	69 (45.4%)	83 (56.5%)	152 (50.8%)	- -
Gray	1 (0.7%)	1 (0.7%)	2 (0.7%)	- -
Green	13 (8.6%)	7 (4.8%)	20 (6.7%)	- -
Hazel	22 (14.5%)	22 (15.0%)	44 (14.7%)	- -
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	- -
Iris Color (study eye) (n, %)[e]				0.2008 [b]
Light Irides	69 (45.4%)	56 (38.1%)	125 (41.8%)	- -
Dark Irides	83 (54.6%)	91 (61.9%)	174 (58.2%)	- -

Source: **Table 14.1.2.1**

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from a t-test.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test.

[c] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test.

[d] Other races included Middle Eastern (1 subject, 03-06-142), Armenian (1 subject, 03-08-144), Arabic (1 subject, 09-03-007), Egyptian (1 subject, 21-08-227) (**Listing 16.2.4.1**)

[e] Light Irides: Blue, Gray, Hazel, Other. Dark Irides: Black, Brown, Green

6.1.3 Subject Disposition

Study QD-ER

	Bromfenac ophthalmic solution 0.09%	Placebo	P-value
Number of Subjects Randomized	63	63	N/A
Subjects who Completed the Study [a]	61 (96.8%)	61 (96.8%)	1.0000 [b]
Subjects who Terminated the Study prior to Post-surgery Day 22 or prior to 1 Week Follow-up	2 (3.2%)	2 (3.2%)	- -
Primary Reason for Early Termination:			
Withdrawal of Consent/Non-compliance	1 (1.6%)	2 (3.2%)	1.0000 [b]
Lost to Follow-up	0 (0.0%)	0 (0.0%)	N/A
Death	0 (0.0%)	0 (0.0%)	N/A
Other [c]	1 (1.6%)	0 (0.0%)	1.0000 [b]

Source: **Table 14.1.1.4**

[a] A subject was considered to have completed the study if the subject either completed at or after post-surgery Day 22 or if the subject completed a follow-up visit 1 week (7 +3 days) after discontinuing investigational product.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test.

[c] The Other reason for early termination was cancelled surgery for 1 subject.

N/A: Not Applicable

Study QD-WR

	Bromfenac ophthalmic solution 0.09%	Placebo	P-value
Number of Subjects Randomized	78	78	N/A
Subjects who Completed the Study[a]	73 (93.6%)	72 (92.3%)	0.7545 [b]
Subjects who Terminated the Study prior to Post-surgery Day 22 or prior to 1 Week Follow-up	5 (6.4%)	6 (7.7%)	N/A
Primary Reason for Early Termination:			
Withdrawal of Consent/Non-compliance	2 (2.6%)	0 (0%)	0.4968 [c]
Lost to Follow-up	0 (0%)	0 (0%)	N/A
Death	0 (0%)	0 (0%)	N/A
Other	3 (3.8%)	6 (7.7%)	0.4947 [c]

Source: **Table 14.1.1.4**

[a] A subject was considered to have completed the study if the subject either completed at or after post-surgery Day 22 or if the subject completed a follow-up visit 1 week (7 +3 days) after discontinuing investigational product.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test

[c] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test

N/A: Not Applicable

Study QDII

	Bromfenac ophthalmic solution 0.09%	Placebo	P-value
Number of Subjects Randomized	152	147	- -
Subjects who Completed the Study [a]	146 (96.1 %)	144 (98.0%)	0.5017 [b]
Subjects who Terminated the Study prior to Post-surgery Day 22 or prior to 1 Week Follow-up	6 (3.9%)	3 (2.0%)	- -
Primary Reason for Early Termination:			
Withdrawal of Consent/Non-compliance	2 (1.3%)	1 (0.7%)	1.0000 [b]
Lost to Follow-up	0 (0.0%)	0 (0.0%)	N/A
Death	0 (0.0%)	0 (0.0%)	N/A
Other [c]	4 (2.6%)	2 (1.4%)	0.6846 [b]

Source: **Table 14.1.1.4**

[a] A subject was considered to have completed the study if the subject either completed at or after post-surgery Day 22 or if the subject completed a follow-up visit 1 week (7 +3 days) after discontinuing investigational product.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test.

[c] The "Other" reason for early termination was "cancelled surgery" for 5 subjects and "other – withdrew consent" for 1 subject (**Listing 16.2.1.1**).

6.1.4 Analysis of Primary Endpoint(s)

Note: within the efficacy review there are several tables titled "SRMC removed" which present the re-analyzed data with all patient data from the Sall Research Medical Center removed. (see section 3.2 for discussion).

Study QD-ER

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 a SOIS of zero (i.e., zero 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.

Subjects, N (%), with Cleared Ocular Inflammation by Each Visit (LOCF Analysis; ITT Population) - QD-ER

	Bromfenac ophthalmic solution 0.09% N = 63	Placebo N = 63	P-value
Cleared Ocular Inflammation [a]			
Day 1	3 (4.8%)	3 (4.8%)	1.0000 [b]
Day 3	6 (9.5%)	7 (11.1%)	0.7696 [c]
Day 8	20 (31.7%)	15 (23.8%)	0.3200 [c]
Day 15 (Primary Endpoint)	28 (44.4%)	20 (31.7%)	0.1422 [d]

Source: **Table 14.2.1.5**

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

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0167.

[c] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0167.

[d] Primary Efficacy Endpoint, p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using an alpha level of 0.05.

Summed Ocular Inflammation Score: Mean (SD) at Each Visit (LOCF Analysis, ITT Population) - Study QD-ER

	Bromfenac ophthalmic solution 0.09% N = 63	Placebo N = 63	P-value [a]
Baseline (Screening)	0.0 (0.0)	0.0 (0.0)	N/A
Day 1	2.7 (1.4)	2.7 (1.3)	0.9139
Day 3	2.3 (1.6)	2.6 (1.7)	0.1743
Day 8	1.5 (1.6)	2.6 (2.0)	0.0031
Day 15	1.3 (1.6)	2.5 (2.0)	0.0010
Day 22	1.0 (1.6)	2.2 (1.9)	0.0003

Source: **Table 14.2.1.11**

Note: The anterior chamber cells score component of the SOIS was transformed as follows: 0=0, 0.5=1, 1=2, 2=3, 3=4, and 4=5.

N/A = not applicable.

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Wilcoxon Rank Sum test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.01.

Subjects, N (%), with Cleared Ocular Inflammation by Each Visit (LOCF Analysis; ITT Population) - Study QD-WR

	Bromfenac ophthalmic solution 0.09% N = 78	Placebo N = 78	P-value
Cleared Ocular Inflammation [a]			
Day 1	5 (6.4%)	9 (11.5%)	0.2625 [b]
Day 3	9 (11.5%)	10 (12.8%)	0.8066 [b]
Day 8	20 (25.6%)	14 (17.9%)	0.2446 [b]
Day 15 (Primary Endpoint)	36 (46.2%)	23 (29.5%)	0.0318 [c]

Source: **Table 14.2.1.5**

[a] Cleared ocular inflammation by each visit is defined as a SOIS of Grade 0 at or prior to each visit.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0167.

[c] Primary Efficacy Endpoint, p-value is for bromfenac ophthalmic solution 0.09% versus placebo and is from the Chi-square test. Statistical significance is determined using an alpha level of 0.05.

Reanalysis of Primary Endpoint – SMRC removed

	Bromfenac ophthalmic solution 0.09% N=75	**Placebo N=75**	**p-value**
Cleared ocular Inflammation			
Day 1	5 (6.7%)	9 (12%)	0.2616
Day 3	9 (12%)	10 (13.3%)	0.8061
Day 8	19 (25.3%)	14 (18.7%)	0.3244
Day 15 (primary endpoint)	35 (46.7%)	22 (29.3%)	0.0288

Summed Ocular Inflammation Score: Mean (SD) at Each Visit (LOCF Analysis, ITT Population) - Study QD-WR

	Bromfenac Ophthalmic Solution 0.09% N = 78	Placebo N = 78	P-value [a]
Baseline (Screening)	0.0 (0.0)	0.0 (0.0)	N/A
Day 1	2.8 (1.4)	3.3 (1.7)	0.0192
Day 3	2.3 (1.4)	3.2 (1.9)	0.0017
Day 8	1.7 (1.6)	3.2 (2.0)	<0.0001
Day 15	1.3 (1.6)	2.8 (2.3)	<0.0001
Day 22	1.0 (1.7)	2.6 (2.4)	<0.0001

Source: **Table 14.2.1.11**

Note: The anterior chamber cells score component of the Summed Ocular Inflammation Score was transformed as follows: 0=0, 0.5=1, 1=2, 2=3, 3=4, and 4=5

N/A = not applicable.

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Wilcoxon Rank Sum test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.01.

Reanalysis of Primary Endpoint – SMRC removed

	Bromfenac ophthalmic solution 0.09% N=75	**Placebo N=75**	**p-value**
Baseline (Screening)	0	0	N/A
Day 1	2.8	3.2	0.0290
Day 3	2.3	3.1	0.0047
Day 8	1.7	3.3	<0.0001
Day 15	1.3	2.9	<0.0001
Day 22	1.0	2.7	<0.0001

Study QD-ER and QD-WR were conducted under a common protocol; however, the results between these two trials are inconsistent. Study QD-ER fails to demonstrate efficacy for clearance of ocular inflammation while study QD-WR demonstrates efficacy for this endpoint. It is noted that study QD-WR has approximately 30 more patients than QD-ER which may have contributed to this result.

The re-analysis of the data for study QD-WR with data from the SRMC site removed does not change the efficacy results for this study.

Subjects, N (%), with Cleared Ocular Inflammation by Each Visit (LOCF Analysis; ITT Population) - Study QDII

	Bromfenac ophthalmic solution 0.09% N = 152	Placebo N = 147	P-value
Cleared Ocular Inflammation [a]			
Day 1	12 (7.9%)	9 (6.1%)	0.5488[b]
Day 3	17 (11.2%)	12 (8.2%)	0.3775 [b]
Day 8	36 (23.7%)	23 (15.6%)	0.0808 [b]
Day 15 (Primary Endpoint)	70 (46.1%)	36 (24.5%)	<0.0001[c]

Source: Table 14.2.1.1 and Table 14.2.1.5

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

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0167.

[c] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using an alpha level of 0.05.

Summed Ocular Inflammation Score: Mean (SD) at Each Visit (LOCF Analysis, ITT Population) - QDII

	Bromfenac ophthalmic solution 0.09% N = 152	Placebo N = 147	P-value [a]
Baseline (Screening)	0.0 (0.0)	0.0 (0.0)	N/A
Day 1	3.1 (1.6)	3.2 (1.7)	0.6271
Day 3	2.4 (1.5)	3.1 (1.8)	0.0011
Day 8	1.5 (1.4)	3.0 (1.9)	<0.0001
Day 15	1.0 (1.3)	2.8 (2.1)	<0.0001
Day 22	0.8 (1.3)	2.2 (2.2)	<0.0001

Source: Table 14.2.1.7

Note: The anterior chamber cells score component of the SOIS was transformed as follows: 0=0, 0.5=1, 1=2, 2=3, 3=4, and 4=5.

N/A = not applicable.

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Wilcoxon Rank Sum test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.01.

Study QDII demonstrates that bromfenac QD is statistically superior to placebo in the clearance of ocular inflammation on day 15. This study enrolled twice as many patients as the QD-ER and QD-WR trials and may have been overpowered.

6.1.5 Analysis of Secondary Endpoints(s)

A subject was considered to be pain free by a particular visit if there was a score of 'None' on the pain scale of the Ocular Comfort Grading Assessment in the subject diary at or prior to that visit.

Subjects, N (%), Pain Free by Each Visit (LOCF Analysis, ITT Population) - Study 0415081-ER

	Bromfenac ophthalmic solution 0.09% N = 63	Placebo N = 63	P-value
Day 1	51 (81.0%)	46 (73.0%)	0.2900 [a]
Day 3	59 (93.7%)	53 (84.1%)	0.0890 [a]
Day 8	60 (95.2%)	57 (90.5%)	0.4915 [b]
Day 15	60 (95.2%)	59 (93.7%)	1.0000 [b]

Source: **Table 14.2.4.3**

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0125.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Fisher's exact test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0125.

Ocular Pain Score, Mean (SD), at Each Visit (LOCF Analysis, ITT Population) - Study 0415081-ER

	Bromfenac ophthalmic solution 0.09% N =63	Placebo N = 63	P-value [a]
Baseline	0.00 (0.00)	0.00 (0.00)	N/A
Day 1	0.19 (0.40)	0.32 (0.56)	0.2431
Day 3	0.16 (0.48)	0.40 (0.73)	0.0246
Day 8	0.08 (0.37)	0.43 (0.76)	0.0004
Day 15	0.10 (0.39)	0.40 (0.73)	0.0022

Source: **Table 14.2.4.9**

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Wilcoxon Rank Sum test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0125.

Subjects, N (%), Pain Free by Each Visit (LOCF Analysis, ITT Population) - Study QD-WR

	bromfenac ophthalmic solution 0.09% N = 78	Placebo[c] N = 77	P-value[b]
Day 1	65 (83.3%)	40 (51.9%)	<0.0001
Day 3	74 (94.9%)	51 (66.2%)	<0.0001
Day 8	75 (96.2%)	54 (70.1%)	<0.0001
Day 15	76 (97.4%)	57 (74.0%)	<0.0001

Source: **Table 14.2.4.3**

[a] Grade 0 by each visit is defined as grade 0 on the pain scale of the Ocular Comfort Grading in the subject diary at or prior to each visit

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo, and is from the Chi-square test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0125.

[c] Subject 42-012-143 (placebo) had no pain entries in the diary for any visit; **Listing 16.2.6.2**

Reanalysis – SMRC removed

	Bromfenac ophthalmic solution 0.09% N=75	**Placebo N=75**	**p-value**
Day 1	62 (82.7%)	38 (51.4%)	<0.0001
Day 3	71 (94.7%)	48 (64.9%)	<0.0001
Day 8	72 (96%)	51 (68.9%)	<0.0001
Day 15	73 (97.3%)	54 (73%)	<0.0001

Ocular Pain Score, Mean (SD), at Each Visit (LOCF Analysis, ITT Population) - Study QD-WR

	bromfenac ophthalmic solution 0.09% N = 78	Placebo[b] N = 78	P-value [a]
Subjects with pain scores [b]	n = 78	n = 77	
Baseline	0.00 (0.00)	0.00 (0.00)	N/A
Day 1	0.21 (0.49)	0.69 (0.85)	< 0.0001
Day 3	0.06 (0.29)	0.56 (0.80)	< 0.0001
Day 8	0.06 (0.25)	0.55 (0.80)	< 0.0001
Day 15	0.06 (0.25)	0.49 (0.79)	< 0.0001

Source: **Table 14.2.4.9**

Note: Obtained from the pain scale of the Ocular Comfort Grading in the subject diary.

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from Wilcoxon Rank Sum test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0125.

[b] Subject 42-012-143 (placebo) had no pain entries in the diary for any visit; **Listing 16.2.6.2**.

Reanalysis - SMRC removed

	Bromfenac ophthalmic solution 0.09% N=75	**Placebo N=75**	**p-value**
Baseline	0	0	N/A
Day 1	0.21	0.70	<0.0001
Day 3	0.07	0.57	<0.0001
Day 8	0.07	0.55	<0.0001
Day 15	0.07	0.49	<0.0001

The ocular pain results were consistent with the primary efficacy endpoint conclusions. Study QD-ER failed to demonstrate efficacy for pain while study QD-WR demonstrated that bromfenac 0.9% qd was statistically superior to placebo for the absence of pain in the first day post-op. The reanalysis of the paid data with SRMC removed did not change the efficacy conclusions.

Subjects, N (%), Pain Free by Each Visit (LOCF Analysis, ITT Population) - Study QDII

	Bromfenac ophthalmic solution 0.09% N = 152	Placebo N = 147	P-value
Day 1 (Secondary Endpoint)	135 (88.8%)	105 (71.4%)	0.0002 [a]
Day 3	139 (91.4%)	105 (71.4%)	<0.0001 [b]
Day 8	142 (93.4%)	106 (72.1%)	<0.0001 [b]
Day 15	145 (95.4%)	107 (72.8%)	<0.0001 [b]

Source: Table 14.2.4.1 and Table 14.2.4.3

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using an alpha level of 0.05.

[b] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Chi-square test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0167.

Ocular Pain Score, Mean (SD), at Each Visit (LOCF Analysis, ITT Population) - Study QDII

	Bromfenac ophthalmic solution 0.09% N = 152	Placebo N = 147	P-value [a]
Baseline	0.00 (0.00)	0.00 (0.00)	N/A
Day 1	0.15 (0.47)	0.41 (0.71)	0.0001
Day 3	0.11 (0.37)	0.41 (0.75)	<0.0001
Day 8	0.08 (0.32)	0.44 (0.79)	<0.0001
Day 15	0.06 (0.29)	0.43 (0.79)	<0.0001

Source: Table 14.2.4.5

[a] p-value is for bromfenac ophthalmic solution 0.09% vs. placebo and is from the Wilcoxon Rank Sum test. Statistical significance is determined using a Bonferroni corrected alpha level of 0.0125.

Study QDII demonstrates that bromfenac QD is statistically superior to placebo in the percentage of subjects that are pain free after surgery.

6.1.6 Other Endpoints

All endpoints have been discussed in section 6.1.4 and 6.1.5.

6.1.7 Subpopulations

Subgroup analyses were not performed.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There are no additional dosing recommendations.

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.

6.1.10 Additional Efficacy Issues/Analyses

N/A – There are no additional efficacy issues.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study	Study Design	Test product	Number of Subjects	Duration of Treatment
CL-S&E-0415081-P-ER	Phase 3 double-masked, placebo controlled	Bromfenac 0.09% 1 drop QD	126	16 days
CL-S&E-0415081-P-WR	Phase 3 double-masked, placebo controlled	Bromfenac 0.09% 1 drop QD	156	16 days
CL-S&E-1205081-P	Phase 3 double-masked, placebo controlled	Bromfenac 0.09% 1 drop QD	299	16 days

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. The MedDRA version used for clinical study BromCom evaluating was 6.1 and for QD-ER, QD-WR, and QDII was 8.1.

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

The adverse event data from 4 studies of bromfenac ophthalmic solution 0.09% QD are presented throughout the safety review to estimate and compare the incidence of adverse events. The data from each trial is presented individually. In addition, simple pooling was used to evaluate overall exposure and to estimate the adverse event rate across studies. The studies included in the safety evaluation are studies QD-ER and QD-WR which were conducted under a common protocol, study QDII and BromCom which was a Phase 2 multi-center, randomized, double-masked, parallel group clinical study which compared bromfenac 0.09% QD to bromfenac 0.18% QD.

7.2 Adequacy of Safety Assessments

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

Subjects participating in studies QD-ER, QD-WR, QDII and BromCom were assigned to receive bromfenac 0.09% qd for a maximum of 16 days. The mean number of doses received in the pooled analysis was 14.3 (1.0 to 16.0). There was over an 89% compliance rate in the pooled studies.

7.2.2 Explorations for Dose Response

Bromfencac was evaluated at one does level (0.09%) for approval. (b) (4)

7.2.3 Special Animal and/or In Vitro Testing

Special animal or in vitro testing was not conducted as part of this supplement.

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

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

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

The adverse events related to topical non-steroidal anti-inflammatory agents are well known. No further evaluation was conducted as part of this supplement.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the studies evaluating bromfenac 0.09% or 0.18% QD.

7.3.2 Nonfatal Serious Adverse Events

Study QD-ER			
	Event	**Bromfenac N=61**	**Placebo N=61**
	Dementia	1 (1.6%)	0
	Dizziness	1 (1.6%)	0
	Dysuria	1 (1.6%)	0
	Hyperhidrosis	1 (1.6%)	0
	Nausea	1 (1.6%)	0
	Neck pain	1 (1.6%)	0
	Renal failure	1 (1.6%)	0
	Vomiting	1 (1.6%)	0
Study QD-WR	(no events reported)		
Study QDII			
		Bromfenac N=147	**Placebo N= 144**
	Acute pancreatitis	0	1 (0.7%)
	Cataract operation complication	0	2 (1.4%)

The types of serious non-fatal events reported in the three efficacy trials do not appear to be drug related.

7.3.3 Dropouts and/or Discontinuations

A subject was considered to have completed the study if the subject either completed at or after post-surgery Day 22 or if the subject completed a follow-up visit 1 week (7 + 3 days) after prematurely discontinuing investigational product.

A subject could have prematurely discontinued treatment for the following reasons: AE (ocular or systemic), use of prohibited concomitant medication, lack of efficacy, or "other" reason specified by the investigator. By protocol, subjects were not withdrawn from the study at the time that the investigational product was discontinued, but were followed for 7+3 days after the discontinuation of investigational product, unless they prematurely terminated from the study.

Discontinued Investigational Product – Study QD-ER

	Bromfenac ophthalmic solution 0.09% N = 63	**Placebo N = 63**	**P-value[a, b]**
Subjects who discontinued investigational product	14 (22.2%)	31 (49.2%)	0.0016 [b]
Primary reason for early discontinuation:			
AE	5 (7.9%)	9 (14.3%)	0.2568 [b]
Disallowed concurrent medication	1 (1.6%)	0 (0.0%)	1.0000 [a]
Lack of efficacy	6 (9.5%)	20 (31.7%)	0.0021 [b]
Other [c]	2 (3.2%)	2 (3.2%)	1.0000 [a]

Discontinued Investigational Product – Study QD-WR

	bromfenac ophthalmic solution 0.09% N = 78	**Placebo N = 78**	**P-value**
Subjects who discontinued investigational product	16 (20.5%)	47 (60.3%)	<0.0001 [a]
Primary reason for early discontinuation:			
AE	5 (6.4%)	12 (15.4%)	0.0721 [a]
Disallowed concurrent medication	1 (1.3%)	2 (2.6%)	1.0000 [b]
Lack of efficacy	2 (2.6%)	27 (34.6%)	<0.0001 [a]
Other [c]	8 (10.3%)	6 (7.7%)	0.5753 [a]

Discontinued Investigational Product – Study QDII

	Bromfenac ophthalmic solution 0.09% N = 152	Placebo N = 147	P-value[a, b]
Subjects who discontinued investigational product	29 (19.1%)	84 (57.1%)	<0.0001 [b]
Primary reason for early discontinuation:			
Adverse Event	8 (5.3%)	24 (16.3%)	0.0020[b]
Disallowed concurrent medication	3 (2.0%)	5 (3.4%)	0.4955[a]
Lack of efficacy	5 (3.3%)	47 (32.0%)	<0.0001[b]
Other	13 (8.6%)	8 (5.4%)	0.2927[b]

There were significantly more patients that discontinued the study in the placebo arm in all three trials. The main reason for discontinuing was lack of efficacy.

Adverse Events Leading to Discontinuation

Study QD-ER			
	Subject ID	**Treatment**	**Reason for Discontinuation**
	12-012-700	Bromfenac	Pain and photophobia
	14-008-604	Bromfenac	Dizziness, nausea, vomiting, neck pain
	47-004-560	Bromfenac	Conjunctival erythema, increased cell and flare, decreased vision
	48-001-629	Bromfenac	Intraoperative capsular tear
	12-06-650	Placebo	Photophobia
	12-010-698	Placebo	Photophobia, decreased vision
	17-001-529	Placebo	Pain, photophobia
	17-002-530	Placebo	Pain, photophobia, foreign body sensation, increased inflammation, blurred vision
	17-005-577	Placebo	Pain, redness, eyelid swelling, sensation of pressure
	17-009-665	Placebo	Pain, photophobia,
	34-006-573	Placebo	Iritis
	34-014-624	Placebo	Uveitis
	47-002-558	Placebo	Post-op inflammation, posterior capsule rupture
Study QD-WR			
	20-003-015	Bromfenac	Erythema
	46-003-035	Bromfenac	Increased post-op inflammation

	46-016-152	Bromfenac	Increased post-op inflammation
	52-007-139	Bromfenac	Facial rash
	54-006-178	Bromfenac	Eye surgery (pupil stretch)
	13-001-041	Placebo	Worsening inflammation
	13-006-074	Placebo	Ocular inflammation
	13-009-101	Placebo	photophobia
	30-009-113	Placebo	Posterior capsule opacification
	36-001-021	Placebo	Iritis
	42-003-047	Placebo	Iritis
	42-012-143	Placebo	Posterior capsule rupture
	43-006-097	Placebo	Iritis
	52-004-120	Placebo	Pain, photophobia
	52-005-137	Placebo	Pain, inflammation
	52-006-138	Placebo	Conjunctival edema, eye discomfort
	53-002-130	Placebo	Increased inflammation
Study QDII			
	15-20-191	Bromfenac	Constipation
	15-21-192	Bromfenac	Descemets fold
	20-08-104	Bromfenac	Gout
	21-05-040	Bromfenac	Headache
	24-03-111	Bromfenac	Increased inflammation
	35-04-188	Bromfenac	Cataract wound leakage
	45-02-306	Bromfenac	Ocular hypertension
	52-01-353	Bromfenac	Pain, discharge, itching, foreign body sensation, photophobia
	01-02-034	placebo	Refractive surgery
	05-12-172	placebo	Foreign body sensation, soreness
	05-17-261	placebo	Posterior capsule rupture
	05-19-263	placebo	IOL dislocation
	10-03-031	placebo	Edema
	10-10-213	placebo	Corneal edema
	12-08-096	placebo	Erythema
	12-09-121	placebo	Conjunctival redness, ciliary flush
	20-04-068	placebo	Increased inflammation
	20-06-102	placebo	Inflammation
	20-07-103	placebo	Inflammation, foreign body sensation
	20-12-108	placebo	Pain, photophobia, conjunctival erythema, tearing
	22-03-079	placebo	Inflammation
	31-07-250	placebo	Brow ache
	35-01-185	placebo	Inflammation

	35-14-382	placebo	Inflammation
	37-03-147	placebo	Eyelid pain
	37-07-211	placebo	Inflammation
	42-03-219	placebo	Uveitis
	42-06-309	placebo	Uveitis
	50-03-299	placebo	Eye pain
	50-07-303	placebo	Cataract operation complication
	50-15-402	placebo	Pain, photophobia, foreign body sensation
	53-05-293	placebo	Redness, eye ache

The types of adverse events related to dropouts in each of the trials are similar between the drug and placebo groups. The adverse events reported are consistent with those expected following cataract surgery.

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuations are presented in section 7.3.3. There were no other significant adverse events identified.

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

Common adverse events have been presented in two separate tables in this section. The first table presents the adverse event data for each trial individually. The second table presents the pooled adverse event data.

Systemic Adverse Events Reported in any Treatment Group – Individual Trial Results

	BromCom		QD-ER		QD-WR		QDII	
	0.09% QD[1]	0.18% QD[1]	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD
Safety Population, N	278	266	61	61	73	73	147	144
Subjects with any Adverse Event, n (%)	83 (29.9)	65 (24.4)	24 (39.3)	36 (59.0)	20 (27.4)	31 (42.5)	69 (46.9)	86 (59.7)
p-value[2]	0.156		0.030		0.056		0.029	
Conjunctival infections, irritations and inflammations, n (%)								
Conjunctival hyperemia	19 (6.8)	13 (4.9)	2 (3.3)	1 (1.6)	0 (0.0)	2 (2.7)	7 (4.8)	9 (6.3)
Conjunctival edema	4 (1.4)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)	1 (0.7)	0 (0.0)
Ocular infections, inflammations and associated manifestions, n (%)								
Eye discharge	0 (0.0)	2 (0.8)	1 (1.6)	3 (4.9)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)
Eye inflammation	10 (3.6)	3 (1.1)*	8 (13.1)	14 (23.0)	4 (5.5)	10 (13.7)	15 (10.2)	21 (14.6)
Eye pruritus	1 (0.4)	1 (0.4)	6 (9.8)	2 (3.3)	0 (0.0)	0 (0.0)	8 (5.4)*	4 (2.8)
Ocular hyperemia	1 (0.4)	0 (0.0)	0 (0.0)	6 (9.8)	2 (2.7)	2 (2.7)	5 (3.4)*	15 (10.4)
Eye irritation	4 (1.4)	2 (0.8)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.4)	4 (2.7)	3 (2.1)*
Corneal infections, edemas and inflammations, n (%)								
Corneal edema	9 (3.2)	8 (3.0)	4 (6.6)	2 (3.3)	0 (0.0)	4 (5.5)	3 (2.0)	4 (2.8)
Conjunctival and corneal bleeding and vascular disorders, n (%)								
Conjunctival hemorrhage	8 (2.9)	7 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Eye and ear procedural complications, n (%)								
Eye operation complications	4 (1.4)	5 (1.9)	1 (1.6)	1 (1.6)	0 (0.0)	2 (2.7)	1 (0.7)	5 (3.5)
Eyelid movement disorders, n (%)								
Eyelid ptosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)*	0 (0.0)	0 (0.0)
Ocular disorders NEC, n (%)								
Eye pain	7 (2.5)	9 (3.4)	5 (8.2)	7 (11.5)	2 (2.7)	5 (6.8)	13 (8.8)	34 (23.6)
Ocular discomfort	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)	1 (1.4)	3 (4.1)	3 (2.0)	4 (2.8)

	BromCom		QD-ER		QD-WR		QDII	
	0.09% QD[1]	0.18% QD[1]	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD
Ocular sensation disorders, n (%)								
Abnormal sensation in eyes	6 (2.2)	5 (1.9)*	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)
Foreign body sensation in eyes	0 (0.0)	0 (0.0)	8 (13.1)	6 (9.8)	2 (2.7)*	1 (1.4)	18 (12.2)	21 (14.6)*
Photophobia	3 (1.1)	1 (0.4)	8 (13.1)	17 (27.9)	0 (0.0)	2 (2.7)	11 (7.5)	26 (18.1)
Iris and uveal tract infections, irritations and inflammations, n (%)								
Iridocyclitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Iritis	9 (3.2)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ciliary hyperemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	4 (2.8)
Lacrimal disorders, n (%)								
Lacrimation increased	1 (0.4)	2 (0.8)	3 (4.9)	6 (9.8)	0 (0.0)	3 (4.1)*	5 (3.4)	11 (7.6)
Lacrimation decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)*	0 (0.0)	0 (0.0)
Dry eye (keratoconjunctivitis sicca)	3 (1.1)*	1 (0.4)	0 (0.0)	0 (0.0)	2 (2.7)*	0 (0.0)	6 (4.1)**	2 (1.4)
Ophthalmic function diagnostic procedures, n (%)								
Intraocular pressure increased	5 (1.8)*	4 (1.5)	1 (1.6)	1 (1.6)	2 (2.7)	1 (1.4)	5 (3.4)	3 (2.1)
Visual disorders NEC, n (%)								
Vision blurred	1 (0.4)	0 (0.0)	4 (6.6)	2 (3.3)	0 (0.0)	0 (0.0)	15 (10.2)	11 (7.6)
Partial vision loss, n (%)								
Visual acuity reduced	2 (0.7)	1 (0.4)	2 (3.3)	1 (1.6)	0 (0.0)	0 (0.0)	2 (1.4)	1 (0.7)

	BromCom		QD-ER		QD-WR		QDII	
	0.09% QD[1]	0.18% QD[1]	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD	0.09% QD[1]	Placebo QD
Retinal, choroid and vitreous infections and inflammations, n (%)								
Macular edema	1 (0.4)	0 (0.0)	1 (1.6)	2 (3.3)	0 (0.0)	1 (1.4)	2 (1.4)	1 (0.7)
Headaches NEC, n (%)								
Headache	13 (4.7)	5 (1.9)	1 (1.6)	0 (0.0)	1 (1.4)	1 (1.4)	4 (2.7)	2 (1.4)
Nausea and vomiting symptoms, n (%)								
Nausea	2 (0.7)	3 (1.1)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Rashes, eruptions and exanthems NEC, n (%)								
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.1)*	0 (0.0)	0 (0.0)	1 (0.7)

Systemic Adverse Events Reported in any Treatment Group – Pooled Data

	Bromfenac 0.09% QD Studies	
	Pooled 0.09%	Pooled Placebo
Safety Population, N	559	278
Subjects with any Adverse Event, n (%)	196 (35.1)	153 (55.0)
Cataracts (exludes congenital), n (%)		
Posterior capsule opacification	2 (0.4)	0 (0.0)
Conjunctival infections, irritations and inflammations, n (%)		
Conjunctival hyperemia	28 (5.0)	12 (4.3)
Conjunctival edema	5 (0.9)	2 (0.7)
Corneal disorders NEC, n (%)		
Descemet's membrane disorder	1 (0.2)	2 (0.7)
Corneal infections, edemas and inflammations, n (%)		
Corneal edema	16 (2.9)	10 (3.6)
Corneal structural change, deposit and degeneration, n (%)		
Corneal striae	0 (0.0)	1 (0.4)
Headaches, n (%)		
Headache	19 (3.4)	3 (1.1)
Iris and uveal tract infections, irritations and inflammations, n (%)		
Iritis	9 (1.6)	0 (0.0)
Lacrimal disorders, n (%)		
Lacrimation increased	9 (1.6)	19 (6.8)
Lid, lash and lacrimal infections, irritations and inflammations, n (%)		
Eyelid edema	2 (0.4)	1 (0.4)
Ocular disorders NEC, n (%)		
Eye pain	27 (4.8)	46 (16.5)
Ocular discomfort	5 (0.9)	7 (2.5)
Ocular infections, inflammations and associated manifestations, n (%)		
Eye inflammation	37 (6.6)	45 (16.2)
Eye irritation	8 (1.4)	5 (1.8)
Eye pruritus	15 (2.7)	6 (2.2)
Eye redness	4 (0.7)	0 (0.0)
Ocular hyperemia	7 (1.3)	23 (8.3)
Ocular sensation disorders, n (%)		
Abnormal sensation in eye	6 (1.1)	4 (1.4)
Foreign body sensation in eyes	28 (5.0)	28 (10.1)
Photophobia	22 (3.9)	45 (16.2)

	Bromfenac 0.09% QD Studies	
	Pooled 0.09%	Pooled Placebo
Ophthalmic function diagnostic procedures, n (%)		
Intraocular pressure increased	13 (2.3)	5 (1.8)
Partial vision loss, n (%)		
Vision blurred	1 (0.2)	0 (0.0)
Visual acuity reduced	6 (1.1)	2 (0.7)
Retinal, choroid and vitreous infections and inflammations, n (%)		
Macular edema	4 (0.7)	4 (1.4)
Visual disorders NEC, n (%)		
Vision blurred	19 (3.4)	13 (4.7)

The most commonly reported adverse reactions were eye inflammation, conjunctival hyperemia, foreign body sensation, eye pain, photophobia, headache, blurred vision, corneal edema, eye pruritus and increased IOP.

7.4.2 Laboratory Findings

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

7.4.3 Vital Signs

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

7.4.4 Electrocardiograms (ECGs)

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

7.4.5 Special Safety Studies/Clinical Trials

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

7.4.6 Immunogenicity

Immunogenicity studies were not conducted for this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency was not evaluated for this submission.

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

This review has not revealed any clinically meaningful demographic effects on the safety profile.

7.5.4 Drug-Disease Interactions

Study of potential drug interactions were not conducted as a part of this submission. There are no known drug interactions with bromfenac.

7.5.5 Drug-Drug Interactions

Study of potential drug interactions were not conducted as a part of this submission. There are no known drug interactions with bromfenac.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity was not study as part of this submission.

7.6.2 Human Reproduction and Pregnancy Data

Human reproduction and pregnancy was not study as part of this submission.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatrics and effects on growth were not study as part of this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose, drug abuse and withdrawal were not study as part of this submission.

7.7 Additional Submissions / Safety Issues

The 120 day safety update did not raise any new safety concerns.

8 Postmarket Experience

Bromfenac sodium ophthalmic solution was approved in the United States in 2005 and in Japan in 2000. Periodic safety update reports have been submitted and reviewed by the FDA since drug approval. Since NDA approval there have been no significant new safety findings related to the use of bromfenac ophthalmic solution.

9 Appendices

9.1 Literature Review/References

N/A-an independent literature review was not conducted for this submission.

9.2 Labeling Recommendations

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

9.3 Advisory Committee Meeting

N/A-an advisory committee meeting is not required for this submission.

List of Investigators – Study 0802071-P-

List of Investigators				
Site No.	**Investigator**	**Role**	**Site**	**No. Subjects Enrolled**
11	**Jason Bacharach, MD**	PI	104 Lynch Creek Way, Suites 12 & 15 Petaluma, CA 94954	1
12	**Donald E. Beahm, MD**	PI	3923 Broadway Great Bend, KS 67530 Surgical and Diagnostic Center of Great Bend 514 Cleveland Great Bend, KS 67530	27
13	**Gregg J. Berdy, MD, FACS**	PI	Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131 St. Louis Eye Surgery and Laser Center 12990 Manchester Road St. Louis, MO 63131	2
14	**Thomas T. Macejko, MD**	PI	563 Wessel Drive Fairfield, OH 45014 Surgery Center of Evandale 3155 Glendale Milford Rd Cincinnati, OH 45241	4
15	**Robert L. Berry, MD**	PI	Eye Care Arkansas, PA 9800 Lile Drive, Suite 301 Little Rock, AR 72205	30
16	**James D. Boyce, MD, FACS**	PI	Orange County Eye Surgical Center 12665 Garden Grove Blvd., # 401 Garden Grove, CA 92843	24
18	**Leonard R. Cacioppo, MD**	PI	Hernando Eye Institute 14543 Cortez Boulevard Brooksville, FL 34613 All Saints Surgery Center 11373 Cortez Boulevard Brooksville, FL 34613	19
19	**Michael B. Caplan, MD, FACS**	PI	Berkeley Eye Center 3100 Weslayan, Suite 400 Houston, 77027 Caplan Surgery Center 3100 Weslayan, Suite 400 Houston, 77027	2
20	**William C. Christie, MD**	PI	Scott & Christie and Associates, PC 105 Brandt Drive, Suite 201 Cranberry Township, PA 16066 Fox Chapel 1101 Freeport Road Pittsburgh, PA 15238	18

List of Investigators				
Site No.	**Investigator**	**Role**	**Site**	**No. Subjects Enrolled**
21	**Y. Ralph Chu, MD**	PI	Chu Vision Institute 7760 France Avenue S, Suite 140 Edina, MN 55435 Pine Eye Associates 110 Evergreen Square SW Pine City, MN 55063 Minneapolis Eye Center 8401 Golden Valley Road Golden Valley, MN 55427 Lakeside Medical Center 129 East 6th Avenue Pine City, MN 55063	7
22	**Lisa M. Cibik, MD, FACS**	PI	Associates in Ophthalmology, Ltd 9970 Mountain View Drive, 1st Floor West Mifflin, PA 15122	2
24	**E. Randy Craven, MD**	PI	Glaucoma Consultants of Colorado 26 West Dry Creek Circle, Suite 225 Littleton, CO 80120 Littleton Day Surgery Center 8381 Southpark Lane Littleton, CO 80120 Lowry Surgery Center 8101 East Lowry Boulevard, #100 Denver, CO 80230 Glaucoma Consultants of Colorado 8101 East Lowry Boulevard, Suite 110 Denver, CO 80230	1
25	**Lawrence R. DeBarge, MD**	PI	2498 LaFayette Road Fort Oglethorpe, GA 30742 Physicians Surgery Center 924 Spring Creek Road Chattanooga, TN 37412	3
26	**Monte S. Dirks, MD**	PI	Black Hills Regional Eye Institute 2800 Third Street Rapid City, SD 57701	2
27	**Harvey B. DuBiner, MD**	PI	Eye Care Centers Management, Inc Clayton Eye Center 1000 Corporate Center Drive Suites 100, 200, 180 Morrow, GA 30260	14

List of Investigators				
Site No.	Investigator	Role	Site	No. Subjects Enrolled
29	Gary Foster, MD	PI	Eye Center of Northern Colorado 1725 East Prospect Road Fort Collins, CO 80525 Eye Center – Windsor 1455 West Main Windsor, CO 80550 Eye Center – Loveland 2555 East 13th Street, #225 Loveland, CO 80537 Eye Center Surgery Center 1725 East Prospect Road Fort Collins, CO 80525	3
30	Stephen S. Lane, MD	PI	2950 Curve Crest Boulevard Stillwater, MN 55082 280 North Smith Avenue, Suite 840 St. Paul, MN 55102	12
31	Joshua M. Gould, DO	PI	The Eye Care Center of New Jersey 108 Broughton Avenue Bloomfield, NJ 07003 Essex Eye Surgery and Laser Center 1460 Broad Street Bloomfield, NJ 07003	2
33	Marvin E. Greenberg, MD	PI	Marvin E. Greenberg, MD, PA 7421 North University Drive, Suite 109 Tamarac, FL 33321 Surgery Center at Coral Springs 967 University Drive Coral Springs, FL 33071 Foundation for Advanced Eye Care 3737 North Pine Island Road Sunrise, FL 33351	7

List of Investigators				
Site No.	Investigator	Role	Site	No. Subjects Enrolled
34	Robert H. Gross, MD	PI	Cornea Consultants of Arizona 3815 East Bell Road, Suite 2500 Phoenix, AZ 85032 Spectra Eye Institute 9849 West Thunderbird Boulevard Sun City, AZ 85351 Scottsdale Eye Surgery Center, P.C. 3320 North Miller Road Scottsdale, AZ 85251 Cornea Consultants of Arizona 9185 West Thunderbird Boulevard Peoria, AZ 85382 Cornea Consultants of Arizona 1520 South Dobson, Road, Suite 211 Mesa, AZ 85202	12
35	Kerry B. Hagen, MD	PI	Eye Health Northwest 1955 NW Northrup Portland, OR 97209 West Side Surgery Center 13240 SW Pacific Highway Tigard, OR 97223	4
36	Barry Schechter, MD	PI	Florida Eye Microsurgical Institute, Inc. 1717 Woolbright Road Boynton Beach, FL 33426 Boynton Beach ASC, LLC 1717 Woolbright Road Boynton Beach, FL 33426	1
37	Paul J. Hartman, MD	PI	Rochester Ophthalmological Group, P.C. 2100 South Clinton Avenue Rochester, NY 14618 Rochester Ophthalmological Group, P.C. 2300 W. Ridge Road Rochester, NY 14623 Westfall Surgery Center 1065 Senator Keating Blvd. Rochester, NY 14618	12
38	Gregory L. Henderson, MD, FACS, PA	PI	Brandon Cataract Center 403 Vonderburg Drive, Suite 101 Brandon, FL 33511 Brandon Surgery Center 711 South Parson Avenue Brandon, FL 33511	7

List of Investigators

Site No.	Investigator	Role	Site	No. Subjects Enrolled
39	Barry Katzman, MD	PI	West Coast Eye Care Associates 6945 El Cajon Boulevard San Diego, CA 92115 Grossmont Surgery Center 8881 Fletcher Parkway, #100 La Mesa, CA 91942	11
41	Robert P. Lehmann, MD, FACS	PI	Lehmann Eye Center 5300 North Street Nacogdoches, TX 75965 Doctors Surgery Center 5300 North Street Nacogdoches, TX 75965	16
43	James E. McDonald II, MD	PI	McDonald Eye Associates 3318 N. North Hills Blvd Fayetteville, AR 72703 Arkansas Outpatient Eye Surgery, LLC 3318 N. North Hills Blvd Fayetteville, AR 72703	3
44	Ryan McKinnon, MD	PI	Saltzer Medical Group 215 East Hawaii Ave. Nampa, ID 83686 Mercy Medical Center 4400 Flamingo Avenue Nampa, ID 83687 Saltzer Medical Group 1818 South 10th Avenue Caldwell, ID 83605 Idaho Surgery Center 3115 Medical Way Caldwell, ID 83605	4
45	John C. Meyer, MD	PI	The Eye Care Institute 1536 Story Avenue Louisville, KY 40206 Jewish East Medical Center 3920 Dutchmans Lane Louisville, KY 40207 Jewish Downtown Hospital 200 Abraham Flexnor Way Louisville, KY 40202 North Audubon Hospital 1 Plaza Drive Louisville, KY 40217 The Eye Care Institute 2355 Poplar Level Road Louisville, KY 40217	11

List of Investigators				
Site No.	Investigator	Role	Site	No. Subjects Enrolled
46	Sebastian A. Mora, DO	PI	Belle Vue Eye Centre 1327 SW Military Drive San Antonio, TX 78221 NovaMed Surgical Center San Antonio 7810 Louis Pasteur San Antonio, TX 78229	15
47	Mark Packer, MD, FACS	PI	Drs. Fine, Hoffman and Packer, LLC 1550 Oak Street, Suite 5 Eugene, OR 97401	4
48	Gregory J. Pamel, MD	PI	Pamel Vision & Laser Group 115 East 61st Street, Suite 1B New York, NY 10065 Mid Manhattan Surgical Center 61 West 23rd Street, 7th Floor New York, NY 10016 Retina Surgery Center of NY 140 East 80th Street New York, NY 10028	14
49	James H. Peace, MD	PI	United Medical Research Institute 431 North Prairie Avenue Inglewood, CA 90301	39
50	Bernard R. Perez, MD, FACS	PI	International Eye Center 4506 Wishart Boulevard Tampa, FL 33603 Memorial Hospital of Tampa 2911 Swann Avenue Tampa, FL 33609	8
51	James E. Pickett, III, MD	PI	Central Texas Eye Center 1300 Wonderworld Drive San Marcos, TX 78666 San Marco Surgery Center 1891 Medical Parkway San Marcos, TX 78666 Wimberley Eye Associates 14500 Ranch Road 12 Wimberley, TX 78676	3
52	Eugene E. Protzko, MD	PI	520 Upper Chesapeake Dr., Suite 401 Bel Air, MD 21014 930 Revolution Street Havre de Grace, MD 21078 Mid-Atlantic Surgery Pavillion 1111 Beards Hill Road, Suite 700 Aberdeen, MD 21001	17

List of Investigators

Site No.	Investigator	Role	Site	No. Subjects Enrolled
54	Tushina A. Reddy, MD	PI	Ophthalmic Associates 3016 West Charleston Boulevard, #100 Las Vegas, NV 89102 Las Vegas Surgery 870 South Rancho Drive Las Vegas, NV 89106 American Surgery Center 2575 Lindell Road Las Vegas, NV 89146	1
55	Harvey J. Reiser, MD	PI	Eye Care Specialists 703 Rutter Avenue Kingston, PA 18704 Kingston Surgery Center 601 Wyoming Avenue Kingston, PA 18704 Eye Care Specialists 425 Adams Avenue Scranton, PA 18510 Eye Care Specialists 126 West Front Street Berwick, PA 18603	27
57	Kenneth Sall, MD	PI	Sall Research Medical Center 11423 187th Street, Suite 200 Artesia, CA 90701	11
58	David L. Schwartz, MD	PI	2000 South Wheeling Avenue, Suite 401 Tulsa, OK 74104	29
59	David G. Shulman, MD, PA	PI	999 East Basse, Suite 127 San Antonio, TX 78209	3
60	Steven M. Silverstein, MD, FACS	PI	Silverstein Eye Centers 4240 Blue Ridge Boulevard, Suite 1000 Kansas City, MO 64133	4
61	Stephen E. Smith, MD	PI	Eye Associates of Fort Myers 4225 Evans Avenue Fort Myers, FL 33901 University Eye Surgery Center 13051 University Drive, Suite 102 Fort Myers, FL 33907	7

List of Investigators				
Site No.	Investigator	Role	Site	No. Subjects Enrolled
62	Robert H. Stewart, MD, FACS	PI	Houston Eye Associates 2855 Gramercy Drive Houston, TX 77025 Summit Ambulatory Surgical Center 4126 Soutwest Fwy #108 Houston, TX 77027 Gramercy Outpatient Surgery Center 2727 Gramercy Street Houston, TX 77025	22
66	Rolando Toyos, MD	PI	Toyos Clinic 569 Skyline Drive, Suite 200 Jackson, TN 38301 Union City Surgical Center 1722 East Reelfoot Avenue, Suite 1 Union City, TN 38261 Kentucky Lake Surgery Center 1002 Cornerstone Drive Paris, TN 38242 Toyos Clinic 224 Memorial Drive Paris, TN 38242	14
67	William Trattler, MD	PI	Center for Excellence in Eye Care 8940 North Kendall Drive, Suite 400E Miami, FL 33176 Surgical Eye Center 9100 SW 87th Ave Miami, FL 33176 Medical Arts Surgery Center 8940 North Kendall Drive 2nd Floor, East Tower Miami, FL 33176	32
68	Farrell C. Tyson II, MD	PI	Cape Coral Eye Center 4120 Del Prado Boulevard Cape Coral, FL 33904	13

List of Investigators				
Site No.	Investigator	Role	Site	No. Subjects Enrolled
69	Thomas R. Walters, MD	PI	Texan Eye, PA 5717 Balcones Drive Austin, TX 78731 Texas Surgery Center 7000 N. Mopac, Suite 120 Austin, TX 78731 Texan Eye, PA 1700 South Mopac Austin, TX 78731 Texan Eye, PA 7000 N. Mopac Suite 110 Austin, TX 78731	38
71	Michael Y. Wong, MD	PI	Princeton Eye Group 419 North Harrison Street Princeton, NJ 08540 Surgery Center of Central New Jersey 107 North Center Drive North Brunswick, NJ 08902 Concordia Medical Building 1600 Perrineville Road Monroe Twp, NJ 08831	5
72	Mark T. Bergmann, MD	PI	Eye Care Associates of Greater Cincinnati, Inc. 2859 Boudinot Avenue, Suite 301 Cincinnati, OH 45238 Leon Reid, III, MD 4631 Ridge Road, Suite A Cincinnati, OH 45209	1

List of Investigators – Study 0415081-P-ER

Investigator	Site Number	Site Address
Robert L. Berry, MD	12	Eyecare Arkansas, P.A. 9800 Lile Drive, Suite 301 Little Rock, AR 72205
Leonard R. Cacioppo, MD	14	Hernando Eye Institute 14543 Cortez Boulevard Brooksville, FL 34613
William C. Christie, MD	15	105 Brandt Drive, Suite 201 Cranberry Township, PA 16066
Charles J. Crane, MD	17	71 Second Street South Orange, NJ 07079
L. Raymond DeBarge, MD	19	2498 LaFayette Road Fort Oglethorpe, GA 30742
Mark T.Bergmann, MD	21	2859 Boudinot Avenue, Suite 301 Cincinnati, OH 45238
Joshua Gould, DO	25	Eye Care Center of New Jersey 108 Broughton Ave Bloomfield, NJ 07003
John C. Meyer, MD	29	The Eye Care Institute 1536 Story Avenue Louisville, KY 40206
Bernard R. Perez, MD	31	International Eye Center 4506 Wishart Place Tampa, FL 33603
Eugene E. Protzko, MD	32	520 Upper Chesapeake Drive, Suite 401 Bel Air, MD 21014
Peter A. Rapoza, MD	33	EyeCare Specialists 50 Staniford Street Boston, MA 02114
Harvey J. Reiser, MD	34	703 Rutter Avenue Kingston, PA 18704
Rolando Toyos, MD	38	Toyos Clinic 569 Skyline Drive, Suite 200 Jackson, TN 38301
Carlos Buznego, MD	39	Center for Excellence in Eye Care 8940 North Kendall Drive, Suite 400-E Miami, FL 33176
Farrell C.Tyson, MD	40	Cape Coral Eye Center 4120 Del Prado Boulevard Cape Coral, FL 33904
David A. Kinsler, MD	45	426 West Main Street Salem, VA 24153

Investigator	Site Number	Site Address
Michael S. Korenfeld. MD	47	901 East 3rd Street Washington, MO 63090
Mark S. Rubin, MD	48	550 Memorial Circle, Suite N Ormond Beach, FL 32174
Jodi Luchs, MD	50	South Shore Eye Care, LLP 2185 Wantagh Avennue Wantagh, NY 11793
Parag A. Majmudar, MD	51	1585 North Barrington Road, Suite 502 Hoffman Estates, IL 60169

List of Investigators – Study 0415081-P-WR

Investigator	Site Number	Site Address
Donald E. Beahm, MD	11	3923 Broadway Great Bend, KS 67530
James D. Boyce, MD	13	12665 Garden Grove Boulevard Suite 401 Garden Grove, CA 92843
Y. Ralph Chu, MD	16	Chu Vision Institute 7760 France Avenue South Suite 140 Edina, MN 55435
E. Randy Craven, MD	18	Glaucoma Consultants of Colorado 26 Dry Creek Circle, #225 Littleton, CO 80120
Monte S. Dirks, MD	20	Black Hills Regional Eye Institute 2800 Third St. Rapid City, SD 57701
Robert Hollis Gross, MD	24	3815 East Bell Road, Suite 2500 Phoenix, AZ 85032
Barry Katzman, MD	26	6945 El Cajon Blvd San Diego, CA 92115
Robert Paul Lehmann, MD, FACS	28	Lehmann Eye Center 5300 North Street Nacogdoches, TX 75965
James H. Peace, MD	30	United Medical Research Institute 431-433 North Prarie Avenue Inglewood, CA 90301
Kenneth Sall, MD	35	Sall Research Medical Center 11423 187th Street, Suite 200 Artesia, CA 90701
David L. Schwartz, MD	36	2000 S. Wheeling Avenue, Suite 401 Tulsa, OK 74104
Steven M. Silverstein, MD, FACS	37	4240 Blue Ridge Boulevard, Suite 1000 Kansas City, MO 64133
David G. Shulman, MD	41	999 E. Basse Street, Suite 127 San Antonio, TX 78209
William John Flynn, MD	42	5430 Fredricksburg Road San Antonio, TX 78229
Kerry Brent Hagen, MD	43	Eye Health Northwest 1955 NW Northrup Portland, OR 97209

Investigator	Site Number	Site Address
Thomas R. Walters, MD	46	Texan Eye, PA 5717 Balcones Drive Austin, TX 78731
Paul Albert Jorizzo, MD	49	2727 Barnett Road Medford, OR 97504
Scott Smetana, MD	52	2920 North Cascade Colorado Springs, CO 80907
William Colby Stewart, MD	53	2855 Gramercy Street Houston, TX 77025
Jon-Marc Weston, MD, FACS	54	Roseburg Research Associates, LLC 2435 NW Kline Roseburg, OR 97470

Investigator	Site Number	Site Address
Louis M Alpern, MD	18	4171 North Mesa Building D, Suite 100 El Paso, TX 79902
Pranav Amin, MD	01	Sutter North Medical Foundation 460 Plumas Boulevard, Suite 102 Yuba City, CA 95991
Jason Bacharach, MD	42	104 Lynch Creek Way, Suite 12 Petaluma, CA 94954
Robert Benza, MD	48	7850 Camargo Road Cincinnati, OH 45243
Mark H. Blecher, MD	11	Philadelphia Eye Associates 1703 South Broad Street Philadelphia, PA 19148
Jeffrey A. Boomer, MD	02	Hunkeler Eye Institute 7950 B College Boulevard Overland Park, KS 66210
Melissa G. Cable, MD	49	Discover Vision Centers 4741 South Cochise Drive Independence, MD 64055
David L. Cooke, MD	13	Great Lakes Eye Care 2848 Niles Road St. Joseph, MI 49085
Scott M. Corin, MD	52	Advanced Eye Centers, Inc. 500 Faunce Corner Road, Suite 110 Dartmouth, MA 02747
Sherif M. El-Harazi, MD, MPH	03	Lugene Eye Institute 801 South Chevy Chase Drive Suite 103 Glendale, CA 91205
Arthur Fishman, MD	19	Eye Surgery Associates 603 North Flamingo Road Suite 250 Pembroke, FL 33028
John Foley, MD	16	3297 Broad Street Exmore, VA 23350
Raymond Fong, MD	54	109 Lafayette Street New York, NY 10013
Gary Foster, MD	14	Eye Center of Northern Colorado 1725 East Prospect Road Fort Collins, CO 80525

Investigator	Site Number	Site Address
Ryan McKinnon, MD	15	Saltzer Medical Group 215 East Hawaii Avenue Nampa, ID 83686
Satish Modi, MD	35	Alterman, Modi and Wolter 23 David Avenue Poughkeepsie, NY 12603
Sebastian A. Mora, DO	10	Belle Vue Eye Centre 1327 SE Military Drive San Antonio, TX 78221
Francis W. Price, Jr, MD	24	Price Vision Group 9002 North Meridian Street, Suite 100 Indianapolis, IN 46260
Rajesh K. Rajpal, MD	25	See Clearly/Cornea Consultants 8180 Greensboro Drive, Suite 140 McLean, VA 22102
William J. Rand, MD	36	Rand Eye Institute 5 West Sample Road Deerfield Beach, FL 33064
Steven H. Rauchman, MD	9	North Valley Eye Medical Group 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345
Michael H. Rotberg, MD	22	Charlotte Eye Ear Nose & Throat Associates 6035 Fairview Road Charlotte, NC 28210
Ehsan Sadri, MD	41	361 Hospital Road, Suite 327 Newport Beach, CA 92663
Zachary Kaufman Segal, MD	51	A. James Segal, MD, PA dba MedEye Associates 5950 Sunset Drive Miami, FL 33143
John Sheppard, MD	26	Virginia Eye Consultants 241 Corporate Boulevard Norfolk, VA 23502
Michael E. Tepedino, MD	37	Cornerstone Eye Care 307 North Lindsay Street High Point, NC 27262
Steven D. Vold, MD	56	Boozman-Hof Regional Eye Clinic, PA 3737 West Walnut Street Rogers, AR 72756
Robert J. Weinstock, MD	8	The Eye Institute of West Florida 148 13th Street SW Largo, FL 33770

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

JENNIFER D HARRIS
07/14/2010

WILLIAM M BOYD
07/19/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

CHEMISTRY REVIEW(S)

Chemistry Review: # 2	**1. Division:** HFD 520	**2. NDA Number:** 21-664

3. Name and Address of Applicant:
ISTA® Pharmaceutical, Inc.
15295 Alton Parkway
Irvine, CA 92618

4. Supplement(s):
Number: S-013 Efficacy supplement
Date(s): Ammendment September 6, 2010

5. Name of Drug:
XIBROM™

6. Nonproprietary name:
Bromfenac Ophthalmic solution

7. Supplement Provides Complete response to CMC/clinical issues raised in CMC review # 1.

8. Amendment(s):
None

9. Pharmacological Category:
Ophthalmic topical instillation

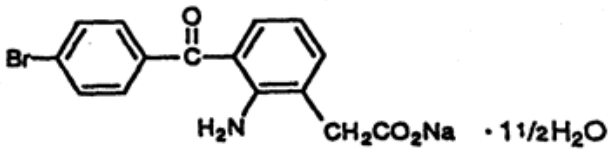
10. How Dispensed:
R_x

11. Related Documents:
None

12. Dosage Form:
Solution

13. Potency:
0.09%

14. Chemical Name and Structure: Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate.



15. Comments: This amendment to supplement 13 is the response to the Complete Response (CR) CMC/clinical issues that were conveyed to the applicant through several telephone conversations during the review cycle.

The CMC/clinical issues, and the responses by the applicant were as follows:

- Naming of (b) (4) acid.
- Potency of the final drug product.
- Clinical issue with the (b) (4) mL size, drug product market size.

The applicant responded and revised the labeling according to the suggestions made by The Agency. That is:

The proposed name XIBROM™ was revised to the agreed upon BROMDAY™ and the name remained in the acid form as (bromfenac Ophthalmic Solution).

The potency of the drug product remained as 0.09% in the acid form and,

the carton and container labels were revised to reflect these changes as well as the final (and only commercial presentation) 1.7 mL content, bottle.

See revised carton and container labeling at the end of this review.

16: Conclusions and Recommendations: The labeling was revised according to the suggestions made by The Agency. From the CMC point of view, this supplement is recommended for approval.

17. Name: **Signature:** **Date:**
Libaniel Rodriguez, Chemist

18. Concurrence: **Signature:** **Date:**
Terrance Ocheltree, Ph.D., R.Ph., Division Director ONDQAII

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)
NDA-21664	SUPPL (b) (4)	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

LIBANIEL RODRIGUEZ
09/10/2010

TERRANCE W OCHELTREE
09/10/2010

Chemistry Review: # 1	**1. Division:** HFD 520	**2. NDA Number:** 21-664

3. Name and Address of Applicant:
ISTA® Pharmaceutical, Inc.
15295 Alton Parkway
Irvine, CA 92618

4. Supplement(s):
Number: S-013 Efficacy supplement
Date(s): December 18, 2009

5. Name of Drug:
XIBROM™

6. Nonproprietary name:
Bromfenac Ophthalmic solution

7. Supplement Provides For a change in name and dosage for the currently approved Xibrom bromphenac ophthalmic solution 0.09%, to XIDAY bromphenac sodium (b) (4) ophthalmic solution (b) (4)

8. Amendment(s):
None

9. Pharmacological Category:
Ophthalmic topical instillation

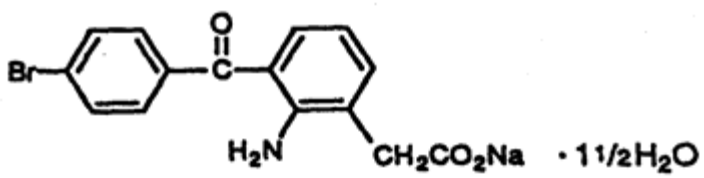
10. How Dispensed:
R_x

11. Related Documents:
None

12. Dosage Form:
Solution

13. Potency:
0.09%

14. Chemical Name and Structure: Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate.



15. Comments: This supplement is for the change in dosing regime from the currently approved twice-a-day following cataract extraction surgery to once-a-day (QD) dosing beginning one day prior to surgery; continue on the day of surgery and for 14 days after surgery.

ISTA intends to rename the already approved XIBROM bromphenac ophthalmic solution 0.09% drug product above with the name XIDAY bromphenac sodium (b) (4) ophthalmic solution (b) (4)

There are no changes either for drug substance or drug product to the currently approved XIBROM drug product. All the CMC information remains as referenced to the currently approved NDA 21-664. An exclusion from the requirement to provide an environmental assessment for the proposed drug product has been requested. The request has been granted on the basis of categorical exclusions listed on 21 CFR 25.31(a).

16: Conclusions and Recommendations: There are no changes to any of the CMC aspects of this application. The only change to the currently approved drug product requested by this supplement is a name change. Labeling aspects of this request remain to be resolved between (potency, sample size) the clinical reviewer and the applicant. The CMC aspects of this application are acceptable, however, due to remaining labeling issues, from the CMC point of view, this supplement is recommended for a Complete Response (CR).

Labeling Issues:

- Naming (b) (4) acid.
- Potency of the final drug product.
- Clinical issue with the (b) (4) mL size, drug product market size.

CMC recommends no changes to the first two issues

Labeling issues will be discussed with the applicant on a labeling meeting scheduled for July26, 2010. In the mean time,

clinical, recommends (July 12, 2010 meeting) entering of this review into DARRTS.		
17. Name: **Libaniel Rodriguez, Chemist**	**Signature:**	**Date:**
18. Concurrence: **Hasmukh Patel, Branch Chief**	**Signature:**	**Date:**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

LIBANIEL RODRIGUEZ
07/12/2010

DAVID B LEWIS
07/12/2010
Concur; recommend COMPLETE RESPONSE regarding nomenclature issues. Signing for H. Patel.

NDA 21-664 XIDAY™ (bromfenac sodium (b) (4) ophthalmic solution) (b) (4)
74-day letter

ISTA Pharmaceuticals, Inc.
1595 Alton Parkway
Irvine, CA 62618

CMC review, February 23, 2010.

This NDA is for a change in dosing regime from the currentlyapproved twice-a-day (BID) dosing following cataract extraction surgery to once-a-day (QD) dosing beginning one day prior to surgery; continue on the day of surgery and for 14 days after surgery.

There are no changes to the CMC information for both drug substance and drug product. All the CMC information remains as referenced to the currently approved NDA 21-664. An exclusion from the preparation of an Environmental Assessment has been requested and will be reviewed. All facilities responsible for manufacturing testing and release of Xiday (bromphenac sodium (b) (4) ophthalmic solution) (b) (4) are ready for inspection.

Input for the 74-day letter: Because of the absence of any changes or modifications to any of the approved CMC aspects, no CMC comments for the 74-day letter will be issued.

Therefore, at this time in the review cycle (February 23, 2010), CMC has no issues to communicate in the 74-days letter.

Libaniel Rodriguez, Ph.D., Review Chemists, ONDQA

Swapan De, PH.D., Pharmaceutical Assessment Lead, ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

LIBANIEL RODRIGUEZ
02/23/2010

SWAPAN K DE
02/23/2010

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 21-664	**Supplement Number and Type: S/-013**	**Established/Proper Name: Bromfenac Ophthalmic Solution**
Applicant: ISTA Pharmaceuticals, INC.	**Letter Date: December 15, 2009**	**Stamp Date:**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		Approved NDA product, indicated for a more convenient administration regime.
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	X		

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			N/A
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			N/A

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			N/A
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			N/A

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?			Provided in original NDA
33.	Have the immediate container and carton labels been provided?			Provided in original NDA

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?			Describe potential review issues here or on additional sheets

{See appended electronic signature page}

Name of Libaniel Rodriguez, Ph.D.
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer Date 01 -22-2010
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

{See appended electronic signature page}

Name of Hasmukh Patel, Ph.D.
Branch Chief Date 01-22-2010
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

LIBANIEL RODRIGUEZ
01/21/2010

HASMUKH B PATEL
01/21/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-664
SERIAL NUMBER:	000, Efficacy Supplement
DATE RECEIVED BY CENTER:	12/15/09
DRUG NAME:	XiDay
INDICATION:	For the treatment of postoperative inflammation and for the reduction of (b) (4) in patients who have undergone cataract extraction
SPONSOR:	ISTA Pharmaceuticals, Inc.
DOCUMENTS REVIEWED:	Labeling
REVIEW DIVISION:	Division of Anti-Infective and Ophthalmology Products
PHARM/TOX REVIEWER:	Conrad H. Chen, Ph.D.
PHARM/TOX SUPERVISOR:	Wendelyn Schmidt, Ph.D.
DIVISION DIRECTOR:	Wiley Chambers, M.D.
PROJECT MANAGER:	Jane Dean

Date of review submission to Division File System (DFS):

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
The approval of this NDA is recommended.

B. Recommendation for nonclinical studies
None

C. Recommendations on labeling
The proposed labeling is similar to that of Xibrom which is currently marketed. The calculation of ratio of animal dose vs. human dose in the labeling is based on average human body weight of 60 kg. Since the recommended human daily dose of XiDay is one-half of Xibrom, the ratio of animal dose vs. human dose in the labeling should be recalculated.
The recommended labeling is as follows.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (722 times the recommended human ophthalmic dose [RHOD] of 0.83 μg/kg in a 60 kg person on a mg/kg/basis, assuming 100% absorbed) and 5.0 mg/kg/day (6,024 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 (1,084 and 360 times RHOD, respectively).

Pregnancy: Teratogenic Effects
Pregnancy Category C. Reproduction studies performed in rats at oral doses up to 0.9 mg/kg/day (1,084 times RHOD) and in rabbits at oral doses up to 7.5 mg/kg/day (9,036 times RHOD) revealed no evidence of teratogenicity due to bromfenac. However, 0.9 mg/kg/day in rats caused embryo-fetal lethality, reduced neonatal survival, and reduced postnatal growth. Pregnant rabbits treated with 7.5 mg/kg/day caused increased post-implantation loss.

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.

Note: The ratios of animal dose and human ocular dose in the labeling are calculated using 0.83 μg/kg/day as the human clinical dose.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
Bromfenac sodium was effective in inhibiting the active ocular inflammation in animal models. Bromfenac sodium inhibited both arachidonic acid and carrageenan-induced conjunctival edema in a dose-dependent manner, and the increase of aqueous humor protein typically seen in response to paracentesis and laser energy application.

B. Pharmacologic activity
Bromfenac sodium is a cyclooxygenase inhibitor possessing analgesic, anti-inflammatory, and antipyretic activities in various animal experimental models. It belongs to a non-steroidal anti-inflammatory drug class (NSAID) without any narcotic-like activity.

C. Non-clinical safety issues relevant to clinical use
In an ocular toxicity study in rabbits, a 0.5% bromfenac sodium ophthalmic solution was instilled into the eye 9 times daily for 4 weeks. In another ocular toxicity study in rabbits, 0.1%, 0.2% and 0.4% bromfenac sodium ophthalmic solution were instilled into the eye 4 times daily for 13 weeks. No ocular abnormalities were observed at any concentration in either study.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

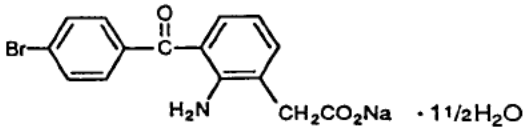
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-664
Review number: No.2
Sequence number/date/type of submission: SN000/December 15, 2009 / Efficacy Supplement
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: ISTA Pharmaceuticals, Inc.
Manufacturer for drug substance: [redacted] (b) (4)

Reviewer name: Conrad H. Chen, Ph.D.
Division name: Anti-infective and Ophthalmology Drug Products
Review completion date: July 9, 2010

Drug:

Trade name: XiDay™
Generic name: Bromfenac Sodium [redacted] (b) (4) Ophthalmic Solution [redacted] (b) (4) (each mL containing 1.035 mg bromfenac sodium equivalent to 0.9 mg bromfenac free acid)
Code name: AHR-10282B
Chemical name: Sodium 2-[amino-3-(4-bromobenzoyl) phenyl] acetate sesquihydrate
CAS registry number: 120638-55-3
Molecular formula/molecular weight: $C_{15}H_{11}BrNNaO_3 \cdot 1.5\,H_2O$
Structure:



Relevant INDs/NDAs/DMFs: The relevant non-clinical studies are contained in IND 60,295 and original NDA 21-664 (bromfenac sodium ophthalmic solution) and NDA 20-535 (Duract, bromfenac sodium capsules). The original NDA 21-664 was submitted on 5/26/04 and reviewed on 1/14/05.

Drug class: NSAID

Indication: For the treatment of postoperative inflammation and for the reduction of [redacted] (b) (4) in patients who have undergone cataract extraction

Clinical formulation:

Drug product quantitative composition

Components	Function	Amount/mL	%
Bromfenac sodium hydrate	Active ingredient	0.001035 g (b) (4) (b) (4)	0.1035*
Boric acid	(b) (4)		
Sodium borate			
Sodium sulfite, anhydrous			
Disodium edetate			
Povidone (b) (4)			
Polysorbate 80			
Benzalokonium chloride solution			
Sodium hydroxide			
Purified water (b) (4)			

Route of administration: Ophthalmic instillation

Proposed use: One drop of Xibrom ophthalmic solution should be applied to the affected eye(s) once daily beginning 1 day prior to surgery (b) (4)

Studies reviewed within this submission: No new non-clinical studies are submitted. The review of non-clinical studies contained in the initial submission of NDA 21-664 will not be repeated here.

OVERALL CONCLUSIONS AND RECOMMENDATIONS FOR INITIAL SUBMISSION OF NDA 21-664 (dated 1/14/05)

Conclusions:
Bromfenac sodium, AHR-10282B, is a cyclooxygenase inhibitor possessing analgesic, anti-inflammatory, and antipyretic activities in various animal experimental models. It belongs to a non-steroidal anti-inflammatory drug class (NSAID) without any narcotic-like activity. Bromfenac did not possess any significant effects on the central nervous system and cardiovascular function.
The oral formulation of bromfenac (Duract capsules) was developed by Wyeth-Ayerst and was approved for marketing under NDA 20-535 in 1997. However, because of the clinical findings of hepatotoxicity after marketing, Duract was withdrawn from the market in June 1998.
Bromfenac sodium was licensed to Senju Pharmaceutical Co., Ltd, Osaka, Japan for development as an ophthalmic solution. Senju conducted non-clinical and clinical studies for bromfenac ophthalmic solution and obtained approval for marketing in Japan in 2000. Senju recently sublicensed bromfenac for ophthalmic use in the United States to ISTA Pharmaceuticals, Inc. The non-clinical studies submitted in this NDA were conducted by Wyeth-Ayerst and Senju Pharmaceuticals.

Bromfenac sodium was effective in inhibiting the active ocular inflammation in animal models. Bromfenac sodium inhibited both arachidonic acid and carrageenan-induced conjunctival edema in a dose-dependent manner, and the increase of aqueous humor protein typically seen in response to paracentesis and laser energy application.
The systemic toxicity studies for bromfenac sodium were previously reviewed under NDA 21-535. Bromfenac sodium caused predominantly the GI toxicity in animal studies through a systemic administration. Kidney and hepatic toxicity was also observed. Oral formulation of bromfenac sodium was withdrawn from the market after the discovery of critical liver toxicity in the clinical use.
In an ocular toxicity study in rabbits, a 0.5% bromfenac sodium ophthalmic solution was instilled into the eye 9 times daily for 4 weeks. In another ocular toxicity study in rabbits, 0.1%, 0.2% and 0.4% bromfenac sodium ophthalmic solution were instilled into the eye 4 times daily for 13 weeks. No ocular abnormalities were observed at any concentration in either study. The proposed clinical dose of Xibrom (0.1% bromfenac sodium ophthalmic solution) is one drop twice daily for up to 2 weeks. At the similar dosing regimen, no adverse effects, systemic or ocular, were observed in the rabbit studies.
Following instillation of ^{14}C-bromfenac in the eyes of male rabbits at a dose of 0.1 mg (two 0.05 mL drops of a 0.1% solution), plasma C_{max} of 113 ng·eq/mL was observed at 30 minutes following administration. The calculated plasma half-life was 2.2 hours, and the AUC_{0-12} was 156 ng·eq·hr/mL. The plasma radioactivity was below detectable levels (0.4 ng·eq/mL) at 24 hours following a single administration.
Following repeated instillation of ^{14}C-bromfenac in the eyes of male rabbits at a dose of 0.1 mg/day for 21 days, the plasma concentration of bromfenac at 24 hours following the last dose was measured as 1.3 ± 0.2 ng·eq/mL. At 72 and 168 hours following the last dose, the plasma radioactivity levels were measured to be 0.8 ± 0.0 ng·eq/mL and below detectable levels, respectively.
The recommended clinical dose of Duract (oral formulation of bromfenac sodium) is 25 to 50 mg every 6 to 8 hours, not to exceed 150 mg/day (2.5 mg/kg/day in a 60 kg body weight person). In an oral pharmacokinetic study in monkeys with single dose or repeat dose at 3 mg/kg/day, the C_{max} were 2,440 and 5,860 ng/mL, respectively and the AUC_{0-24} were 2,970 and 4,490 ng·hr/mL, respectively. Based on these data, it appeared that the ratios between the AUC of 3 mg/kg/day oral dose in monkeys and 0.1 mg/day ocular dose in rabbits were 19 (2970/156) for single dose and 29 (4490/156) for repeat dose, respectively. Please note that two different animal species were compared here because no data from the same species were available for this calculation.
The daily administration of 2 drops/eye (or 100 µL) of 0.1% (1 µg/ 1 µL) Xibrom in a 60 kg body weight person equals to 100 µg/person/day or 1.67 µg/kg/day. The previously approved clinical dose of Duract (oral formulation of bromfenac sodium) is 25 to 50 mg every 6 to 8 hours, not to exceed 150 mg/day (2.5 mg/kg/day in a 60 kg body weight person). Therefore, the ratio of the recommended daily oral dose and daily ocular dose is 1500 (2.5 mg/kg/day or 2,500 µg/kg/day ÷ 1.67 µg/kg/day = 1,500). The chance of adverse effects, which is found in the oral administration of Duract, is probably very small in the administration of Xibrom.

Recommendations:

The approval of 0.1% bromfenac sodium ophthalmic solution (Xibrom™) is recommended.

OVERALL CONCLUSIONS AND RECOMMENDATIONS FOR CURRENT sNDA SUBMISSION (efficacy supplement dated 12/15/09)

Since the recommended human clinical dose of XiDay is one-half of Xibrom, the labeling of XiDay should be modified accordingly.

The daily administration of 1 drops/eye (or 50 μL) of 0.1% (1 μg/ 1 μL) XiDay in a 60 kg body weight person equals to 50 μg/person/day or 0.83 μg/kg/day. The previously approved clinical dose of Duract (oral formulation of bromfenac sodium) is 25 to 50 mg every 6 to 8 hours, not to exceed 150 mg/day (2.5 mg/kg/day in a 60 kg body weight person). Therefore, the ratio of the recommended daily oral dose and daily ocular dose is 3,012 (2.5 mg/kg/day or 2,500 μg/kg/day ÷ 0.83 μg/kg/day = 3,012). The chance of adverse effects, which is found in the oral administration of Duract, is probably very small in the administration of XiDay.

Suggested labeling:

The proposed label for XiDay is similar to label for marketed Xibrom. Since the recommended daily dose of XiDay is one-half of Xibrom, the ratio of animal dose vs. human clinical ocular dose should be recalculated. Human clinical ocular dose of 0.83 μg/kg/day for XiDay should be used in recalculation. The recommended label for XiDay is shown in the Executive Summary in the page 1.

Signatures (optional):

Reviewer Signature _____
Conrad H. Chen, Ph.D., Pharmacologist

Supervisor Signature_____ Concurrence Yes ___ No ___
Wendelyn Schmidt, Ph.D., Pharmacology Team Leader

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

CONRAD H CHEN
07/15/2010

WENDELYN J SCHMIDT
07/15/2010
I concur with the reviewer's assessment of the acceptability and conclusions.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

M E M O R A N D U M

DATE: September 3, 2010

FROM: Yan Wang, Ph.D.
Statistical Team Leader
Division of Biometrics IV
Office of Biostatistics/OTS

SUBJECT: Statistical team leader's efficacy evaluation of NDA 21664/S013 for Bromfenac ophthalmic solution 0.09% for the treatment of ocular inflammation and pain associated with cataract extraction.

This memorandum is to state that I concur with the primary statistical reviewer's assessment of the acceptability and conclusions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

YAN WANG
09/03/2010

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21664/S013
Drug Name:	Bromfenac Ophthalmic Solution 0.09%
Indication(s):	Treatment of ocular inflammation and pain associated with cataract extraction
Applicant:	ISTA Pharmaceuticals, Inc.
Date(s):	Submitted: 12/16/2009
PDUFA Date:	10/16/2010
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Yunfan Deng, Ph.D.
Concurring Reviewer:	Yan Wang, Ph.D.
Medical Division:	Division of Anti-Infective and Ophthalmologic Drug Products (HFD-520)
Clinical Team:	Jennifer Harris, MD, Clinical Reviewer William Boyd, MD, Clinical Team Leader
Project Manager:	Jane Dean

Keywords:

NDA, Superiority, Ocular Inflammation, Ocular Pain, Cataract Surgery

TABLE OF CONTENTS

LIST OF TABLES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This NDA is a supplement NDA for bromfenac sodium (b) (4) ophthalmic solution 0.09%. Xibrom™ (bromfenac opthalmic solution 0.09%) was approved by the FDA for the treatment of post-operative ocular inflammation in March 2005 and in January 2006 for the treatment of post-operative pain. The approved dosing regimen is dosed **twice daily (BID)**. This submission is seeking approval for bromfenac opthalmic solution 0.09% (AKA bromfenac sodium (b) (4) ophthalmic solution (b) (4) dosed **once daily (QD)** regimen in the treatment of both inflammation and pain in subjects undergoing cataract surgery.

The Applicant conducted four studies in support of the approval of this supplement. Study CL-S&E-0802071-P was a multi-center, randomized, double-masked, active-control study comparing bromfenac ophthalmic solution 0.18% once daily versus 0.09% once daily. Since the non-inferiority margin for study CL-S&E-0802071-P can't be justified clinically, this study will not be evaluated for the efficacy purpose. Studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P were all randomized, double-masked, multi-center, placebo-controlled superiority studies; and they will be the focus of this statistical review for evaluating efficacy.

For studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P, the primary efficacy endpoints were the same – defined as the proportion of subjects who had cleared ocular inflammation in the study eye by Day 15. The secondary efficacy endpoints for all three studies were also the same – defined as the proportion of subjects who had an ocular pain response of "None" in the study eye at Day 1.

Primary Efficacy Endpoint

For study CL-S&E-0415081-P-ER, there was no statistically significance difference between the bromfenac group 44.4% (28/63) and the placebo group 31.7% (20/63) in the proportion of subjects who had cleared ocular inflammation by Day 15. The treatment difference was 12.7% with 95% CI of (-4.1%, 29.5%), and the p-value was 0.14.

Both studies CL-S&E-0415081-P-WR and CL-S&E-1205081-P showed statistically significant difference between the bromfenac group and the placebo group in the proportion of subjects who had cleared ocular inflammation by Day 15.

For study CL-S&E-0415081-P-WR, the proportion of subjects who had cleared ocular inflammation by Day 15 was 46.2% (36/78) for the bromfenac group and 29.5% (23/78) for the placebo group. The treatment difference was 16.7% with 95% CI of (1.7%, 31.7%), and the p-value was 0.032.

For study CL-S&E-1205081-P, the proportion of subjects who had cleared ocular inflammation by Day 15 was 46.1% (70/152) for the bromfenac group and 24.5% (36/147) for the placebo

group. The treatment difference was 21.6% with 95% CI of (11.0%, 32.1%), and the p-value was <0.0001.

Secondary Efficacy Endpoint

For study CL-S&E-0415081-P-ER, there was no statistically significance difference between the bromfenac group 81.0% (51/63) and the placebo group 73.0% (46/63) in the proportion of subjects who had ocular pain response of "None" at Day 1. The treatment difference was 7.9% 95% CI of (-6.7%, 22.6%), and the p-value was 0.29.

Both studies CL-S&E-0415081-P-WR and CL-S&E-1205081-P showed statistically significant difference between the bromfenac group and the placebo group in the proportion of subjects who had ocular pain response of "None" at Day 1.

For study CL-S&E-0415081-P-WR, the proportion of subjects who had ocular pain response of "None" at Day 1 was 83.3% (65/78) for the bromfenac group and 51.9% (40/78) for the placebo group. The treatment difference was 31.4% with 95% CI of (17.5%, 45.3%), and the p-value was <0.0001.

For study CL-S&E-1205081-P, the proportion of subjects who had cleared ocular inflammation by Day 15 was 88.8% (135/152) for the bromfenac group and 71.4% (105/147) for the placebo group. The treatment difference is 17.4% with 95% CI of (8.5%, 26.2%), and the p-value was 0.0002.

Conclusion

Based on the analysis results of the primary and secondary efficacy endpoints for studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P, we recommend the approval of bromfenac ophthalmic solution 0.09% dosed once daily (QD) regimen for the treatment of both inflammation and pain in subjects undergoing cataract surgery.

1.2 Brief Overview of Clinical Studies

Studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P were all phase 3 studies. All three studies were multi-center, randomized, double-masked, vehicle-controlled, parallel-group studies.

Data for studies CL-S&E-0415081-P-ER and CL-S&E-0415081-P-WR were collected under a common protocol; and conducted and analyzed as two independent studies. The sites for these two studies apportioned to each study geographically, adhering as close as possible to sites west of the Mississippi River in one study and sites east of the Mississippi River in the second study; and separate randomization sequences were used for each study. Study CL-S&E-0415081-P-ER showed no statistically significant difference between the bromfenac group and the placebo group; while study CL-S&E-0415081-P-WR was successful. In order to obtain approval for

bromfenac ophthalmic solution 0.09% QD, the Applicant conducted study CL-S&E-1205081-P, which had similar study design as the previous two studies.

For all three studies, subjects who met the criteria for enrollment were randomly assigned to use either bromfenac ophthalmic solution 0.09% or placebo once daily in the study eye in a 1:1 ratio. Dosing with study drug began 1 day prior to surgery (Day -1) and continued on the day of surgery (Day 0) and for 14 days after surgery. Subjects were seen for evaluation on Days 1, 3 ± 1, 8 ± 1, and 15 ± 1 following surgery. Subjects were seen for a follow-up visit on Day 22 + 3 following surgery or 7 +3 days after their last dose of study drug if they discontinued the study drug prematurely.

The primary efficacy endpoints for all three studies were 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 a summed ocular inflammation score (SOIS) 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. The secondary efficacy endpoints for all three studies were the proportion of subjects who had an ocular pain response of "None" at Day 1.

All three studies were conducted in the U.S. Study CL-S&E-0415081-P-ER randomized 126 patients from 18 study sites; 63 patients were randomized to the bromfenac group and 63 to the placebo group. Study CL-S&E-0415081-P-WR randomized 156 patients from 19 study sites; 78 patients were randomized to the bromfenac group and 78 to the placebo group. Study CL-S&E-1205081-P randomized 299 patients from 41 study sites; 152 patients were randomized to the bromfenac group and 147 to the placebo group.

1.3 Statistical Issues and Findings

There are no major statistical issues for studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P.

The primary efficacy endpoints for all three studies were the proportion of subjects who had cleared ocular inflammation in the study eye by Day 15. The secondary efficacy endpoints for all three studies were the proportion of subjects who had an ocular pain response of "None" in the study eye at Day 1. The primary and secondary analyses were all conducted on the intent-to-treat (ITT) population, which included all randomized patient. Treatment difference between the bromfenac group and the placebo group was tested using the chi-square test.

Missing values were imputed using the last-observation-carried-forward (LOCF) method in both primary and secondary analyses. There were two types of missing values: 1) from subjects who did not respond to study drug treatment (based on assessment of ocular inflammation and ocular pain) and who required alternative medical management (i.e., rescue therapy) and 2) from subjects who missed scheduled evaluations but continued on study drug treatment during the study. For the first type of missing data, those subjects who received a rescue medication prior to Day 15, the observed outcome nearest (on or before) the date of receiving rescue medication

were carried forward and used in the determination of the missing outcome. For the second type of missing data, the outcome from the last visit at which it was measured was carried forward.

The analyses results for the proportion of patients who had cleared ocular inflammation by each visit and the proportion of patients who had ocular pain response of "None" by each visit are presented in the following two tables, where the highlighted rows correspond with the primary and secondary efficacy endpoints for each of the three studies.

The statistical reviewer analyzed the data treating patients who discontinued the study early as treatment failure (i.e. not having cleared ocular inflammation) and also analyzed the data using observed data only. Results of both approaches are in general consistent with the primary efficacy analyses results.

Table 1: Proportion of Subjects with Cleared Ocular Inflammation by Each Visit (ITT LOCF)

Study CL-S&E-0415081-P-ER				
	Bromfenac 0.09% N=63	**Placebo N=63**	**p-value**	**Difference (95% CI)**
Day 1	3 (4.8%)	3 (4.8%)	1.00	0.0% (-7.4%, 7.4%)
Day 3	6 (9.5%)	7 (11.1%)	0.77	-1.6% (-12.2%, 9.0%)
Day 8	20 (31.7%)	15 (23.8%)	0.32	7.9% (-7.6%, 23.5%)
Day 15	28 (44.4%)	20 (31.7%)	0.14	12.7% (-4.1%, 29.5%)
Study CL-S&E-0415081-P-WR				
	Bromfenac 0.09% N=78	**Placebo N=78**	**p-value**	**Difference (95% CI)**
Day 1	5 (6.4%)	9 (11.5%)	0.26	-5.1% (-14.1%, 3.8%)
Day 3	9 (11.5%)	10 (12.8%)	0.81	-1.3% (-11.5%, 9.0%)
Day 8	20 (25.6%)	14 (17.9%)	0.24	7.7% (-5.2%, 20.6%)
Day 15	36 (46.2%)	23 (29.5%)	0.032	16.7% (1.7%, 31.7%)
Study CL-S&E-1205081-P				
	Bromfenac 0.09% N=152	**Placebo N=147**	**p-value**	**Difference (95% CI)**
Day 1	12 (7.9%)	9 (6.1%)	0.55	1.8% (-4.0%, 7.6%)
Day 3	17 (11.2%)	12 (8.2%)	0.38	3.0% (-3.6%, 9.7%)
Day 8	36 (23.7%)	23 (15.6%)	0.08	8.0% (-0.9%, 17.0%)
Day 15	70 (46.1%)	36 (24.5%)	<0.0001	21.6% (11.0%, 32.1%)

Source: Table 8 of the Applicant's CL-S&E-0415081-P-ER study report, Table 8 of the Applicant's CL-S&E-0415081-P-WR study report, and Table 8 of the Applicant's CL-S&E-1205081-P study report.

Table 2: Proportion of Subjects with Ocular Pain Response of "None" by Each Visit (ITT LOCF)

	Bromfenac 0.09% N=63	Placebo N=63	p-value	Difference (95% CI)
Study CL-S&E-0415081-P-ER				
Day 1	51 (81.0%)	46 (73.0%)	0.29	7.9% (-6.7%, 22.6%)
Day 3	56 (88.9%)	46 (73.0%)	0.023	15.9% (2.4%, 29.3%)
Day 8	60 (95.2%)	45 (71.4%)	0.0003	23.8% (11.5%, 36.1%)
Day 15	59 (93.7%)	46 (73.0%)	0.0019	20.6% (8.1%, 33.1%)
Study CL-S&E-0415081-P-WR				
	Bromfenac 0.09% N=78	**Placebo N=78**	**p-value**	**Difference (95% CI)**
Day 1	65 (83.3%)	40 (51.9%)	<0.0001	31.4% (17.5%, 45.3%)
Day 3	74 (94.9%)	51 (66.2%)	<0.0001	28.6% (17.0%, 40.3%)
Day 8	75 (96.2%)	54 (70.1%)	<0.0001	26.0% (15.0%, 37.1%)
Day 15	76 (97.4%)	57 (74.0%)	<0.0001	23.4% (13.0%, 33.8%)
Study CL-S&E-1205081-P				
	Bromfenac 0.09% N=152	**Placebo N=147**	**p-value**	**Difference (95% CI)**
Day 1	135 (88.8%)	105 (71.4%)	0.0002	17.4% (8.5%, 26.2%)
Day 3	139 (91.4%)	105 (71.4%)	<0.0001	20.0% (11.5%, 28.6%)
Day 8	142 (93.4%)	106 (72.1%)	<0.0001	21.3% (13.1%, 29.6%)
Day 15	145 (95.4%)	107 (72.8%)	<0.0001	22.6% (14.7%, 30.5%)

Source: Table 20 of the Applicant's CL-S&E-0415081-P-ER study report, Table 20 of the Applicant's CL-S&E-0415081-P-WR study report, and Table 16 of the Applicant's CL-S&E-1205081-P study report.

2. INTRODUCTION

2.1 Overview

Bromfenac belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs), which function by blocking the production of prostaglandins, mediators of various kinds of systemic and localized (e.g., ocular) inflammation. Bromfenac inhibits prostaglandin production by inhibiting cyclooxygenase (COX), the enzyme that converts arachidonic acid to cyclic endoperoxides, precursors of prostaglandins. Bromfenac was developed by brominating the 4 position of the benzoyl group of a 2-amino-3-benzoylphenylacetic acid derivative, resulting in sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate, with the goal of achieving anti-inflammatory, antipyretic, and analgesic effects greater than other commercially available NSAIDs. Bromfenac has been shown to be an extremely potent inhibitor of COX and subsequent prostaglandin synthesis. The *in-vitro* inhibitory effects of bromfenac on COX activity and

prostaglandin synthesis in bovine seminal vesicle gland microsomes was found to be 12 times greater than that of indomethacin. Another *in-vitro* study utilizing cloned cDNA from human monocytes showed that bromfenac produced very low IC_{50}'s for rhCOX – 1 and rhCOX – 2 of 5.1 nM and 4 nM, respectively.

Xibrom (bromfenac ophthalmic solution)® 0.09% BID, which is dosed twice a day, was approved by the Food and Drug Administration (FDA) in March 2005 for the treatment of post-operative ocular inflammation and in January 2006 for the treatment of post-operative ocular pain. Bronuck® (bromfenac sodium ophthalmic solution) 0.1% was approved in Japan in July 2000, and it is indicated for the treatment of blepharitis, conjunctivitis, scleritis (including episcleritis) and post-operative inflammation in Japan. The formulation of bromfenac that was approved for use in Japan is identical to that approved for use in the US. In computing concentrations, the Japanese formulation is represented as the salt (0.1%) while the US formulation is represented as the free acid (0.09%)

2.2 Data Sources

The Sponsor's study reports and study data for all four submitted studies are available on the EDR at \\CDSESUB1\EVSPROD\NDA021664.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Designs and Endpoints

Studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P were all phase 3 studies. All three studies were multi-center, randomized, double-masked, parallel-group, vehicle-controlled studies.

Data for studies CL-S&E-0415081-P-ER and CL-S&E-0415081-P-WR were collected under a common protocol and conducted and analyzed as two independent studies. The sites for these two studies apportioned to each study geographically, adhering as close as possible to sites west of the Mississippi River in one study and sites east of the Mississippi River in the second study; and separate randomization sequences were used for each study. However, study CL-S&E-0415081-P-ER failed its primary efficacy endpoint while study CL-S&E-0415081-P-WR was successful. In order to obtain approval for bromfenac ophthalmic solution 0.09% QD, the Applicant conducted study CL-S&E-1205081-P, which had similar study design as the previous two studies.

For all three studies, subjects who met the criteria for enrollment were randomly assigned to use either bromfenac ophthalmic solution 0.09% or placebo once daily in the study eye in a 1:1 ratio. Dosing with study drug began 1 day prior to surgery (Day -1) and continued on the day of surgery (Day 0) and for 14 days after surgery. The study investigators and study staff, as well as subjects, were masked to the identity of the study drug. Subjects recorded whether or not they

administered the study drug each day in the Subject Diary. Subjects were seen for evaluation on Days 1, 3 ± 1, 8 ± 1, and 15 ± 1 following surgery. Subjects were seen for a follow-up visit on Day 22 + 3 following surgery or 7 +3 days after their last dose of study drug if they discontinued the study drug prematurely.

The key inclusion criteria for all three studies were:

1. Male or female at least 18 years of age who were scheduled for unilateral cataract surgery (phacoemulsification or extracapsular) with posterior chamber intraocular lens implantation and for whom no other ophthalmic surgical procedures (e.g., 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 study drug or throughout the duration of the study.
3. Had a Best Corrected Visual Acuity of 20/200 or better in the fellow (non-study) eye.

The primary efficacy endpoints for all three studies were the proportion of subjects who had cleared ocular inflammation in the study eye by Day 15. A subject was considered to have cleared ocular inflammation if the subject achieved a summed ocular inflammation score (SOIS) of 0 (i.e., 0 cells and absence of flare). The SOIS is defined as the sum of the mean anterior chamber cells score and anterior flare score. The secondary efficacy endpoints for all three studies were the proportion of subjects who had an ocular pain response of "None" in the study eye at Day 1.

The primary objective of all three studies was to investigate the efficacy of bromfenac ophthalmic solution 0.09% QD for the treatment of ocular inflammation and pain associated with cataract surgery in subjects who have undergone cataract extraction with posterior chamber intraocular lens implantation.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Study CL-SE-0415081-P-ER

A total of 131 patients were screened; and 126 patients from 18 study sites were randomized to receive any study treatment and included in the intent-to-treat (ITT) population. Two subjects (3.2%) in each treatment group terminated the study early (prior to Day 22 or prior to 1 week follow-up); the reasons for early termination in the bromfenac ophthalmic solution 0.09% group was withdrawal of consent/non-compliance for 1 subject and other reason (cancelled surgery) for 1 subject, and in the placebo group, it was withdrawal of consent/noncompliance for 2 subjects.

A subject could have prematurely discontinued study drug for the following reasons: AE (ocular or systemic), use of prohibited concomitant medication, lack of efficacy, or "other" reason specified by the investigator. By protocol, a subject was considered to have completed the study if the subject either completed (on or after) post-surgery Day 22 visit or if the subject completed a follow-up visit 1 week (7 + 3 days) after prematurely discontinuing study drugs. In this study,

61/63 (96.8%) subjects in the bromfenac group and 61/63 (96.8%) subjects in the placebo group completed the study.

The proportion of subjects who discontinued study drug in the bromfenac ophthalmic solution 0.09% treatment group (14/63, 22.2%) was much lower than the proportion who discontinued study drug in placebo group (31/63, 49.2%; see the following table).

Among reasons for early discontinuation of study drug, greater proportion of subjects in the placebo group (20/63, 31.7%) discontinued due to lack of efficacy compared with the bromfenac group (6/63, 9.5%). The proportion of subjects who discontinued treatment for an adverse event (AE) in the placebo group (9/63, 14.3%) was higher than in the bromfenac group (5/63, 7.9%). Other reasons for discontinuation of study drug were disallowed medication (1 subject, 1.6% in the bromfenac ophthalmic solution 0.09% treatment group), and 4 subjects overall (3.2%) also discontinued study drug prematurely for other reasons (withdrawal of consent by 3 subjects; and cancelled surgery, 1 subject).

Disposition of all randomized patients is shown in the following table.

Table 3: Study CL-SE-0415081-P-ER Summary of Subject Disposition

	Bromfenac Ophthalmic Solution 0.09%	**Placebo**	**Total**
Number of Subjects Randomized	63	63	126
Subjects who Completed Study	61 (96.8%)	61 (96.8%)	122 (96.8%)
Subjects who Terminated the Study Prior to Post-Surgery Day 22 or Prior to 1 Week Follow-up	2 (3.2%)	2 (3.2%)	4 (3.2%)
Primary Reason for Early Termination			
Withdrawal of Consent/Non-compliance	1 (1.6%)	2 (3.2%)	3 (2.4%)
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (1.6%)	0 (0.0%)	1 (0.8%)
Subjects Who Discontinued Study Drug Early	14 (22.2%)	31 (49.2%)	45 (35.7%)
Primary Reason for Early Discontinuation of Study Drug			
Adverse Event	5 (7.9%)	9 (14.3%)	14 (11.1%)
Disallowed Concurrent Medication	1 (1.6%)	0 (0.0%)	1 (0.8%)
Lack of Efficacy	6 (9.5%)	20 (31.7%)	26 (20.6%)
Other	2 (3.2%)	2 (3.2%)	4 (3.2%)

Source: Table 4 and Table 6 of the Applicant's CL-S&E-0415081-P-ER study report.

The number and proportion of subjects completing Day 1, Day 3, Day 8, Day 15, and Day 22 visit are presented in the following table. It is noted that there were more patients completed Day 15 visit in the bromfenac group (49/63, 77.8%) compared to the placebo group (32/63, 50.8%).

Table 4: Study CL-SE-0415081-P-ER's Visit Completed (ITT Population)

# of Subjects Completing	Bromfenac Ophthalmic Solution 0.09% N=63	Placebo N=63
Day 1	60 (95.2%)	60 (95.2%)
Day 3	58 (92.1%)	59 (93.7%)
Day 8	51 (81.0%)	49 (77.8%)
Day 15	49 (77.8%)	32 (50.8%)
Day 22	61 (96.8%)	61 (96.8%)

Source: Table 5 of the Applicant's CL-S&E-0415081-P-ER study report.

Of the total number of subjects 14/126 (11.1%) in the ITT Population who discontinued study drug due to an AE, 2/63 (3.2%) in the bromfenac ophthalmic solution 0.09% treatment group and 1/63 (1.6%) in the placebo treatment group did so on or before the day of surgery, Day 0, none in the bromfenac ophthalmic solution 0.09% group and 1/63 (1.6%) in the placebo group at Day 1, 2/63 (3.2%) in the bromfenac ophthalmic solution 0.09% and 2/63 (3.2%) in the placebo group by Day 3, none in the bromfenac ophthalmic solution 0.09% compared with 4/63 (6.3%) in the placebo group on Day 8 and 1/63 (1.6%) in the bromfenac ophthalmic solution 0.09% and 1/63 (1.6%) in the placebo group by Day 15.

Only 1/126 (0.8%) subject discontinued study drug due to a disallowed concurrent medication; this subject discontinued at Day 3 in the bromfenac ophthalmic solution 0.09% treatment group.

The 26/126 (20.6%) subjects who discontinued due to lack of efficacy did so on Days 3, 8, and 15. The day when the largest proportions of subjects discontinued for lack of efficacy differed between the two treatment groups, 4/63 (6.3%) of the subjects in the bromfenac ophthalmic solution 0.09% treatment group discontinued at Day 3 while 14/63 (22.2%) of the subjects in the placebo treatment group discontinued at Day 8.

The following table presents the number of patients discontinued study treatment by visit.

Table 5: Study CL-SE-0415081-P-ER Number of Patients Discontinued Study Treatment by Visit

	Bromfenac Ophthalmic Solution 0.09% N=63	Placebo N=63	Total N=126
Subjects Who Discontinued Study Drug Early	14 (22.2%)	31 (49.2%)	45 (35.7%)
Primary Reason for Early Discontinuation of Study Drug			
Adverse Event	5 (7.9%)	9 (14.3%)	14 (11.1%)
Day 0	2 (3.2%)	1 (1.6%)	3 (2.4%)
Day 1	0	1 (1.6%)	1 (0.8%)
Day 3	2 (3.2%)	2 (3.2%)	4 (3.2%)
Day 8	0	4 (6.3%)	4 (3.2%)
Day 15	1 (1.6%)	1 (1.6%)	2 (1.6%)
Day 22	0	0	0
Disallowed Concurrent Medication	1 (1.6%)	0	1 (0.8%)
Day 3	1 (1.6%)	0	1 (0.8%)
Lack of Efficacy	6 (9.5%)	20 (31.7%)	26 (20.6%)
Day 0	0	0	0
Day 1	0	0	0
Day 3	4 (6.3%)	4 (6.3%)	8 (6.3%)
Day 8	1 (1.6%)	14 (22.2%)	15 (11.9%)
Day 15	1 (1.6%)	2 (3.2%)	3 (2.4%)
Day 22	0	0	0
Other	2 (3.2%)	2 (3.2%)	4 (3.2%)

Source: Table 14.1.1.7 of the Applicant's CL-S&E-0415081-P-ER study report.

The summaries of baseline demographic characteristics are presented in Table 6. There was no marked difference in the baseline characteristics between the two treatment groups.

Table 6: Study CL-SE-0415081-P-ER Baseline Demographics (ITT Population)

		Bromfenac Ophthalmic Solution 0.09% N=63		Placebo N=63		Total N=126	
		n	(%)	n	(%)	n	(%)
Gender	**Male**	23	36.5	25	39.7	48	38.1
	Female	40	63.5	38	60.3	78	61.9
Age	**MEAN**		67.1		68.6		67.9
	SD		10.8		8.6		9.8
	MEDIAN		70		69		69
	RANGE		41 to 86		51 to 87		41 to 87
Race	**Asian**	0	0.0	1	1.6	1	0.8
	Black	4	6.3	4	6.3	8	6.3
	Caucasian	53	84.1	53	84.1	106	84.1
	Hispanic	5	7.9	4	6.3	9	7.1
	Other	1	1.6	1	1.6	2	1.6
Iris Color	**Black**	0	0	0	0	0	0
	Blue	22	34.9	22	34.9	44	34.9
	Brown	25	39.7	28	44.4	53	42.1
	Gray	0	0	2	3.2	2	1.6
	Green	6	9.5	5	7.9	11	8.7
	Hazel	10	15.9	6	9.5	16	12.7
	Other	0	0	0	0	0	0
Iris Color	**Light Irides**	32	50.8	30	47.6	62	49.2
	Dark Irides	31	49.2	33	52.4	64	50.8

Source: Table 14.1.2.1 of the Applicant's CL-S&E-0415081-P-ER study report.

Study CL-SE-0415081-P-WR

A total of 159 patients were screened; and 156 patients from 19 study sites were randomized to receive any study treatment and included in the intent-to-treat (ITT) population. Five subjects (3.2%) in each treatment group were randomized, but never dosed with study drug.

A subject could have prematurely discontinued study drug for the following reasons: AE (ocular or systemic), use of prohibited concomitant medication, lack of efficacy, or "other" reason specified by the investigator. By protocol, a subject was considered to have completed the study if the subject either completed (on or after) post-surgery Day 22 visit or if the subject completed a follow-up visit 1 week (7 + 3 days) after prematurely discontinuing study drugs. Seventy-three (73/78, 93.6%) subjects in the bromfenac ophthalmic solution 0.09% treatment group and 72/78 (92.3%) subjects in the placebo group completed the study.

The proportion of subjects who discontinued study drug in the bromfenac ophthalmic solution 0.09% group (16/78, 20.5%) was much lower than the proportion of subjects who discontinued study drug in the placebo group (47/78, 60.3%; see the following table).

Among reasons for early discontinuation of study drug, greater proportion of subjects in the placebo group (27/78, 34.6%) discontinued due to lack of efficacy compared with the bromfenac group (2/78, 2.6%). The proportion of subjects who discontinued treatment for an AE in the placebo group (12/78, 15.4%) was higher than in the bromfenac group (5/78, 6.4%).

Disallowed concurrent medication was another reason for discontinuation of study drug (1/78 subject, 1.3% in the bromfenac ophthalmic solution 0.09% treatment group and 2/78, 2.6%, in the placebo group). Other reasons were the primary reason for discontinuation of study drug for 8/78 (10.3%) subjects in the bromfenac ophthalmic solution 0.09% group and 6/78 (7.7%) subjects in the placebo group. The Other reasons for early discontinuation of study drug included: withdrew consent (6 subjects), over enrollment (4 subjects), protocol violation (2 subjects) and (1 subject each) non compliance and surgery postponement.

Disposition of all randomized patients is shown in the following table.

Table 7: Study CL-SE-0415081-P-WR Summary of Subject Disposition

	Bromfenac Ophthalmic Solution 0.09%	**Placebo**	**Total**
Number of Subjects Randomized	78	78	156
Subjects who Completed Study	73 (93.6%)	72 (92.3%)	145 (92.9%)
Subjects who Terminated the Study Prior to Post-Surgery Day 22 or Prior to 1 Week Follow-up	5 (6.4%)	6 (7.7%)	11/156 (7.1%)
Primary Reason for Early Termination			
Withdrawal of Consent/Non-compliance	2 (2.6%)	0 (0%)	2/156 (1.3%)
Lost to Follow-up	0 (0%)	0 (0%)	
Death	0 (0%)	0 (0%)	
Other	3 (3.8%)	6 (7.7%)	9/156 (57.7%)
Subjects Who Discontinued Study Drug Early	16 (20.5%)	47 (60.3%)	63/156 (40.4%)
Primary Reason for Early Discontinuation of Study Drug			
Adverse Event	5 (6.4%)	12 (15.4%)	17/156 (10.9%)
Disallowed Concurrent Medication	1 (1.3%)	2 (2.6%)	3/156 (1.9%)
Lack of Efficacy	2 (2.6%)	27 (34.6%)	29/156 (18.6%)
Other	8 (10.3%)	6 (7.7%)	14/156 (9.0%)

Source: Table 4 and Table 6 of the Applicant's CL-S&E-0415081-P-WR study report.

The number and proportion of subjects completing Day 1, Day 3, Day 8, Day 15, and Day 22 visit are presented in the following table. It is noted that there were much more patients completed Day 15 visit in the bromfenac group (62/78, 79.5%) compared to the placebo group (32/78, 41.0%).

Table 8: Study CL-SE-0415081-P-WR's Visit Completed (ITT Population)

# of Subjects Completing	**Bromfenac Ophthalmic Solution 0.09% N=78**	**Placebo N=78**
Day 1	73 (93.6%)	70 (89.7%)
Day 3	70 (89.7%)	65 (83.3%)
Day 8	65 (83.3%)	41 (52.6%)
Day 15	62 (79.5%)	32 (41.0%)
Day 22	73 (93.6%)	72 (92.3%)

Source: Table 5 of the Applicant's CL-S&E-0415081-P-WR study report.

Of the 17/156 (10.9%) subjects in the ITT Population who discontinued study drug due to an AE: 3/156 (1.9%) subjects (1/78, 1.3% in the bromfenac group and 2/78, 2.6% in the placebo group) discontinued at the study visit Day 0; 6/156 (3.8%) subjects discontinued at the Day 3 visit (2/78 [2.6%] subjects in the bromfenac group and 4/78 [5.1%] subjects in the placebo group); and 8/156 (5.1%) subjects discontinued at the Day 8 visit (2/78 [2.6%] in the bromfenac group and 6/78 [7.7%] in the placebo treatment group).

The subject in the bromfenac group who discontinued study drug use due to disallowed concurrent medication (1/78 [1.3%]), did so at the Day 3 visit, whereas the 2/78 (2.6%) subjects in the placebo group discontinued at the Day 0 visit.

The majority of the 27/78 (34.6%) subjects in the placebo group who discontinued due to lack of efficacy did so earlier in the study, at the Day 3 visit (16/78, 20.5%) and Day 1 visit (4/78, 5.1%), whereas others in the placebo group discontinued due to lack of efficacy at the Day 8 (6/78, 7.7%) and Day 15 (1/78, 1.3%) visits.

The Other reasons for discontinuation of study drug (in addition to those mentioned for Other reasons for premature termination from the study) in the bromfenac ophthalmic solution 0.09% treatment group were over enrollment (Subjects 13-016-192 and 49-006-198), noncompliance (Subject 13-002-042), withdrawal of consent (Subjects 26-003-039, 28-013-089, 49-003-171), protocol deviation (Subject 18-005-157), and postponement of surgery (Subject 28-001-017) and in the placebo group were over enrollment (subjects 13-015-191 and 49-007-199) withdrawal of consent (Subjects 37-005-133, 42-004-048, and 41-002-030), and protocol deviation (Subject 20-002-014).

The following table presents the number of patients discontinued study treatment by visit.

Table 9: Study CL-SE-0415081-P-WR Number of Patients Discontinued Study Treatment by Visit

	Bromfenac Ophthalmic Solution 0.09% N=78	Placebo N=78	Total N=156
Subjects Who Discontinued Study Drug Early	16 (20.5%)	47 (60.3%)	63 (40.4%)
Primary Reason for Early Discontinuation of Study Drug			
Adverse Event	5 (6.4%)	12 (15.4%)	17 (10.9%)
Day 0	1 (1.3%)	2 (2.6%)	3 (1.9%)
Day 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 3	2 (2.6%)	4 (5.1%)	6 (3.8%)
Day 8	2 (2.6%)	6 (7.7%)	8 (5.1%)
Day 15	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 22	0 (0.0%)	0 (0.0%)	0 (0.0%)
Disallowed Concurrent Medication	1 (1.4%)	1 (1.4%)	2 (1.4%)
Day 0	0 (0.0%)	1 (1.4%)	1 (0.7%)
Day 1	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 3	1 (1.4%)	0 (0.0%)	1 (0.7%)
Lack of Efficacy	2 (2.7%)	27 (37.0%)	29 (19.9%)
Day 0	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 1	0 (0.0%)	4 (5.5%)	4 (2.7%)
Day 3	0 (0.0%)	16 (21.9%)	16 (11.0%)
Day 8	2 (2.7%)	6 (8.2%)	8 (5.5%)
Day 15	0 (0.0%)	1 (1.4%)	1 (0.7%)
Day 22	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	8 (10.3%)	6 (7.7%)	14 (9.0%)

Source: Table 14.1.1.7 of the Applicant's CL-S&E-0415081-P-WR study report.

The summaries of baseline demographic characteristics are presented in Table 10. There was no marked difference in the baseline characteristics between the two treatment groups.

Table 10: Study CL-SE-0415081-P-WR Baseline Demographics (ITT Population)

		Bromfenac Ophthalmic Solution 0.09% N=78		Placebo N=78		Total N=156	
		n	(%)	n	(%)	n	(%)
Gender	**Male**	33	42.3	30	38.5	63	40.4
	Female	45	57.7	48	61.5	103	59.6
Age	**MEAN**		68.7		68.0		68.4
	SD		11.1		9.7		10.4
	MEDIAN		70		68		69
	RANGE		27 to 90		43 to 86		27 to 90
Race	**Asian**	3	3.8	4	5.1	7	4.5
	Black	3	3.8	10	12.8	13	8.3
	Caucasian	59	75.6	53	67.9	112	71.8
	Hispanic	11	14.1	10	12.8	21	13.5
	Native American	2	2.6	1	1.3	3	1.9
Iris Color	**Black**	0	0	0	0	0	0
	Blue	24	30.8	23	29.5	47	30.1
	Brown	35	44.9	38	48.7	73	46.8
	Gray	0	0	0	0	0	0
	Green	4	5.1	4	5.1	8	5.1
	Hazel	14	17.9	12	15.4	26	16.7
	Other	1	1.3	1	1.3	2	1.3
Iris Color	**Light Irides**	39	50.0	36	46.2	75	48.1
	Dark Irides	39	50.0	42	53.8	81	51.9

Source: Table 14.1.2.1 of the Applicant's CL-S&E-0415081-P-WR study report.

Study CL-SE-1205081-P

A total of 326 patients were screened; and 299 patients from 41 study sites were randomized to receive any study treatment and included in the intent-to-treat (ITT) population. Of the 299 patients in the ITT population, 152 were randomized to the bromfenac group and 147 were randomized to the placebo group.

A subject could have prematurely discontinued study drug for the following reasons: AE (ocular or systemic), use of prohibited concomitant medication, lack of efficacy, or "other" reason specified by the investigator. By protocol, a subject was considered to have completed the study if the subject either completed (on or after) post-surgery Day 22 visit or if the subject completed a follow-up visit 1 week (7 + 3 days) after prematurely discontinuing study drugs. One hundred forty six (146/152, 96.1%) subjects in the bromfenac ophthalmic solution 0.09% treatment group and 144/147 (98.0%) subjects in the placebo group completed the study.

The proportion of subjects who discontinued study drug in the bromfenac ophthalmic solution 0.09% group (29/152, 19.1%) was much lower than the proportion of subjects who discontinued study drug in the placebo group (84/147, 57.1%; see the following table).

Among reasons for early discontinuation of study drug, greater proportion of subjects in the placebo group (47/147, 32.0%) discontinued due to lack of efficacy compared with the bromfenac group (5/152, 3.3%). The proportion of subjects who discontinued treatment for an

AE in the placebo group (24/147, 16.3%) was also higher than in the bromfenac group (8/152, 5.3%).

Disposition of all randomized patients is shown in the following table.

Table 11: Study CL-SE-1205081-P Summary of Subject Disposition

	Bromfenac Ophthalmic Solution 0.09%	Placebo	Total
Number of Subjects Randomized	152	147	299
Subjects who Completed Study	146 (96.1%)	144 (98.0%)	290 (97.0%)
Subjects who Terminated the Study Prior to Post-Surgery Day 22 or Prior to 1 Week Follow-up	6 (3.9%)	3 (2.0%)	9 (3.0%)
Primary Reason for Early Termination			
Withdrawal of Consent/Non-compliance	2 (1.3%)	1 (0.7%)	3 (1.0%)
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	4 (2.6%)	2 (1.4%)	6 (2.0%)
Subjects Who Discontinued Study Drug Early	29 (19.1%)	84 (57.1%)	113 (37.8%)
Primary Reason for Early Discontinuation of Study Drug			
Adverse Event	8 (5.3%)	24 (16.3%)	32 (10.7%)
Disallowed Concurrent Medication	3 (2.0%)	5 (3.4%)	8 (2.7%)
Lack of Efficacy	5 (3.3%)	47 (32.0%)	52 (17.4%)
Other	13 (8.6%)	8 (5.4%)	21 (7.0%)

Source: Table 4 and Table 6 of the Applicant's CL-S&E-1205081-P study report.

The number and proportion of subjects completing Day 1, Day 3, Day 8, Day 15, and Day 22 visit are presented in the following table. It is noted that there were much more patients completed Day 15 visit in the bromfenac group (123/152, 80.9%) compared to the placebo group (63/147, 42.9%).

Table 12: Study CL-SE-1205081-P's Visit Completed (ITT Population)

# of Subjects Completing	Bromfenac Ophthalmic Solution 0.09% N=152	Placebo N=147
Day 1	141 (92.8%)	139 (94.6%)
Day 3	137 (90.1%)	128 (87.1%)
Day 8	129 (84.9%)	90 (61.2%)
Day 15	123 (80.9%)	63 (42.9%)
Day 22	146 (96.1%)	144 (98.0%)

Source: Table 5 of the Applicant's CL-S&E-1205081-P study report.

Of all randomized subjects, 32/299 (10.7%), in the ITT population who discontinued study drug due to an adverse event, 0/152 (0.0%) in the bromfenac ophthalmic solution 0.09% treatment group and 2/147 (1.4%) in the placebo treatment group did so on or before the day of surgery (Day 0), 3/152 (2.0%) in the bromfenac ophthalmic solution 0.09% group and 4/147 (2.7%) in the placebo group did so at Day 1, 0/152 (0.0%) in the bromfenac ophthalmic solution 0.09% and 5/147 (3.4%) in the placebo group did so by Day 3, 4/152 (2.6%) in the bromfenac ophthalmic solution 0.09% and 13/147 (8.8%) in the placebo group did so by Day 8, and 1/152

(0.7%) in the bromfenac ophthalmic solution 0.09% and 0/147 (0.0%) in the placebo group did so by Day 15.

Only 8/299 (2.7%) subjects discontinued study drug due to a disallowed concurrent medication; 2/152 (1.3%) subjects discontinued at Day 8, and 1/152 (0.7%) subject discontinued by Day 15 in the bromfenac ophthalmic solution 0.09% treatment group.

The 5/152 (3.4%) subjects in the bromfenac ophthalmic solution 0.09% group who discontinued due to lack of efficacy did so on Days 1, 3, and 8. The largest proportions of subjects discontinued for lack of efficacy on a particular study day did differ between the 2 treatment groups; 3/152 (2.0%) of the subjects in the bromfenac ophthalmic solution 0.09% treatment group discontinued at Day 3 while 28/147 (19.0%) of the subjects in the placebo treatment group discontinued at Day 8. Similar patterns in the time course of discontinuation of study drug due to an adverse event, disallowed medication, or lack of efficacy were demonstrated for subjects in the Safety population.

The following table presents the number of patients discontinued study treatment by visit.

Table 13: Study CL-SE-1205081-P Number of Patients Discontinued Study Treatment by Visit

	Bromfenac Ophthalmic Solution 0.09% N=152	**Placebo N=147**	**Total N=299**
Subjects Who Discontinued Study Drug Early	29 (19.1%)	84 (57.1%)	113 (37.8%)
Primary Reason for Early Discontinuation of Study Drug			
Adverse Event	8 (5.3%)	24 (16.3%)	32 (10.7%)
Day 0	0 (0.0%)	2 (1.4%)	2 (0.7%)
Day 1	3 (2.0%)	4 (2.7%)	7 (2.3%)
Day 3	0 (0.0%)	5 (3.4%)	5 (1.7%)
Day 8	4 (2.6%)	13 (8.8%)	17 (5.7%)
Day 15	1 (0.7%)	0 (0.0%)	1 (0.3%)
Day 22	0 (0.0%)	0 (0.0%)	0 (0.0%)
Disallowed Concurrent Medication	3 (2.0%)	5 (3.4%)	8 (2.7%)
Day 0	0 (0.0%)	2 (1.4%)	2 (0.7%)
Day 1	0 (0.0%)	2 (1.4%)	2 (0.7%)
Day 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 8	2 (1.3%)	1 (0.7%)	3 (1.0%)
Day 15	1 (0.7%)	0 (0.0%)	1 (0.3%)
Day 22	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lack of Efficacy	5 (3.3%)	47 (32.0%)	52 (17.4%)
Day 0	0 (0.0%)	1 (0.7%)	1 (0.3%)
Day 1	1 (0.7%)	4 (2.7%)	5 (1.7%)
Day 3	3 (2.0%)	11 (7.5%)	14 (4.7%)
Day 8	1 (0.7%)	28 (19.0%)	29 (9.7%)
Day 15	0 (0.0%)	3 (2.0%)	3 (1.0%)
Day 22	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	13 (8.6%)	8 (5.4%)	21 (7.0%)

Source: Table 14.1.1.7 of the Applicant's CL-S&E-1205081-P study report.

The summaries of baseline demographic characteristics are presented in Table 14. There was no marked difference in the baseline characteristics between the two treatment groups.

Table 14: Study CL-SE-1205081-P Baseline Demographics (ITT Population)

		Bromfenac Ophthalmic Solution 0.09% N=152		Placebo N=147		Total N=299	
		n	(%)	n	(%)	n	(%)
Gender	**Male**	63	41.4	48	32.7	111	37.1
	Female	89	58.6	99	67.3	188	62.9
Age	**MEAN**		70.4		69.1		66.3
	SD		10.1		10.4		10.6
	MEDIAN		72		70		68
	RANGE		34 to 87		40 to 90		46 to 85
Race	**Asian**	5	3.3	3	2.0	8	2.7
	Black	13	8.6	10	6.8	23	7.7
	Caucasian	113	74.3	109	74.1	222	74.2
	Hispanic	17	11.2	25	17.0	42	14.0
	Native American	0	0.0	0	0.0	0	0.0
	Other	4	2.6	0	0.0	4	1.3
Iris Color	**Black**	1	0.7	1	0.7	2	0.7
	Blue	46	30.3	33	22.4	79	26.4
	Brown	69	45.4	83	56.5	152	50.8
	Gray	1	0.7	1	0.7	2	0.7
	Green	13	8.6	7	4.8	20	6.7
	Hazel	22	14.5	22	15.0	44	14.7
	Other	0	0.0	0	0.0	0	0.0
Iris Color	**Light Irides**	69	45.4	56	38.1	125	41.8
	Dark Irides	83	54.6	91	61.9	174	58.2

Source: Table 14.1.2.1 of the Applicant's CL-S&E-1205081-P study report.

3.1.3 Statistical Methodologies

Studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P were three similarly designed pivotal studies. The studies had the same primary and secondary efficacy endpoints. The statistical methodologies were the same for all the three studies.

Efficacy Analysis Sets

Efficacy analyses were conducted on the Intent-to-Treat Population (ITT), which included all randomized subjects. Subjects were analyzed in the group to which they were randomized. Two analyses of efficacy were performed: an analysis of data based on last observation carried forward (LOCF) and an analysis of data based on observed cases (OC). The observed cases analysis included all available data, with no imputation for missing values.

Safety analyses were conducted on the Safety Population, which included all randomized subjects who received at least 1 dose of study drug. Subjects were analyzed in the group within which they were treated.

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects with cleared ocular inflammation in the study eye by Day 15. The primary hypothesis for efficacy compares the primary efficacy endpoint between the Xibrom™ (bromfenac ophthalmic solution) 0.09% treatment group and the placebo treatment group. The null hypothesis (H_o) was that there was no difference between the Xibrom™ (bromfenac ophthalmic solution 0.09%) (π_{Xibrom}) and placebo ($\pi_{placebo}$) groups in the proportion of subjects with cleared ocular inflammation, while the alternative hypothesis (H_A) was that there was a difference between the groups:

H_o: $\pi_{Xibrom} = \pi_{placebo}$ vs. H_A: $\pi_{Xibrom} \neq \pi_{placebo}$

The percentage of subjects with cleared ocular inflammation at Day 1, 3, 8 and 15 was presented. Statistical difference between the Xibrom™ (bromfenac ophthalmic solution) 0.09% and placebo subjects was tested using the chi-square test.

There were two types of missing values: 1) from subjects who did not respond to study drug treatment (based on assessment of ocular inflammation and ocular pain) and who required alternative medical management (i.e., rescue therapy) and 2) from subjects who missed scheduled evaluations but continued on study drug treatment during the study. For the first type of missing data, those subjects who received a rescue medication prior to Day 15, the observed outcome nearest (on or before) the date of receiving rescue medication were carried forward and used in the determination of the missing outcome. For the second type of missing data, the outcome from the last visit at which it was measured was carried forward.

Analysis of Secondary Efficacy Endpoint

The protocol-defined secondary efficacy endpoint was the proportion of subjects who had an ocular pain response of "None" at Day 1. The analysis of the secondary efficacy outcome was conducted on the ITT population using the LOCF method for imputing the missing values the same way as for the primary efficacy endpoint. Statistical difference between the Xibrom™ (bromfenac ophthalmic solution 0.09%) and placebo subjects was determined using the chi-square test.

Determination of Sample Size

For studies CL-S&E-0415081-P-ER and CL-S&E-0415081-P-WR, the sample size and power calculation were based on the assumption that 20% of subjects would have cleared ocular inflammation for the placebo group and 44% for the bromfenac treated group by Day 15. With a sample size of 63 patients per treatment group per study, the power would be 80% to detect statistical significance using a t-test with a two-sided 0.05 alpha level.

For study CL-S&E-120508-P, the sample size and power calculation were based on the assumption that 29.5% of subjects would have cleared ocular inflammation in the placebo group and 47.4% in the bromfenac treated group by Day 15. With a sample size of 125 patients per treatment group per study, the power would be 80% to detect statistical significance using a

Fisher's exact test with a two-sided 0.05 alpha level. In order to account for a potential dropout rate of 10%, the required sample was increased to 280 subjects, 140 per group.

3.1.4 Results and Conclusions

3.1.4.1 Primary Efficacy Endpoint

Studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P had the same primary efficacy endpoint. This primary endpoint of efficacy was the proportion of subjects in the LOCF analysis who had cleared ocular inflammation by Day 15. A subject was considered to have cleared ocular inflammation by Day 15 if the subject achieved a SOIS of zero (i.e., zero cells and absence of flare) at or prior to Day 15.

The following table presents the proportion of subjects with cleared ocular inflammation defined as a SOIS of grade 0 by visit for the three studies, where the shaded rows are the primary efficacy results for each of the three studies.

Table 15: Proportion of Subjects with Cleared Ocular Inflammation by Each Visit (ITT LOCF)

Study CL-S&E-0415081-P-ER				
	Bromfenac 0.09% N=63	**Placebo N=63**	**p-value**	**Difference (95% CI)**
Day 1	3 (4.8%)	3 (4.8%)	1.00	0.0% (-7.4%, 7.4%)
Day 3	6 (9.5%)	7 (11.1%)	0.77	-1.6% (-12.2%, 9.0%)
Day 8	20 (31.7%)	15 (23.8%)	0.32	7.9% (-7.6%, 23.5%)
Day 15	28 (44.4%)	20 (31.7%)	0.14	12.7% (-4.1%, 29.5%)
Study CL-S&E-0415081-P-WR				
	Bromfenac 0.09% N=78	**Placebo N=78**	**p-value**	**Difference (95% CI)**
Day 1	5 (6.4%)	9 (11.5%)	0.26	-5.1% (-14.1%, 3.8%)
Day 3	9 (11.5%)	10 (12.8%)	0.81	-1.3% (-11.5%, 9.0%)
Day 8	20 (25.6%)	14 (17.9%)	0.24	7.7% (-5.2%, 20.6%)
Day 15	36 (46.2%)	23 (29.5%)	0.032	16.7% (1.7%, 31.7%)
Study CL-S&E-1205081-P				
	Bromfenac 0.09% N=152	**Placebo N=147**	**p-value**	**Difference (95% CI)**
Day 1	12 (7.9%)	9 (6.1%)	0.55	1.8% (-4.0%, 7.6%)
Day 3	17 (11.2%)	12 (8.2%)	0.38	3.0% (-3.6%, 9.7%)
Day 8	36 (23.7%)	23 (15.6%)	0.08	8.0% (-0.9%, 17.0%)
Day 15	70 (46.1%)	36 (24.5%)	<0.0001	21.6% (11.0%, 32.1%)

Source: Table 8 of the Applicant's CL-S&E-0415081-P-ER study report, Table 8 of the Applicant's CL-S&E-0415081-P-WR study report, and Table 8 of the Applicant's CL-S&E-1205081-P study report.

Statistical Reviewer's Comments:

For study CL-S&E-0415081-P-ER, there was no statistically significance difference between the bromfenac group (44.4%, 28/63) and the placebo group (31.7%, 20/63) in the proportion of subjects who had cleared ocular inflammation by Day 15. The treatment difference was 12.7% with 95% CI of (-4.1%, 29.5%), and the p-value was 0.14.

Both studies CL-S&E-0415081-P-WR and CL-S&E-1205081-P showed statistically significant difference between the bromfenac group and the placebo group in the proportion of subjects who had cleared ocular inflammation by Day 15.

For study CL-S&E-0415081-P-WR, the proportion of subjects who had cleared ocular inflammation by Day 15 was 46.2% (36/78) for the bromfenac group and 29.5% (23/78) for the

placebo group. The treatment difference was 16.7% with 95% CI of (1.7%, 31.7%), and the p-value was 0.032.

For study CL-S&E-1205081-P, the proportion of subjects who had cleared ocular inflammation by Day 15 was 46.1% (70/152) for the bromfenac group and 24.5% (36/147) for the placebo group. The treatment difference was 21.6% with 95% CI of (11.0%, 32.1%), and the p-value was <0.0001.

In addition, the Applicant also analyzed the proportion of subjects who had cleared ocular inflammation based on subjects who completed the study (completers) and the results are presented in the following table.

Table 16: Proportion of Subjects with Cleared Ocular Inflammation[1] by Each Visit (Completers)

	Bromfenac 0.09% N=63	Placebo N=63	p-value	Difference (95% CI)
Study CL-S&E-0415081-P-ER				
Day 1	n = 60	n = 60		
	0 (0.0%)	0 (0.0%)	n/a	0.0%
Day 3	n = 60	n = 60		
	3 (5.0%)	4 (6.7%)	1.0	-1.7% (-10.1%, 6.7%)
Day 8	n = 60	n = 60		
	17 (28.3%)	12 (20.0%)	0.29	8.3% (-6.9%, 23.6%)
Day 15	n = 60	n = 60		
	25 (41.7%)	17 (28.3%)	0.13	13.3% (-3.6%, 30.2%)
Study CL-S&E-0415081-P-WR				
	Bromfenac 0.09% N=78	**Placebo N=78**	**p-value**	**Difference (95% CI)**
Day 1	n = 73	n = 70		
	0 (0.0%)	1 (1.4%)	0.49	-1.4% (-4.2%, 1.4%)
Day 3	n = 73	n = 70		
	4 (5.5%)	2 (2.9%)	0.68	2.6% (-3.9%, 9.1%)
Day 8	n = 73	n = 73		
	15 (20.5%)	6 (8.6%)	0.04	12.0% (0.6%, 23.3%)
Day 15	n = 73	n = 70		
	31 (42.5%)	15 (21.4%)	0.007	21.0% (6.2%, 35.9%)
Study CL-S&E-1205081-P				
	Bromfenac 0.09% N=152	**Placebo N=147**	**p-value**	**Difference (95% CI)**
Day 1	n = 141	n = 139		
	1 (0.7%)	1 (0.7%)	1.00	0.0% (-2.0%, 2.0%)
Day 3	n = 141	n = 139		
	6 (4.3%)	4 (2.9%)	0.75	1.4% (-3.0%, 5.7%)
Day 8	n = 141	n = 139		
	25 (17.7%)	15 (10.8%)	0.097	6.9% (-1.2%, 15.1%)
Day 15	n = 141	n = 139		
	59 (41.5%)	28 (20.1%)	0.0001	21.4% (10.9%, 31.9%)

Source: Table 10 of the Applicant's CL-S&E-0415081-P-ER study report, Table 10 of the Applicant's CL-S&E-0415081-P-WR study report, and Table 10 of the Applicant's CL-S&E-1205081-P study report.

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

Statistical Reviewer's Comments:

The sensitivity analyses results for the completers were consistent with their primary ITT analyses results based on LOCF imputation for missing values respectively.

The statistical reviewer performed additional sensitivity analyses treating patients who discontinued the study early as treatment failure (i.e. not having cleared ocular inflammation) by each visit for all three studies, and the results are presented in the following table. These analysis results are consistent with the primary efficacy analyses results.

Table 17: Statistical Review's Sensitivity Analyses Treating Patients Who Discontinued the Study Early as Not Having Cleared Ocular Inflammation by Each Visit (ITT)

Study CL-S&E-0415081-P-ER				
	Bromfenac 0.09% N=63	**Placebo N=63**	**p-value**	**Difference (95% CI)**
Day 1	0 (0.0%)	0 (0.0%)	n/a	0.0%
Day 3	3 (4.8%)	4 (6.3%)	1.0	-1.6% (-9.6%, 6.4%)
Day 8	17 (27.0%)	12 (19.1%)	0.29	7.9% (-6.7%, 22.6%)
Day 15	25 (39.7%)	17 (27.0%)	0.13	12.7% (-3.6%, 29.0%)
Study CL-S&E-0415081-P-WR				
	Bromfenac 0.09% N=78	**Placebo N=78**	**p-value**	**Difference (95% CI)**
Day 1	0 (0.0%)	1 (1.3%)	1.0	-1.3% (-3.8%, 1.2%)
Day 3	4 (5.1%)	2 (2.6%)	0.68	2.6% (-3.6%, 8.6%)
Day 8	15 (19.2%)	6 (7.7%)	0.035	11.5% (1.0%, 22.1%)
Day 15	31 (39.7%)	15 (19.2%)	0.005	20.5% (6.6%, 34.5%)
Study CL-S&E-1205081-P				
	Bromfenac 0.09% N=152	**Placebo N=147**	**p-value**	**Difference (95% CI)**
Day 1	1 (0.7%)	1 (0.7%)	1.0	0.0% (-1.8%, 1.8%)
Day 3	6 (4.0%)	4 (2.7%)	0.75	1.2% (-2.8%, 5.3%)
Day 8	25 (16.5%)	15 (10.2%)	0.11	6.2% (-1.4%, 13.9%)
Day 15	59 (38.8%)	28 (19.1%)	0.0002	19.8% (9.8%, 29.8%)

The statistical reviewer analyzed the proportion of subjects who had cleared ocular inflammation based on the observed data by study day for each of the three studies, and the results are presented in the following tables.

Table 18: Statistical Reviewer's Sensitivity Analysis of Proportion of Subjects with Cleared Ocular Inflammation by Study Day for Study CL-S&E-0415081-P-ER (Observed[1])

	Bromfenac 0.09% (N=63) n/N (%)	**Placebo (N=63)** n/N (%)	**Difference**
Day 1 Visit	0/60 (0.0%)	0/60 (0.0%)	0.0%
Day 1	0/60 (0.0%)	0/60 (0.0%)	0.0%
Day 3 Visit	3/58 (5.2%)	4/58 (6.9%)	-1.7%
Day 2	2/33 (6.1%)	4/27 (14.8%)	-8.7%
Day 3	1/18 (5.6%)	0/22 (0.0%)	5.6%
Day 4	0/7 (0.0%)	0/9 (0.0%)	0.0%
Day 8 Visit	16/50 (32.0%)	10/49 (20.4%)	11.6%
Day 7	3/11 (27.3%)	2/16 (12.5%)	14.8%
Day 8	13/35 (37.1%)	4/27 (14.8%)	22.3%
Day 9	1/5 (20.0%)	3/5 (60.0%)	-40..0%
Day 10	0/0	1/1 (100.0%)	n/a
Day 15 Visit	22/49 (44.9%)	13/32 (39.4%)	6.6%
Day 12	0/0	0/1 (0.0%)	n/a
Day 13	0/0	0/0	n/a
Day 14	7/16 (43.8%)	3/5 (60.0%)	-16.2%
Day 15	14/29 (48.3%)	7/19 (36.8%)	11.5%
Day 16	1/4 (25.0%)	3/7 (42.9%)	-17.9%
Day 22 Visit	32/50 (64.0%)	15/31 (48.4%)	15.6%
Day 19	1/1 (100.0%)	0/0	n/a
Day 20	0/0	0/0	n/a
Day 21	0/0	3/3 (100.0%)	n/a
Day 22	20/31 (64.5%)	6/18 (33.3%)	31.2%
Day 23	7/10 (70.0%)	4/5 (80.0%)	-10.0%
Day 24	2/3 (66.7%)	0/2 (0.0%)	66.7%
Day 25	1/4 (25.0%)	1/2 (50.0%)	-25.0%
Day 26	0/0	1/1 (100.0%)	n/a
Day 29	1/1 (100.0%)	0/0	n/a

[1] subjects who discontinued the study drug were not included.

Table 19: Statistical Reviewer's Sensitivity Analysis of Proportion of Subjects with Cleared Ocular Inflammation by Study Day for Study CL-S&E-0415081-P-WR (Observed[1])

	Bromfenac 0.09% (N=78) n/N (%)	**Placebo (N=78)** n/N (%)	**Difference**
Day 1 Visit	1/73 (0.0%)	1/70 (1.4%)	-1.4%
Day 1	1/73 (0.0%)	1/70 (1.4%)	-1.4%
Day 3 Visit	4/70 (5.7%)	1/65 (1.5%)	4.2%
Day 2	0/24 (0.0%)	0/31 (0.0%)	0.0%
Day 3	1/33 (3.0%)	0/26 (0.0%)	3.0%
Day 4	3/13 (23.1%)	1/8 (12.5%)	10.6%
Day 8 Visit	15/65 (23.1%)	4/41 (9.8%)	13.3%
Day 5	0/0	1/1 (100.0%)	n/a
Day 6	0/1 (0.0%)	0/1 (0.0%)	0.0%
Day 7	5/20 (25.0%)	2/11 (18.2%)	6.8%
Day 8	8/38 (21.1%)	1/25 (4.0%)	17.1%
Day 9	1/5 (20.0%)	0/3 (0.0%)	20.0%
Day 10	1/1 (100.0%)	0/0	n/a
Day 15 Visit	30/62 (48.4%)	12/32 (37.5%)	10.9%
Day 11	0/0	0/1 (0.0%)	n/a
Day 12	0/0	0/0	n/a
Day 13	0/0	0/0	n/a
Day 14	11/19 (57.9%)	8/10 (80.0%)	-22.1%
Day 15	15/32 (46.7%)	3/18 (16.7%)	30.0%
Day 16	4/10 (40.0%)	0/2 (0.0%)	40.0%
Day 17	0/0	0/0	n/a
Day 18	0/1 (0.0%)	1/1 (100.0%)	-100.0%
Day 22 Visit	44/59 (74.6%)	17/29 (58.6%)	16.0%
Day 20	0/2 (0.0%)	0/1 (0.0%)	0.0%
Day 21	10/12 (83.3%)	6/7 (85.7%)	-2.4%
Day 22	22/31 (71.0%)	8/16 (50.0%)	21.0%
Day 23	6/7 (85.7%)	2/3 (66.7%)	19.0%
Day 24	1/2 (50.0%)	1/1 (100.0%)	-50.0%
Day 25	2/2 (100.0%)	0/1 (0.0%)	100.0%
Day 26	2/2 (100.0%)	0/0	n/a
Day 29	1/1 (100.0%)	0/0	n/a

[1] subjects who discontinued the study drug were not included.

Table 20: Statistical Reviewer's Sensitivity Analysis of Proportion of Subjects with Cleared Ocular Inflammation by Study Day for Study CL-S&E-1205081-P (Observed[1])

	Bromfenac 0.09% (N=152) n/N (%)	**Placebo (N=147)** n/N (%)	**Difference**
Day 1 Visit	1/141 (0.7%)	1/139 (0.7%)	0.0%
Day 1	1/141 (0.7%)	1/139 (0.7%)	0.0%
Day 3 Visit	5/136 (3.7%)	4/127 (3.1%)	0.6%
Day 2	2/61 (3.3%)	1/51 (2.0%)	1.3%
Day 3	0/30 (0.0%)	1/30 (3.3%)	-3.3%
Day 4	2/44 (4.6%)	2/46 (4.4%)	0.2%
Day 5	1/1 (100.0%)	0/0	n/a
Day 8 Visit	22/129 (17.1%)	12/90 (13.3%)	3.8%
Day 6	0/2 (0.0%)	0/0	n/a
Day 7	5/23 (21.7%)	2/19 (10.5%)	11.2%
Day 8	14/88 (15.9%)	7/60 (11.7%)	4.2%
Day 9	3/14 (21.4%)	2/10 (20.0%)	1.4%
Day 10	0/2 (0.0%)	1/1 (100.0%)	-100.0%
Day 15 Visit	50/123 (40.1%)	18/63 (28.6%)	11.5%
Day 13	0/1 (0.0%)	1/1 (100.0%)	-100.0%
Day 14	14/30 (46.7%)	3/8 (37.5%)	9.2%
Day 15	28/78 (35.9%)	11/45 (24.4%)	11.5%
Day 16	6/12 (50.0%)	3/8 (37.5%)	12.5%
Day 17	1/1 (100.0%)	0/1 (0.0%)	100.0%
Day 18	0/0	0/0	n/a
Day 19	1/1 (100.0%)	0/0	n/a
Day 22 Visit	77/124 (62.1%)	43/63 (68.3%)	-6.2%
Day 20	4/4 (100.0%)	1/1 (100.0%)	0.0%
Day 21	5/9 (55.6%)	5/6 (83.3%)	-27.7%
Day 22	42/76 (55.3%)	25/41 (61.0%)	-5.7%
Day 23	8/13 (61.5%)	3/4 (75.0%)	-13.5%
Day 24	7/9 (77.8%)	2/2 (100.0%)	-22.2%
Day 25	8/9 (88.9%)	5/6 (83.3%)	5.6%
Day 26	2/2 (100.0%)	1/1 (100.0%)	0.0%
Day 27	0/0	0/0	n/a
Day 28	0/0	0/1 (0.0%)	n/a
Day 29	1/2 (50.0%)	1/1 (100.0%)	-50.0%

[1] subjects who discontinued the study drug were not included.

For all three studies, the above sensitivity analysis results were in general consistent with the primary efficacy analysis results.

3.1.4.2 Secondary Efficacy Endpoint

Studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P had the same secondary efficacy endpoint. This endpoint was the proportion of subjects who had an ocular pain response of "None" at Day 1.

The analysis results of proportion of subjects with ocular pain response of "None" by each visit based on the protocol-defined ITT LOCF analysis are presented in the following table, where the highlighted row is the secondary efficacy endpoint.

Table 21: Proportion of Subjects with Ocular Pain Response of "None" by Each Visit (ITT LOCF)

	Bromfenac 0.09% N=63	Placebo N=63	p-value	Difference (95% CI)
Study CL-S&E-0415081-P-ER				
Day 1	51 (81.0%)	46 (73.0%)	0.29	7.9% (-6.7%, 22.6%)
Day 3	56 (88.9%)	46 (73.0%)	0.023	15.9% (2.4%, 29.3%)
Day 8	60 (95.2%)	45 (71.4%)	0.0003	23.8% (11.5%, 36.1%)
Day 15	59 (93.7%)	46 (73.0%)	0.0019	20.6% (8.1%, 33.1%)
Study CL-S&E-0415081-P-WR				
	Bromfenac 0.09% N=78	**Placebo N=78**	**p-value**	**Difference (95% CI)**
Day 1	65 (83.3%)	40 (51.9%)	<0.0001	31.4% (17.5%, 45.3%)
Day 3	74 (94.9%)	51 (66.2%)	<0.0001	28.6% (17.0%, 40.3%)
Day 8	75 (96.2%)	54 (70.1%)	<0.0001	26.0% (15.0%, 37.1%)
Day 15	76 (97.4%)	57 (74.0%)	<0.0001	23.4% (13.0%, 33.8%)
Study CL-S&E-1205081-P				
	Bromfenac 0.09% N=152	**Placebo N=147**	**p-value**	**Difference (95% CI)**
Day 1	135 (88.8%)	105 (71.4%)	0.0002	17.4% (8.5%, 26.2%)
Day 3	139 (91.4%)	105 (71.4%)	<0.0001	20.0% (11.5%, 28.6%)
Day 8	142 (93.4%)	106 (72.1%)	<0.0001	21.3% (13.1%, 29.6%)
Day 15	145 (95.4%)	107 (72.8%)	<0.0001	22.6% (14.7%, 30.5%)

Source: Table 20 of the Applicant's CL-S&E-0415081-P-ER study report, Table 20 of the Applicant's CL-S&E-0415081-P-WR study report, and Table 16 of the Applicant's CL-S&E-1205081-P study report.

Statistical Reviewer's Comments:

For study CL-S&E-0415081-P-ER, there was no statistically significance difference between the bromfenac group (81.0%, 51/63) and the placebo group (73.0%, 46/63) in the proportion of

subjects who had ocular pain response of "None" at Day 1. The treatment difference was 7.9% 95% CI of (-6.7%, 22.6%), and the p-value was 0.29.

Both studies CL-S&E-0415081-P-WR and CL-S&E-1205081-P showed statistically significant difference between the bromfenac group and the placebo group in the proportion of subjects who had ocular pain response of "None" at Day 1.
For study CL-S&E-0415081-P-WR, the proportion of subjects who had ocular pain response of "None" at Day 1 was 83.3% (65/78) for the bromfenac group and 51.9% (40/78) for the placebo group. The treatment difference was 31.4% with 95% CI of (17.5%, 45.3%), and the p-value was <0.0001.

For study CL-S&E-1205081-P, the proportion of subjects who had cleared ocular inflammation by Day 15 was 88.8% (135/152) for the bromfenac group and 71.4% (105/147) for the placebo group. The treatment difference is 17.4% with 95% CI of (8.5%, 26.2%), and the p-value is 0.0002.

3.2 Evaluation of Safety

The following tables summarized adverse events (AEs) for Studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-120508-P respectively.

Table 22: Study CL-S&E-0415081-P-ER AEs Affecting the Study Eye in 2% of Subjects in Either Treatment Group

Adverse Event	Bromfenac (n = 61)	Placebo (n = 61)
Conjunctival infections, irritations, and inflammations	2 (3.3%)	1 (1.6%)
Conjunctival hyperemia	2 (3.3%)	1 (1.6%)
Corneal infections, edemas and inflammations	4 (6.6%)	2 (3.3%)
Corneal edema	4 (6.6%)	2 (3.3%)
Iris and uveal tract infections, irritations and inflammations	1 (1.6%)	3 (4.9%)
Iridocyclitis	0 (0.0%)	2 (3.3%)
Lacrimal disorders	3 (4.9%)	6 (9.8%)
Lacrimation increased	3 (4.9%)	6 (9.8%)
Ocular disorders NEC	5 (8.2%)	7 (11.5%)
Eye Pain	5 (8.2%)	7 (11.5%)
Ocular infections, inflammations and associated manifestations	11 (18.0%)	20 (32.8%)
Eye discharge	1 (1.6%)	3 (4.9%)
Eye inflammation	8 (13.1%)	14 (23.0%)
Eye pruritus	6 (9.8%)	2 (3.3%)
Ocular hyperemia	0 (0.0%)	6 (9.8%)

Adverse Event	Bromfenac (n = 61)	Placebo (n = 61)
Ocular sensation disorders	10 (16.4%)	19 (31.1%)
Abnormal sensation in eye	0 (0.0%)	2 (3.3%)
Foreign body sensation in eyes	8 (13.1%)	14 (23.0%)
Photophobia	8 (13.1%)	17 (27.9%)
Partial vision loss	2 (3.3%)	1 (1.6%)
Visual acuity reduced	2 (3.3%)	1 (1.6%)
Retinal, choroid and vitreous infections and inflammations	1 (1.6%)	2 (3.3%)
Macular edema	1 (1.6%)	2 (3.3%)
Visual disorders NEC	4 (6.6%)	2 (3.3%)
Macular edema	4 (6.6%)	2 (3.3%)

Source: Table 29 of the Applicant's CL-S&E-0415081-P-ER study report.

Table 23: Study CL-S&E-0415081-P-WR AEs Affecting the Study Eye in 2% of Subjects in Either Treatment Group

Adverse Event	Bromfenac (n = 73)	Placebo (n = 73)
Conjunctival infections, irritations, and inflammations	0 (0.0%)	4 (5.5%)
Conjunctival hyperemia	0 (0.0%)	2 (2.7%)
Conjunctival edema	0 (0.0%)	2 (2.7%)
Corneal infections, edemas and inflammations	0 (0.0%)	4 (5.5%)
Corneal edema	0 (0.0%)	4 (5.5%)
Eye and ear procedural complications	0 (0.0%)	2 (2.7%)
Eye operation complication	0 (0.0%)	2 (2.7%)
Lacrimal disorders	1 (1.4%)	3 (4.1%)
Lacrimation increased	0 (0.0%)	2 (2.7%)
Ocular disorders NEC	4 (5.5%)	9 (12.3%)
Eye Pain	2 (2.7%)	5 (6.8%)
Ocular discomfort	1 (1.4%)	3 (4.1%)
Ocular infections, inflammations and associated manifestations	6 (8.2%)	12 (16.4%)
Eye inflammation	4 (5.5%)	10 (13.7%)
Ocular hyperemia	2 (2.7%)	2 (2.7%)
Ocular sensation disorders	1 (1.4%)	3 (4.1%)
Photophobia	0 (0.0%)	2 (2.7%)
Ophthalmic function diagnostic procedures	2 (2.7%)	1 (1.4%)
Intraocular pressure increased	2 (2.7%)	1 (1.4%)

Source: Table 29 of the Applicant's CL-S&E-0415081-P-WR study report.

Table 24: Study CL-S&E-1205081-P AEs Affecting the Study Eye in 2% of Subjects in Either Treatment Group

Adverse Event	Bromfenac (n = 147)	Placebo (n = 144)
Conjunctival infections, irritations, and inflammations	7 (4.8%)	9 (6.3%)
Conjunctival hyperemia	7 (4.8%)	9 (6.3%)
Corneal infections, edemas and inflammations	3 (2.0%)	5 (3.5%)
Corneal edema	3 (2.0%)	4 (2.8%)
Eye and ear procedural complications	1 (0.7%)	5 (3.5%)
Cataract operation complication	1 (0.7%)	5 (3.5%)
Iris and uveal tract infections, irritations and inflammations	1 (0.7%)	6 (4.2%)
Ciliary hyperemia	0 (0.0%)	4 (2.8%)
Lacrimal disorders	9 (6.1%)	13 (9.0%)
Dry eye	4 (2.7%)	2 (1.4%)
Lacrimation increased	5 (3.4%)	11 (7.6%)
Ocular disorders NEC	17 (11.6%)	37 (25.7%)
Eye Pain	13 (8.8%)	34 (23.6%)
Ocular discomfort	3 (2.0%)	4 (2.8%)
Ocular infections, inflammations and associated manifestations	23 (15.6%)	34 (23.6%)
Eye inflammation	15 (10.2%)	21 (14.6%)
Eye irritation	4 (2.7%)	2 (1.4%)
Eye pruritus	7 (4.8%)	4 (2.8%)
Ocular hyperemia	4 (2.7%)	15 (10.4%)
Ocular sensation disorders	23 (15.6%)	36 (25.0%)
Foreign body sensation in eyes	18 (12.2%)	20 (13.9%)
Photophobia	11 (7.5%)	26 (18.1%)
Ophthalmic function diagnostic procedures	5 (3.4%)	3 (2.1%)
Intraocular pressure increased	5 (3.4%)	3 (2.1%)
Visual disorders NEC	16 (10.9%)	14 (9.7%)
Visual blurred	15 (10.2%)	11 (7.6%)

Source: Table 21 of the Applicant's CL-S&E-1205081-P study report.

Please see the review of the medical officer for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Study CL-S&E-0415081-P-ER

The primary endpoint and the secondary efficacy endpoint were analyzed by subgroups on age, gender, and race for study CL-S&E-0415081-P-ER. Except for the secondary efficacy endpoint of both the Asian and the Hispanic subgroups, in general, there were no marked differences in the efficacy results among the various subpopulations.

Table 25: Statistical Reviewer's Subgroup Analyses of Ocular Inflammation and Pain by Gender, Age, and Race (Study CL-S&E-0415081-P-ER; ITT LOCF)

Cleared Ocular Inflammation by Day 15					
	Bromfenac (N=63) Observed Response		Placebo (N=63) Observed Response		Observed Differences
	n/m	%	n/m	%	%
Gender					
Male	10/23	43.5%	8/25	32.0%	11.5%
Female	18/40	45.0%	12/38	31.6%	18.4%
Age					
31 – 50	3/7	42.9%	0/0	n/a	n/a
51 – 70	10/28	35.7%	11/35	31.4%	4.3%
> 70 years	15/28	53.6%	9/28	32.1%	21.5%
Race					
Asian	0/0	n/a	0/1	0.0%	n/a
Black	2/4	50.0%	1/4	25.0%	25.0%
Caucasian	24/53	45.3%	17/53	32.1%	13.2%
Hispanic	2/5	40.0%	1/4	25.0%	15.0%
Other	0/1	0.0%	1/1	100.0%	-100.0%
Ocular Pain Response of "None" at Day 1					
	Bromfenac (N=63) Observed Response		Placebo (N=63) Observed Response		Observed Differences
	n/m	%	n/m	%	%
Gender					
Male	16/23	69.6%	17/25	68.0%	1.6%
Female	35/40	87.5%	29/38	76.3%	11.2%
Age					
31 – 50	5/7	71.4%	0/0	n/a	n/a
51 – 70	22/28	78.6%	26/35	74.3%	4.3%
> 70 years	24/28	85.7%	20/28	71.4%	14.3%
Race					
Asian	0/0	n/a	1/1	100.0	n/a
Black	2/4	50.0%	4/4	100.0	-50.0%
Caucasian	44/53	83.0%	36/53	67.9%	15.1%
Hispanic	4/5	80.0%	4/4	100.0%	-20.0%
Other	1/1	100.0%	1/1	100.0%	0.0%

4.2 Study CL-S&E-0415081-P-WR

The primary endpoint and the secondary endpoint were analyzed by subgroups on age, gender, and race for study CL-S&E-0415081-P-WR as well. Except for the primary efficacy endpoint of the Asian subgroup, in general, there were no marked differences in the efficacy results among the various subpopulations (see Table 26).

Table 26: Statistical Reviewer's Subgroup Analyses of Ocular Inflammation and Pain by Gender, Age, and Race (Study CL-S&E-0415081-P-WR; ITT LOCF)

Cleared Ocular Inflammation by Day 15					
	Bromfenac (N=78) Observed Response		Placebo (N=78) Observed Response		Observed Differences
	n/N	%	n/N	%	%
Gender					
Male	13/33	39.4%	8/30	26.7%	12.7%
Female	23/45	51.1%	15/48	31.3%	19.8%
Age					
18 – 30	1/1	100.0%	0/0	n/a	n/a
31 – 50	4/4	100.0%	1/3	33.3%	66.7%
51 – 70	16/36	44.4%	15/42	35.7%	9.7%
> 70 years	15/37	40.5%	7/33	21.2%	19.3%
Race					
Asian	1/3	33.3%	2/4	50.0%	-16.7%
Black	3/3	100.0%	8/10	80.0%	20.0%
Caucasian	24/59	40.7%	11/53	20.8%	19.9%
Hispanic	7/11	63.6%	2/10	20.0%	43.6%
Native American	1/2	50.0%	0/1	0.0%	50.0%
Ocular Pain Response of "None" at Day 1					
	Bromfenac (N=78) Observed Response		Placebo (N=78) Observed Response		Observed Differences
	n/N	%	n/N	%	%
Gender					
Male	24/33	72.7%	13/30	43.3%	29.4%
Female	41/45	91.9%	27/47	57.5%	34.4%
Age					
18 – 30	1/1	100.0%	0/0	n/a	n/a
31 – 50	4/4	100.0%	1/3	33.3%	66.7%
51 – 70	27/36	75.0%	22/41	53.7%	21.3%
> 70 years	33/37	89.2%	17/33	51.5%	37.7%
Race					
Asian	3/3	100.0%	4/4	100.0%	0.0%
Black	3/3	100.0%	5/9	55.6%	44.4%
Caucasian	47/59	79.7%	24/53	45.3%	34.4%
Hispanic	10/11	90.9%	6/10	60.0%	30.9%
Native American	2/2	100.0%	1/1	100.0%	0.0%

4.3 Study CL-S&E-1205081-P

The primary endpoint and the secondary endpoint were analyzed by subgroups on age, gender, and race for study CL-S&E-1206081-P as well. Except for the primary efficacy endpoint of the

Hispanic subgroup, in general, there were no marked differences in the efficacy results among the various subpopulations (see Table 27).

Table 27: Statistical Reviewer's Subgroup Analyses of Ocular Inflammation and Pain by Gender, Age, and Race (Study CL-S&E-1205081-P; ITT LOCF)

Cleared Ocular Inflammation by Day 15					
	Bromfenac (N=152) Observed Response		**Placebo (N=147) Observed Response**		**Observed Differences**
	n/N	%	n/N	%	%
Gender					
Male	32/63	50.8%	16/48	33.3%	17.5%
Female	38/89	42.7%	20/99	20.2%	22.5%
Age					
31 – 50	4/8	50.0%	1/8	12.5%	37.5%
51 – 70	24/60	40.0%	16/69	23.2%	16.8%
> 70 years	42/84	50.0%	19/70	27.1%	22.9%
Race					
Asian	1/5	20.0%	0/3	0.0%	20.0%
Black	8/13	61.5%	2/10	20.0%	41.5%
Caucasian	52/113	46.0%	21/109	19.3%	26.7%
Hispanic	7/17	41.2%	13/25	52.0%	-10.8%
Other	2/4	50.0%	0/0	n/a	n/a
Ocular Pain Response of "None" at Day 1					
	Bromfenac (N=152) Observed Response		**Placebo (N=147) Observed Response**		**Observed Differences**
	n/m	%	n/m	%	%
Gender					
Male	56/63	88.9%	31/48	64.6%	24.3%
Female	79/89	88.8%	74/99	74.8%	14.0%
Age					
31 – 50	6/8	75.0%	3/8	37.5%	37.5%
51 – 70	54/60	90.0%	47/69	68.1%	21.9%
> 70 years	75/84	89.3%	55/70	78.6%	10.7%
Race					
Asian	5/5	100.0%	3/3	100.0%	0.0%
Black	12/13	92.3%	8/10	80.0%	12.3%
Caucasian	99/113	87.6%	72/109	66.1%	21.5%
Hispanic	16/17	94.1%	22/25	88.0%	6.1%
Other	3/4	75.0%	0/0	n/a	n/a

4.4 Sensitivity Analysis Excluding Site 35 from Study CL-S&E-0415081-P-WR

For study CL-S&E-0415081-P-WR, DSI raised concerns regarding site 35 (Principal Investigator [PI]: Dr. Kenneth Sall) because a rouge former employee of the PI might have

tempered the integrity of the study data. To address this DSI concern, the Applicant performed additional sensitivity analyses excluding the site in question according to FDA's request; the following table presents the analysis results for the primary and secondary efficacy endpoint. The sensitivity analysis results are slightly favorable to the test drug compared to the original analysis results including site 35.

Table 28: Study CL-S&E-0415081-P-WR Sensitivity Analysis Excluding Site 35 (ITT LOCF)

Cleared Ocular Inflammation by Day 15				
	Bromfenac 0.09% N=75	**Placebo N=75**	**p-value**	**Difference (95% CI)**
Day 1	5 (6.7%)	9 (12.0%)	0.26	-5.3% (-14.6%, 3.9%)
Day 3	9 (12.0%)	10 (13.3%)	0.81	-1.3% (-12.0%, 9.3%)
Day 8	19 (25.3%)	14 (18.7%)	0.32	6.7% (-6.5%, 19.9%)
Day 15	35 (46.7%)	22 (29.3%)	0.03	17.3% (2.1%, 32.6%)
Ocular Pain Response of "None" at Day 1				
	Bromfenac 0.09% N=75	**Placebo N=75**	**p-value**	**Difference (95% CI)**
Day 1	62 (82.7%)	38 (50.7%)	<0.0001	32.0% (17.8%, 46.2%)
Day 3	71 (94.7%)	45 (60.0%)	<0.0001	34.7% (22.5%, 46.9%)
Day 8	70 (93.3%)	46 (61.3%)	<0.0001	32.0% (19.6%, 44.4%)
Day 15	70 (93.3%)	49 (65.4%)	<0.0001	28.0% (15.8%, 40.2%)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There are no major statistical issues for studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P.

The primary efficacy endpoints for all three studies were the proportion of subjects who had cleared ocular inflammation in the study eye by Day 15. The secondary efficacy endpoints for all three studies were the proportion of subjects who had an ocular pain response of "None" in the study eye at Day 1. The primary and secondary analyses were all conducted on the intent-to-treat (ITT) population, which included all randomized patient. Statistical difference between the bromfenac group and the placebo group was determined using the chi-square test.

Missing values were imputed using the last-observation-carried-forward (LOCF) method in both primary and secondary analyses. There were two types of missing values: 1) from subjects who did not respond to study drug treatment (based on assessment of ocular inflammation and ocular pain) and who required alternative medical management (i.e., rescue therapy) and 2) from

subjects who missed scheduled evaluations but continued on study drug treatment during the study. For the first type of missing data, those subjects who received a rescue medication prior to Day 15, the observed outcome nearest (on or before) the date of receiving rescue medication were carried forward and used in the determination of the missing outcome. For the second type of missing data, the outcome from the last visit at which it was measured was carried forward.

The analyses results for the proportion of patients who had cleared ocular inflammation by each visit and the proportion of patients who had ocular pain response of "None" by each visit are presented in the following two tables, where the highlighted rows corresponding with the primary and secondary efficacy endpoints for each of the three studies.

The statistical reviewer analyzed the data treating patients who discontinued the study early as treatment failure (i.e. not having cleared ocular inflammation) and also analyzed the data using observed data only. Results of both approaches are in general consistent with the primary efficacy analyses results.

Table 29: Proportion of Subjects with Cleared Ocular Inflammation by Each Visit (ITT LOCF)

	Bromfenac 0.09% N=63	**Placebo N=63**	**p-value**	**Difference (95% CI)**
Study CL-S&E-0415081-P-ER				
Day 1	3 (4.8%)	3 (4.8%)	1.00	0.0% (-7.4%, 7.4%)
Day 3	6 (9.5%)	7 (11.1%)	0.77	-1.6% (-12.2%, 9.0%)
Day 8	20 (31.7%)	15 (23.8%)	0.32	7.9% (-7.6%, 23.5%)
Day 15	28 (44.4%)	20 (31.7%)	0.14	12.7% (-4.1%, 29.5%)
Study CL-S&E-0415081-P-WR				
	Bromfenac 0.09% N=78	**Placebo N=78**	**p-value**	**Difference (95% CI)**
Day 1	5 (6.4%)	9 (11.5%)	0.26	-5.1% (-14.1%, 3.8%)
Day 3	9 (11.5%)	10 (12.8%)	0.81	-1.3% (-11.5%, 9.0%)
Day 8	20 (25.6%)	14 (17.9%)	0.24	7.7% (-5.2%, 20.6%)
Day 15	36 (46.2%)	23 (29.5%)	0.032	16.7% (1.7%, 31.7%)
Study CL-S&E-1205081-P				
	Bromfenac 0.09% N=152	**Placebo N=147**	**p-value**	**Difference (95% CI)**
Day 1	12 (7.9%)	9 (6.1%)	0.55	1.8% (-4.0%, 7.6%)
Day 3	17 (11.2%)	12 (8.2%)	0.38	3.0% (-3.6%, 9.7%)
Day 8	36 (23.7%)	23 (15.6%)	0.08	8.0% (-0.9%, 17.0%)
Day 15	70 (46.1%)	36 (24.5%)	<0.0001	21.6% (11.0%, 32.1%)

Source: Table 8 of the Applicant's CL-S&E-0415081-P-ER study report, Table 8 of the Applicant's CL-S&E-0415081-P-WR study report, and Table 8 of the Applicant's CL-S&E-1205081-P study report.

Table 30: Proportion of Subjects with Ocular Pain Response of "None" by Each Visit (ITT LOCF)

	Bromfenac 0.09% N=63	Placebo N=63	p-value	Difference (95% CI)
Study CL-S&E-0415081-P-ER				
Day 1	51 (81.0%)	46 (73.0%)	0.29	7.9% (-6.7%, 22.6%)
Day 3	56 (88.9%)	46 (73.0%)	0.023	15.9% (2.4%, 29.3%)
Day 8	60 (95.2%)	45 (71.4%)	0.0003	23.8% (11.5%, 36.1%)
Day 15	59 (93.7%)	46 (73.0%)	0.0019	20.6% (8.1%, 33.1%)
Study CL-S&E-0415081-P-WR				
	Bromfenac 0.09% N=78	**Placebo N=78**	**p-value**	**Difference (95% CI)**
Day 1	65 (83.3%)	40 (51.9%)	<0.0001	31.4% (17.5%, 45.3%)
Day 3	74 (94.9%)	51 (66.2%)	<0.0001	28.6% (17.0%, 40.3%)
Day 8	75 (96.2%)	54 (70.1%)	<0.0001	26.0% (15.0%, 37.1%)
Day 15	76 (97.4%)	57 (74.0%)	<0.0001	23.4% (13.0%, 33.8%)
Study CL-S&E-1205081-P				
	Bromfenac 0.09% N=152	**Placebo N=147**	**p-value**	**Difference (95% CI)**
Day 1	135 (88.8%)	105 (71.4%)	0.0002	17.4% (8.5%, 26.2%)
Day 3	139 (91.4%)	105 (71.4%)	<0.0001	20.0% (11.5%, 28.6%)
Day 8	142 (93.4%)	106 (72.1%)	<0.0001	21.3% (13.1%, 29.6%)
Day 15	145 (95.4%)	107 (72.8%)	<0.0001	22.6% (14.7%, 30.5%)

Source: Table 20 of the Applicant's CL-S&E-0415081-P-ER study report, Table 20 of the Applicant's CL-S&E-0415081-P-WR study report, and Table 16 of the Applicant's CL-S&E-1205081-P study report.

5.2 Conclusions and Recommendations

For studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P, the primary efficacy endpoints were the same – defined as the proportion of subjects who had cleared ocular inflammation in the study eye by Day 15. The secondary efficacy endpoints for all three studies were also the same – defined as the proportion of subjects who had an ocular pain response of "None" in the study eye at Day 1.

Primary Efficacy Endpoint

For study CL-S&E-0415081-P-ER, there was no statistically significance difference between the bromfenac group (44.4%, 28/63) and the placebo group (31.7%, 20/63) in the proportion of subjects who had cleared ocular inflammation by Day 15. The treatment difference was 12.7% with 95% CI of (-4.1%, 29.5%), and the p-value was 0.14.

Both studies CL-S&E-0415081-P-WR and CL-S&E-1205081-P showed statistically significant difference between the bromfenac group and the placebo group in the proportion of subjects who had cleared ocular inflammation by Day 15.

For study CL-S&E-0415081-P-WR, the proportion of subjects who had cleared ocular inflammation by Day 15 was 46.2% (36/78) for the bromfenac group and 29.5% (23/78) for the placebo group. The treatment difference was 16.7% with 95% CI of (1.7%, 31.7%), and the p-value was 0.032.

For study CL-S&E-1205081-P, the proportion of subjects who had cleared ocular inflammation by Day 15 was 46.1% (70/152) for the bromfenac group and 24.5% (36/147) for the placebo group. The treatment difference was 21.6% with 95% CI of (11.0%, 32.1%), and the p-value was <0.0001.

Secondary Efficacy Endpoint

For study CL-S&E-0415081-P-ER, there was no statistically significance difference between the bromfenac group (81.0%, 51/63) and the placebo group (73.0%, 46/63) in the proportion of subjects who had ocular pain response of "None" at Day 1. The treatment difference was 7.9% 95% CI of (-6.7%, 22.6%), and the p-value was 0.29.

Both studies CL-S&E-0415081-P-WR and CL-S&E-1205081-P showed statistically significant difference between the bromfenac group and the placebo group in the proportion of subjects who had ocular pain response of "None" at Day 1.

For study CL-S&E-0415081-P-WR, the proportion of subjects who had ocular pain response of "None" at Day 1 was 83.3% (65/78) for the bromfenac group and 51.9% (40/78) for the placebo group. The treatment difference was 31.4% with 95% CI of (17.5%, 45.3%), and the p-value was <0.0001.

For study CL-S&E-1205081-P, the proportion of subjects who had cleared ocular inflammation by Day 15 was 88.8% (135/152) for the bromfenac group and 71.4% (105/147) for the placebo group. The treatment difference is 17.4% with 95% CI of (8.5%, 26.2%), and the p-value is 0.0002.

Conclusion

Based on the analysis results of the primary and secondary endpoints for studies CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P, we recommend the approval of bromfenac ophthalmic solution 0.09% dosed once daily (QD) regimen for the treatment of both inflammation and pain in subjects undergoing cataract surgery.

SIGNATURES/DISTRIBUTION LIST

Yunfan Deng, Ph.D.
Primary Statistical Reviewer

Concurring Reviewer:

Yan Wang, Ph.D
Statistical Team Leader

cc:
HFD-520/Project Manager: Jane Dean
HFD-520/Medical Officer: Jennifer Harris, M.D
HFD-520/Medical Team Leader: William Boyd, M.D
HFD-725/Primary Statistical Reviewer: Yunfan Deng, Ph.D.
HFD-725/Statistical Team Leader: Yan Wang, Ph.D
HFD-725/Biometrics Deputy Division Director: Daphne Lin, Ph.D
HFD-725/Biometrics Division Director: Mohammad Huque, Ph.D
HFD-700/Office of Biostatistics: Lillian Patrician

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

YUNFAN DENG
08/10/2010

YAN WANG
08/10/2010

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA: 21664
Name Of Drug: XiDay™ (bromfenac sodium (b) (4) ophthalmic solution (b) (4))
Applicant: ISTA Pharmaceuticals, Inc.
Submission Date: 12/16/2009

Indication(s): Inflammation and pain associated with cataract extraction
Number And Type Of Controlled Clinical Studies (By Indication): 4

Statistical Reviewer: Yunfan Deng
Clinical Reviewer: Jennifer Harris
Project Manager: Jane Dean

45 Day Meeting Date: 01/25/2010
Date Draft Review Expected: 07/12/2010
OAP Goal Date: 08/16/2010
User Fee Date: 10/16/2010

A. ORGANIZATION AND DATA PRESENTATION	**YES**	**NO**	**N/A**
I. Is there a comprehensive table of contents with adequate indexing and pagination?	✓		
II. Are the original protocols, protocol amendments and proposed label provided	✓		
III. Are patient profile listings (for all enrolled patients) provided in each study report?	✓		
IV. Are adverse event listings by center and time of occurrence relative to enrollment date included?	✓		
V. Have the data been submitted electronically?	✓		
a. If so, has adequate documentation of the data sets been provided?	✓		
b. Do the electronic data appear to accurately represent the data described in the study reports?	✓		
c. Can the data be easily merged across studies and indications?	✓		
d. Are inclusion/exclusion and evaluability criteria adequately coded and described?	✓		

B. STATISTICAL METHODOLOGY	**YES**	**NO**	**N/A**
I. Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	✓		

II. For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable subgroups (age, gender, race, etc.)?	✓	
III. Based on the summary analyses of each study, do you believe:		
a. The analyses are appropriate for the type of data collected, the study design, and the study objectives (based on protocol objectives proposed labeling claims)?	✓	
b. Intent-to-treat and evaluable patient analyses are properly performed?	✓	
c. Missing data has been appropriately handled?	✓	
d. Any multiplicity issues (e.g., regarding endpoints, timepoints, or multiple dose groups) have been adequately addressed?	✓	
e. If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?		✓
IV. Were sufficient and appropriate reference included for novel statistical approaches?		✓
V. Are all of the pivotal studies complete?	✓	
VI. Have safety data been comprehensively and adequately summarized?	✓	

C. FILEABILITY CONCLUSIONS

From a statistical perspective is this submission, or indications therein, reviewable with only minor further input from the sponsor?

The NDA is filable. To help expediting the statistical review, please provide us with the 95% confidence intervals of the treatment differences for both primary and secondary efficacy endpoints (inflammation and pain) for studies CL-S&E-0802071-P, CL-S&E-0415081-P-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P. Please also submit the corresponding SAS codes for generating the 95% confidence intervals.

Yunfan Deng
Mathematical Statistician, DB IV

Concur: Yan Wang
Statistics Team Leader, DB IV

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

YUNFAN DENG
02/18/2010

YAN WANG
02/18/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	21-664/SE2-013
Submission Date(s):	18DEC2009
Brand Name	XiDay™
Generic Name	Bromfenac sodium (b) (4) ophthalmic solution (b) (4)
Primary Reviewer	Kimberly L. Bergman, Pharm.D.
Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	ISTA Pharmaceuticals, Inc.
Relevant IND(s)	IND 60,295
Submission Type; Code	S-013; Efficacy Supplement
Formulation; Strength(s)	Bromfenac sodium (b) (4) ophthalmic solution (b) (4)
Indication	Treatment of (b) (4)

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Bromfenac ophthalmic solution (b) (4) s a non-steroidal anti-inflammatory drug (NSAID) studied for the treatment of postoperative inflammation and the reduction of pain in subjects who have undergone cataract extraction. The currently marketed product, Xibrom™ (bromfenac ophthalmic solution) 0.09%, administered twice daily (BID), is indicated for the treatment of postoperative inflammation and the reduction of pain in subjects who have undergone cataract extraction. Xibrom™ 0.09% BID was approved by the US Food and Drug Administration (FDA) in March 2005 for the treatment of post-operative ocular inflammation and in January of 2006 for the treatment of post-operative pain. Bronuck® (bromfenac sodium ophthalmic solution) 0.1% was approved in Japan in July 2000, and is indicated for the treatment of blepharitis, conjunctivitis, scleritis (including episcleritis) and post-operative inflammation.

In this supplement (S-013 dated December 18, 2009), bromfenac ophthalmic solution (b) (4) The proposed dosage and route of administration for bromfenac ophthalmic solution (b) (4) for this indication is as follows: instill one drop into the affected eye(s) once daily beginning one day prior to surgery, continued on the day of surgery and through the first 14 days post-surgery. In summary, this proposal represents a change from the currently approved BID dosing regimen to QD dosing. (b) (4) The current application (NDA 21-664 S-013) presents data from a dose-ranging Phase 2 study comparing bromfenac ophthalmic solution 0.18% QD with bromfenac ophthalmic solution 0.09% QD (Study CL-S&E-0802071-P) and three Phase 3 studies comparing bromfenac ophthalmic solution 0.09% QD to placebo (Studies CL-S&E-0415081-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P) to support once daily use of bromfenac ophthalmic solution (b) (4)

Of note, the approved product Xibrom™ (bromfenac ophthalmic solution)® 0.09% is equivalent to the proposed bromfenac ophthalmic solution (b) (4) drug product formulation. The proposed formulation (bromfenac ophthalmic solution (b) (4) is referred to as bromfenac ophthalmic solution 0.09% in the clinical study reports in the current supplement and throughout this review.

No new clinical pharmacology data was presented in this supplement. Based on the assessment of dose-response information from the Phase 2 and 3 studies, no clear dose-response for the primary efficacy endpoint nor for safety was observed between bromfenac ophthalmic solution 0.18% QD versus bromfenac ophthalmic solution 0.09% QD, nor for bromfenac ophthalmic solution 0.09% QD versus Xibrom™ 0.09% BID.

1.1. Recommendation

This application is acceptable from a clinical pharmacology perspective. No new clinical pharmacology data was presented in this supplement.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology Findings

Bromfenac ophthalmic solution (b) (4) (bromfenac sodium (b) (4) ophthalmic solution) is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. (b) (4) To support this indication, the applicant has conducted a dose-ranging Phase 2 study comparing bromfenac ophthalmic solution 0.18% QD with bromfenac ophthalmic solution 0.09% QD and three Phase 3 studies comparing bromfenac ophthalmic solution 0.09% QD to placebo. Specific clinical pharmacology findings from review of this efficacy supplement are summarized as follows:

- A comparison of proportion of subjects who had cleared ocular inflammation by Day 15 between bromfenac ophthalmic solution 0.09% QD and bromfenac 0.18% QD did not demonstrate dose-response relationship, i.e. there was no significant difference between bromfenac ophthalmic solution 0.09% QD data compared to that of bromfenac 0.18% QD. Pooled data from the Xibrom™ 0.09% BID treatment showed a greater proportion of subjects achieving the primary efficacy outcome compared to the pooled bromfenac ophthalmic solution 0.09% QD subjects, suggesting a dose-response when considering frequency of administration (i.e. total daily dose). The sponsor's analysis of transformed data contradicts this finding; bromfenac ophthalmic solution 0.09% QD subjects show a higher proportion of subjects reaching the primary efficacy endpoint compared to the pooled Xibrom™ 0.09% BID subjects.

- No clear dose-response relationship for safety was observed for adverse events between bromfenac ophthalmic solution 0.18% QD versus bromfenac ophthalmic solution 0.09% QD, nor for bromfenac ophthalmic solution 0.09% QD versus Xibrom™ 0.09% BID.

No new clinical pharmacology data was presented in this submission. Based on the assessment of dose-response information from the Phase 2 and 3 studies, no clear dose-response for the primary efficacy endpoint nor for safety was observed between bromfenac ophthalmic solution 0.18% QD versus bromfenac ophthalmic solution 0.09% QD, nor for bromfenac ophthalmic solution 0.09% QD versus Xibrom™ 0.09% BID.

_____
Kimberly L. Bergman, Pharm.D.
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

_____
Concurrence: Charles R. Bonapace, Pharm.D.
Team Leader

cc:
Division File: NDA 21-664
HFD-520 (CSO/Dean)
HFD-520 (MO/Harris)
HFD-520 (Chambers, Boyd)
HFD-880 (Lazor, Reynolds, Bonapace)

2. QUESTION BASED REVIEW

Since this submission is an efficacy supplement for an already approved locally administered ophthalmic drug product, only relevant questions from the OCP question-based review (QBR) are addressed below.

2.1. General Attributes of the Drug

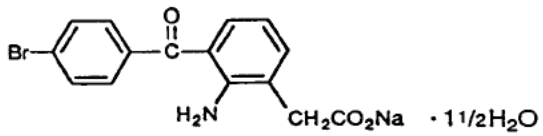
2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Bromfenac ophthalmic solution (b) (4) (bromfenac sodium (b) (4) ophthalmic solution) (b) (4) is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each mL of bromfenac ophthalmic solution (b) (4) contains 1.035 mg bromfenac sodium. The chemical structure and physical-chemical properties of the active ingredient bromfenac sodium hydrate are as follows:

Structural Formula: $C_{15}H_{11}BrNNaO_3 \bullet 1\frac{1}{2}H_2O$

Chemical Name: sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate

Chemical Structure:



Molecular Weight: 383.17

Appearance: Yellow to orange crystalline powder

(b) (4) with a pH of 8.3. The osmolality of bromfenac ophthalmic solution is approximately 300 mOsmol/kg. Each mL of bromfenac ophthalmic solution contains the following: active, bromfenac sodium hydrate 0.1035%; (b) (4) (b) (4) inactives: boric acid, disodium edetate, polysorbate 80, povidone, sodium borate, sodium sulfite anhydrous, sodium hydroxide to adjust pH and water for injection, USP. Bromfenac sodium 1.035 mg is equivalent to 0.9 mg bromfenac free acid. The approved product Xibrom™ (bromfenac ophthalmic solution)® 0.09% is therefore equivalent to the proposed bromfenac ophthalmic solution (b) (4) formulation. **The proposed formulation (bromfenac ophthalmic solution (b) (4) s referred to as bromfenac ophthalmic solution 0.09% in the clinical study reports in the current supplement and throughout this review.** In addition, bromfenac 0.09%, 0.1% (used in the original NDA 21-664 review) and (b) (4) have been used interchangeably across submissions to refer to the same drug product.

For further information on the qualitative and quantitative composition of the bromfenac ophthalmic solution (b) (4) drug product, refer to the Office of Clinical Pharmacology review of the original NDA 21-664 by Dr. Lei Zhang dated March 8, 2005.

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Bromfenac belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs), which exert effects by blocking the production of prostaglandins, mediators of various kinds of systemic and localized (e.g. ocular) inflammation. Bromfenac blocks prostaglandin production by inhibiting cyclooxygenase (COX), the enzyme that converts arachidonic acid to cyclic endoperoxides, precursors of prostaglandins.

Bromfenac ophthalmic solution (b) (4) is proposed for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.

2.1.3. What is the proposed dosage and route of administration?

The proposed dosage and route of administration for bromfenac ophthalmic solution (b) (4) for this indication is as follows: instill one drop into the affected eye(s) once daily beginning one day prior to surgery, continued on the day of surgery and through the first 14 days post-surgery. In summary, this proposal represents a change from the currently approved BID dosing regimen to QD dosing.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?

No new clinical pharmacology studies were submitted in this supplement (NDA 21-664 S-013, dated December 18, 2009). To support the proposed indication of treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction, the applicant has conducted a dose-ranging Phase 2 study comparing bromfenac ophthalmic solution 0.18% QD with bromfenac ophthalmic solution 0.09% QD (Study CL-S&E-0802071-P) and three Phase 3 studies comparing bromfenac ophthalmic solution 0.09% QD to placebo (Studies CL-S&E-0415081-ER, CL-S&E-0415081-P-WR, and CL-S&E-1205081-P).

2.2.2. What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in the Phase 3 studies was 'cleared ocular inflammation', as defined as the proportion of subjects that achieved Summary Ocular Inflammation Score (SOIS) of grade 0 (0 cells and absence of flare). The primary efficacy outcome, cleared ocular inflammation by Day 15, was defined as a SOIS of grade 0 at any post-surgery visit prior to and including Day 15. The SOIS was assessed by the investigator grading the anterior chamber for anterior chamber cells and flare.

2.2.3. Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?

No pharmacokinetic data for bromfenac ophthalmic solution (b) (4) was submitted in the current application.

2.2.4. Exposure-Response

2.2.4.1. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

For ease of presentation, the clinical studies are abbreviated as follows: Study CL-S&E-0802071-P (BromCom); Study CL-S&E-0415081-ER (QD-ER); CL-S&E-0415081-P-WR (QD-WR); and CL-S&E-1205081-P (QDII). The primary efficacy outcome of bromfenac ophthalmic solution 0.09% QD data compared to that of bromfenac 0.18% QD and placebo is presented in Table 2.2.4.1-1. The proportion of subjects who had cleared ocular inflammation by Day 15 was significantly greater in the bromfenac treatment group than in the placebo treatment group for all placebo controlled studies except QD-ER (44.4% versus 31.7%, p = 0.1422). In the Phase 2 study, there was no difference between bromfenac ophthalmic solution 0.09% QD data compared to that of bromfenac 0.18% QD for the primary efficacy outcome of the proportion of subjects who had cleared ocular inflammation by Day 15.

Table 2.2.4.1-1. Primary Efficacy Outcome by Study

	BromCom		QD-ER		QD-WR		QDII	
	0.09% QD	0.18% QD	0.09% QD	Placebo QD	0.09 % QD	Placebo QD	0.09% QD	Placebo QD
ITT Population (N)	291	277	63	63	78	78	152	147
SOIS of Grade 0 by Day 15, n (%)	164 (56.6)	157 (56.9)	28 (44.4)	20 (31.7)	36 (46.2)	23 (29.5)	70 (46.1)	36 (24.5)
p-value [1]	0.9364		0.1422		0.0318		<0.0001	

[1] p-values for all bromfenac ophthalmic solution 0.09% QD vs. placebo QD (or bromfenac ophthalmic solution 0.18% QD vs. bromfenac ophthalmic solution 0.09% QD [BromCom]) is based on the Chi-square test.

Source: Integrated Summary of Efficacy, Table 16

Additionally, the applicant's analysis of efficacy included a cross-study comparison between bromfenac ophthalmic solution 0.09% QD and Xibrom™ 0.09% BID (data from studies submitted previously in the original NDA 21-664). Table 2.2.4.1-2 displays the pooled primary efficacy outcome of the bromfenac ophthalmic solution 0.09% QD data compared to that of Xibrom™ 0.09% BID with no *post-hoc* modification of data. Based on untransformed data, the Xibrom™ 0.09% BID and placebo treatments showed greater proportions of subjects achieving the primary efficacy outcome compared to the pooled bromfenac ophthalmic solution 0.09% QD subjects.

Table 2.2.4.1-2. Primary Efficacy Outcome (Pooled Bromfenac Ophthalmic Solution 0.09% QD vs. Xibrom™ 0.09% BID): Untransformed Data

	Bromfenac Ophthalmic Solution 0.09% QD		Xibrom™ 0.09% BID	
	0.09% QD	Placebo QD	0.09% BID	Placebo BID
ITT Population (N)	584	288	356	171
SOIS of Grade 0 by Day 15, n (%)[3]	298 (51.1)	79 (27.4)	228 (64.0)	74 (43.3)
p-value	<0.0001[1]		<0.0001[2]	

[1] p-value for bromfenac ophthalmic solution 0.09% QD vs. placebo QD is based on the Chi-square test.
[2] p-value for Xibrom™ BID vs. placebo is based on the Cochran-Mantel-Haenszel procedure.
[3] The pooled untransformed Xibrom™ BID primary efficacy endpoint was SOIS of 0 at day 15.
Source: Integrated Summary of Efficacy, Table 18

In the applicant's analysis, Xibrom™ 0.09% BID data was also transformed *post-hoc* for comparison with QD data. Specifically, subject data from the BID studies' SOIS were re-graded. The original CS001 studies graded 0 anterior chamber cells count of 0-5, whereas QD studies graded 0 if there were 0 cells and 1 if there were 1-5 cells. Thus anterior chamber cells scores had to be transformed to the same scale, so that 0 cells receive a score of 0 and 1-5 cells receive a score of 1. Following transformation, pooled bromfenac ophthalmic solution 0.09% QD subjects show a higher proportion of subjects reaching the primary efficacy endpoint compared to the pooled Xibrom™ 0.09% BID subjects (percentages of patients with SOIS of Grade 0 by Day 15: bromfenac ophthalmic solution 0.09% QD, 51.1%; Xibrom™ 0.09% BID, 35.0%).

In summary, a comparison of proportion of subjects who had cleared ocular inflammation by Day 15 between bromfenac ophthalmic solution 0.09% QD and bromfenac 0.18% QD did not demonstrate dose-response relationship, i.e. there was no significant difference between bromfenac ophthalmic solution 0.09% QD data compared to that of bromfenac 0.18% QD. Pooled data from the Xibrom™ 0.09% BID treatment showed a greater proportion of subjects achieving the primary efficacy outcome compared to the pooled bromfenac ophthalmic solution 0.09% QD subjects, suggesting a dose-response when considering frequency of administration (i.e. total daily dose). The sponsor's analysis of transformed data contradicts this finding; bromfenac ophthalmic solution 0.09% QD subjects show a higher proportion of subjects reaching the primary efficacy endpoint compared to the pooled Xibrom™ 0.09% BID subjects. For further discussion of the efficacy results and interpretation of the sponsor's transformation of data, refer to the Medical Officer's and Biostatistician's reviews of this efficacy supplement (NDA 21-664 S-013).

2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Phase 2:

Overall, 27.2% (148/544) of subjects experienced a total of 304 AEs in the Phase 2 study. The bromfenac 0.18% treatment group (24.4%, 65/266) and the bromfenac 0.09% treatment group (29.9%, 83/278) did not differ significantly ($p = 0.1556$) in incidence of AEs. The two treatment groups did not differ significantly ($p = 0.1359$) in incidence of AEs affecting the study eye (bromfenac 0.18% treatment group: 19.2%, 51/266; bromfenac 0.09% treatment group: 24.5%, 68/278) nor the non-study eye (bromfenac 0.18% treatment group: 0.8%, 2/266, bromfenac 0.09% treatment group: 1.1%, 3/278). The two treatment groups did not differ significantly ($p = 0.6672$) in incidence of systemic AEs (bromfenac 0.18% treatment group: 8.6%, 23/266; bromfenac 0.09% treatment group: 9.7%, 27/278). The bromfenac 0.18% treatment group and the bromfenac 0.09% treatment group did not differ statistically in the relationship of AEs to test agent ($p = 0.6936$) nor the severity of AEs ($p = 0.7814$). Seven (7) ocular AEs occurred with incidence $\geq 2.0\%$ in the bromfenac 0.18% and bromfenac 0.09% treatment groups: conjunctival hyperaemia (4.9%, 13/266 and 6.8%, 19/278), eye inflammation (0.8%, 2/266 and 3.6%, 10/278), corneal oedema (3.0%, 8/266 and 3.2%, 9/278), iritis (1.1%, 3/266 and 3.2%, 9/278), eye pain (3.4%, 9/266 and 2.5%, 7/278), conjunctival haemorrhage (2.6%, 7/266 and 2.9%, 8/278), and abnormal sensation in eye (1.5%, 4/266 and 2.2%, 6/278). In summary, there was no consistent dose-response relationship for adverse events observed between the two bromfenac treatment groups administered QD, bromfenac ophthalmic solution 0.18% and bromfenac ophthalmic solution 0.09%.

Phase 3:

Overall, there were no clinically significant differences in the total number of subjects with an adverse event (AE) between bromfenac treatment groups in the Phase 3 studies (incidence rates:

bromfenac ophthalmic solution 0.09% QD [35.1%], Xibrom™ 0.09% BID [43.0%], and placebo [55.0%]). Nor were there differences in AE severity between the two bromefenac treatment groups. The number of serious adverse events was greater in the bromfenac ophthalmic solution 0.09% treatment group (n=12) compared to Xibrom™ 0.09% BID (n=3) and placebo (n=3, combined). Based on a cross-study comparison of Phase 3 safety data, differences in the most frequently (> 2% in any treatment group) reported systemic events between bromfenac treatment groups (via cross-study comparison) were inconsistent and did not exhibit a clear dose-response relationship between bromfenac ophthalmic solution 0.09% QD and Xibrom™ 0.09% BID.

For further discussion of the safety results, refer to the Medical Officer's review of this supplement (NDA 21-664 S-013).

2.2.5. What are the PK characteristics of the drug and its major metabolite?

No new pharmacokinetic data was submitted in this supplement. Pharmacokinetic data for bromfenac was submitted in the original NDA 21-664 for Xibrom™. Upon review of the data submitted under the original NDA, a waiver of submission of in vivo bioavailability information was granted based on the estimation that exposure of bromfenac would be negligible (< 50 ng/mL) following the proposed bromfenac ophthalmic solution (b) (4) dosing regimen and given the fact that bromfenac was not a new molecular entity and there was prior PK knowledge for this compound via other routes of administration (i.e. oral). For further information on the pharmacokinetic characteristics of Xibrom™ (Bromfenac Sodium) 0.1% Ophthalmic Solution, please refer to the Office of Clinical Pharmacology review of the original NDA (by Dr. Lei Zhang dated March 8, 2005).

2.3. Intrinsic Factors
Not applicable.

2.4. Extrinsic Factors
Not applicable.

2.5. General Biopharmaceutics
Not applicable.

2.6. Analytical Section
Not applicable.

3. LABELING RECOMMENDATIONS

In the current submission (NDA 21-664 supplement S-013 dated December 18, 2009), the applicant has proposed no changes to the already existing Clinical Pharmacology section in the approved label for Xibrom. Thus, the labeling proposed for this supplement is acceptable from a clinical pharmacology perspective (see proposed labeling below).

(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

KIMBERLY L BERGMAN
07/12/2010

CHARLES R BONAPACE
07/12/2010

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA:	021664
Drug Name:	XiDay (bromfenac sodium (b) (4) ophthalmic solution, (b) (4))
Applicant:	ISTA
Submission Date:	16DEC2009
Filing Date:	14FEB2010
PDUFA Date:	16DEC2010
OCP Primary Reviewer:	Kimberly L. Bergman, PharmD
OCP Team Leader:	Charles Bonapace, PharmD

QUESTION	***YES***	***NO***	***NA***	***COMMENTS***
Fileability: ***Is the Clinical Pharmacology section of the application fileable?*** ***(if 'NO', please comment as to why it is not fileable)***	***X***			
Fileability Review Components				
1. Is the clinical pharmacology section of the NDA organized in a manner to allow substantive review to begin (including a table of contents, proper pagination, reference links, etc.)?	☒	☐	☐	
2. Are the clinical pharmacology studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?	☐	☐	☒	No new clinical pharmacology studies were submitted with this application.
3. If multiple formulations were used in the clinical development of the product, does the NDA contain appropriate biopharmaceutics information to allow comparison between the clinical development and to-be-marketed product(s) (i.e. pivotal BE)?	☐	☐	☒	Bromfenac solution 0.09% was used in clinical studies and has the same composition as bromfenac sodium (b) (4) (commercial).
4. If unapproved products or altered approved products were used as active controls, was bioequivalence to the approved product demonstrated?	☐	☐	☒	
5. Are complete and relevant bioanalytical reports included in the NDA submission?	☐	☐	☒	
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	☐	☐	☒	
7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	☐	☐	☒	

OCP Primary Reviewer _____ Date _____

OCP Team Leader _____ Date _____

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

KIMBERLY L BERGMAN
01/29/2010

CHARLES R BONAPACE
01/29/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

OTHER REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 12, 2010

TO: Jane A. Dean, RN, MSN, Regulatory Project Manager
Boyd, William M., M.D, Medical Team Leader
Jennifer Harris, MD, Clinical Reviewer
Division of Anti-Infective and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

RE: NDA 21-664, Supplement # 013

SPONSOR: ISTA Pharmaceuticals, Inc.
Paul Nowacki, Director, Regulatory Affairs
15295 Alton Parkway
Irvine, CA 92618
Phone # (949) 789-3109,
pnowacki@istavision.com

DRUG: Bromfenac sodium (b) (4) ophthalmic solution (b) (4)

NEW MOLECULAR ENTITY (NME): No

REVIEW PRIORITY (STANDARD OR PRIORITY): Standard

PROPOSED INDICATION: Treatment of (b) (4)

SUBJECTS < 18 YEARS: No

CONSULTATION REQUEST DATE: April 19, 2010

PDUFA: October 16, 2010

I. BACKGROUND:

DSI received a consult from Division of Anti-Infective and Ophthalmology Products (DAIOP) regarding a clinical investigator, Kenneth Sall, M.D. DAIOP received a letter from Dr. Sall, dated March 29, 2010, in which he indentified concerns with the validity of data submitted to the Agency, potentially for multiple applications, due to concerns with possible falsification of data by an individual previously in his employ. Dr. Sall's site has contributed data to a pivotal study in a supplemental application (NDA 21-664 for bromfenac sodium [redacted] ophthalmic solution submitted by ISTA Pharmaceuticals, Inc.) that is currently undergoing review by DAIOP in CDER for the treatment of [redacted].

ISTA Pharmaceuticals, Inc. (ISTA) submitted this supplemental new drug application under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for bromfenac sodium [redacted] ophthalmic solution, [redacted] (NDA 021664, Supplement # 013) on 15 December, 2009 to support a labeling claim for the treatment of [redacted]

The current marketed product, Xibrom™ (bromfenac ophthalmic solution) 0.09%, which is administered twice daily, was approved by the Food and Drug Administration (FDA) in March 2005 for the treatment of post-operative ocular inflammation and in January 2006 for the treatment of post-operative ocular pain. [redacted]

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase (COX) 1 and 2. A common risk associated with bromfenac ophthalmic solution 0.18% QD in the treatment of inflammation and pain associated with cataract surgery are eye inflammation, conjunctival hyperemia and foreign body sensation. Slow or delayed healing, potential for cross-sensitivity, and increase ocular bleeding and keratitis can be also associated with the use of bromfenac ophthalmic solution.

[redacted] CL-

S&E-0415081-P-WR: Efficacy and Safety of Xibrom™ (Bromfenac Ophthalmic Solution) 0.09% QD vs. Placebo QD for Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery).

The (b) (4) Protocol **CL-S&E-0415081-P-WR**. Brief descriptions of the studies inspected are provided below:

(b) (4)

Protocol: Phase 3: CL-S&E-0415081-P-WR: Efficacy and Safety of Xibrom™ (Bromfenac Ophthalmic Solution) 0.09% QD vs. Placebo QD for Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery

The proposed study was a multicenter, randomized, double-masked, parallel, placebo-controlled study. Subjects were to be instilled one drop of test agent into the study (operative) eye once daily for a maximum of 16 days. Dosing with test agent was to begin one day prior to surgery (Day -1) and continued on the day of surgery (Day 0) and for 14 days after surgery. Subjects were to be seen for evaluation on Days 1, 3±1, 8±1 and 15±1 following surgery. In addition, subjects were to be seen for a follow-up visit on Day 22+3 following surgery or 7+3 days after their last dose of test agent if they prematurely discontinued the test agent. (b) (4) A total of 271 subjects were randomized to receive test agent in Study (b) (4).

Dr Sall's site was selected for inspection, mainly due to concerns with possible falsification of data by an individual previously in his employ. This inspection was a PDUFA/For-Cause inspection.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #/Site #/ # of Subjects:	Inspection Date	Final Classification
Kenneth Sall, MD **SALL** RESEARCHMEDICAL CENTER, INC. 11423 187'h St., Suite 200 Artesia, CA. 90701	(b) (4) Study CL-S&E-0415081-P-WR /35/7	10/07/2010 - 10/08/2010	*Pending (Interim classification: NAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

1. **Kenneth Sall, M.D.**
   Sall Research Medical Center, Inc.
   11423 187'h St., Suite 200
   Artesia, CA. 90701

a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 between 10/07/2010 - 10/08/2010.

At this site, a total of 33 subjects were screened and 30 subjects enrolled and 28 subjects completed in the 2 well-controlled, double-masked, randomized Phase 3 clinical studies (Study (b) (4)
Study CL-S&E-0415081-P-WR).

For Study CL-S&E-0415081-P-WR there were 7 subjects screened and 6 subjects were randomized. All subject records were reviewed and all subjects completed the study. For the I (b) (4) study there were 26 subjects screened, 24 subjects were randomized and 22 subjects completed the study. Twelve (12) subject records were reviewed for the (b) (4) study.

The inspection evaluated informed consent documents and included review of source documents and hard copy reporting. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary**: Based on the discussion with the ORA investigator, in general, the studies were conducted appropriately and no significant issues were identified. There was no evidence of under reporting of adverse events noted. There was no evidence of significant deviations with the investigational plan and/or eligibility requirements. Primary efficacy endpoints were verifiable. A Form FDA 483, Inspectional Observations, was not issued to Dr Sall and the ORA investigator plans to recommend a classification of No Action Indicated (NAI) for this inspection.

With respect to the concern raised by Dr. Sall regarding a prior employee's participation in the studies, it appears that this employee did not have extensive involvement in the conduct of these pivotal studies. It appears that this employee was involved with the studies, but not to an extent where she could have adversely affected the studies and no evidence was noted that this employee's participation negatively impacted the conduct of the study. Further, there was no evidence to suggest falsification or record manipulation by her or any other study staff.

c. **Assessment of data integrity**: Based on preliminary communications with the ORA field investigator, data derived from Dr. Kenneth Sall's site are considered acceptable.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

One domestic clinical investigator site was inspected in support of the NDA. In general, the studies at this site appear to have been conducted adequately and the data in support of the NDA appear reliable.

The preliminary classification of Clinical Investigator inspection of Dr. Sall is No Action Indicated (NAI).

Note: Final classification for Dr. Kenneth Sall's pending and will be determined when the final EIR and associated exhibits are received and reviewed. Should the final classification be different from the current preliminary classification, the Division will be notified and an inspection summary addendum will be generated.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

/s/

KASSA AYALEW
10/12/2010

TEJASHRI S PUROHIT-SHETH
10/12/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

*****Pre-Decisional Agency Information*****

Date: September 23, 2010

To: Jane A. Dean, RN, MSN, Regulatory Health Project Manager
Division of Anti-Infective and Opthalmology Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications

Sheila Ryan, Pharm.D., Group Leader
Division of Drug Marketing, Advertising and Communications

Subject: Bromday (bromfenac sodium (b) (4) ophthalmic solution) 0.09%
NDA: 21664/S-013

DDMAC has reviewed the proposed product labeling, including the package insert (PI), draft carton label, and draft container label for Bromday™ (bromfenac sodium (b) (4) ophthalmic solution) 0.09%, dated 9/8/2010, and we offer the following comments. Please note that DDMAC had no additional comments regarding the draft carton or container label. Please feel free to contact me at (301)796-2653 with any questions or clarifications.

11 Page(s) 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/

CHRISTINE G CORSER
09/28/2010

Medical Officer's Review NDA 21-664/S-002
Labeling Review #1

NDA 21-664	Submission Date:	September 15, 2010
	Review Date:	September 20, 2010
Sponsor:	ISTA Pharmaceuticals 15295 Alton Parkway Irvine, CA 92618	
Drug:	Bromday (bromfenac sodium ophthalmic solution)	
Pharmacologic Category:	non-steroidal anti-inflammatory	

Submitted:

- amended package insert in response to the draft proposed label provided to the applicant on September 15, 2010
- carton and container labels

Reviewer's Comments:
Following is the labeling submitted by the applicant. The Applicant has accepted the proposed changes suggested by the Division for the package insert and carton and container labels.

(b) (4)

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

Recommendations:

The proposed labeling is acceptable and approval is recommended.

Jennifer D. Harris, MD
Medical Officer

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

/s/

JENNIFER D HARRIS
09/22/2010

WILLIAM M BOYD
09/22/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 27, 2010
To:	Wiley Chambers, M.D., Acting Director Division of Anti-Infective and Ophthalmology Product
Through:	Zachary Oleszczuk, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Yelena Maslov, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Bromday (Bromfenac Ophthalmic Solution) 0.09%
Application Type/Number:	NDA 021664/013
Applicant:	ISTA Pharmaceutical
OSE RCM #:	2010-1221

CONTENTS

1 INTRODUCTION

This review was written in response to a request from the Division of Anti-Infective and Ophthalmology Products dated June 03, 2010 to evaluate the container label, carton and package insert labeling for ISTA Pharmaceuticals Inc.'s Bromday (Bromfenac Ophthalmic Solution) for potential to contribute to medication errors.

1.1 REGULATORY HISTORY

Bromday (NDA 021664/S013) is the proprietary name for the once-a-day dosing regimen for the currently marketed product, Xibrom (Bromfenac Ophthalmic Solution) 0.09%. Xibrom was approved on March 24, 2005. ISTA pharmaceuticals, Inc. intends to discontinue Xibrom (b) (4) (b) (4) once Bromday is approved. The applicant submitted Bromday's package insert labeling on May 4, 2010, the container labels, and carton labeling on May 25, 2010.

2 METHODS AND MATERIALS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Since Xibrom has been marketed since 2005, DMEPA conducted a search of the proprietary name, Xibrom, through the FDA Adverse Event Reporting System (AERS) database to determine if there are any medication errors associated with the currently marketed product, which may be indicative of potential issues with the proposed product, Bromday.

A search was conducted on July 19, 2010 using the MedDRA high level group term (HLGT) "Medication Error" along with active ingredient name of "Bromfenac", the trade name "Xibrom", and the verbatim names "Xibr%" and "Bromfen%" with no dates limitations.

2.2 LABELS AND LABELING RISK ASSESSMENT

The Division of Medication Error Prevention and Analysis use Failure Mode and Effects Analysis[1] (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling; thereafter, we provide recommendations that aim at reducing the risk of medication errors.

For Bromday (Bromfenac Ophthalmic Solution) 0.09%, the Applicant submitted (b) (4) mL, 1.7 mL, and (b) (4) mL container labels and carton labeling on May 25, 2010 and insert labeling on May 4, 2010 (See Appendices A through C for container labels and carton labeling images).

[1] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Our search of the Adverse Events Reporting System (AERS) database did not identify any cases of medication errors reports involving Xibrom. However, since medication errors are known to be under reported and negative, our AERS result cannot guarantee that errors are not occurring, only perhaps that errors are not being reported.

3.2 LABELS AND LABELING RISK ASSESSMENT

Our evaluation of the proposed container labels and carton labeling noted areas of needed improvement in order to minimize the potential for medication errors. Specifically, pertinent information such as product's proprietary and established names and strength is less prominent than net quantity and dosing regimen.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the proposed container labels and carton labeling noted areas of needed improvement in order to minimize the potential for medication errors. Section 4.1 *Comments to the Applicant* contains our recommendations for the container labels and the carton labeling. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Brantley Dorch at 301-796-0150.

4.1 COMMENTS TO THE APPLICANT

A. All Container Labels and Carton Labeling

1. As currently presented, the dosing regimen statement "Once Daily" is the most prominent information on all container labels and carton labeling. Decrease the prominence of this dosing regimen by decreasing the font size and bold formatting. The proprietary and established names and strength should be the most prominent information on the principle display panel.

2. Revise the labeling to express the established name and produc (b) (4) in terms of the active moiety, Bromfenac, (b) (4) of the active moiety, (b) (4) . The Agency has determined that expressing the established name (b) (4) (b) (4) e active moiety is confusing and misleading because it implies that Bromday (Bromfenac (b) (4) Xibrom (Bromfenac Ophthalmic Solution) 0.09%, (b) (4) .

B. Carton Labeling (b) (4)

Debold the net quantity statement and relocate to the lower portion of the carton labeling as this statement may be misinterpreted for the strength of the product.

C. Carton Labeling (1.7 mL [redacted] Trade)

1. The [redacted] font of the proprietary and established names and strength on the [redacted] background is difficult to read. Revise either the font color or the background to increase readability.

2. As currently presented, the volume of the product per package is more prominent than proprietary and established names and strength.

   Decrease the prominence of the net quantity statement (1.7 mL [redacted]) on the principle display panel by [redacted]. The proprietary and established names and strength are the most prominent information on the principle display panel.

3. Delete the net quantity statement (1.7 mL [redacted]) located [redacted] the established name as the net quantity is already presented in the lower portion of the carton labeling.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

YELENA L MASLOV
08/27/2010

DENISE P TOYER on behalf of ZACHARY A OLESZCZUK
08/27/2010

DENISE P TOYER
08/27/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # **021664**	NDA Supplement #: **S- 013**	Efficacy Supplement Type: **SE-2**
Proprietary Name: Established/Proper Name: **bromfenac sodium** (b) (4) **ophthalmic solution** (b) (4) Dosage Form: **ophthalmic solution** Strengths: (b) (4)		
Applicant: **ISTA Pharmaceuticals, Inc.** Agent for Applicant (if applicable): **n/a**		
Date of Application: **December 18, 2009** Date of Receipt: **December 16, 2009** Date clock started after UN: **n/a**		
PDUFA Goal Date: **October 16, 2010**	Action Goal Date (if different): **August 16, 2010**	
Filing Date: **February 14, 2010**	Date of Filing Meeting: **January 25, 2010**	
Chemical Classification: (1,2,3 etc.) (original NDAs only) : **n/a**		
Proposed indication(s)/Proposed change(s): **add QD dosing to the currently approved dosing of BID for the treatment of postoperative inflammation in patients who have undergone cataract surgery**		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: **SE-2: New dosing regimen** ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***		☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (*if OTC product*):				
List referenced IND Number(s): **IND 60295**				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***			X	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?			X	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		X		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			Line needed between Highlights and FPI Contents
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		X		

OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 25, 2010

NDA/Supp #: 021664/013

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: bromfenac sodium (b) (4)

DOSAGE FORM/STRENGTH: ophthalmic solution, (b) (4)

APPLICANT: ISTA Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): add QD dosing to the currently approved dosing of BID for the treatment of (b) (4) who have undergone cataract surgery

BACKGROUND: This is a major clinical supplement to the original NDA 021664 for XIBROM (bromfenac ophthalmic solution) 0.09% for the treatment of postoperative inflammation in patients who have undergone cataract extraction. XIBROM was submitted to the Agency on May 26, 2004, and approved on March 24, 2005.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dean	Y
	CPMS/TL:	Dillon-Parker	N
Cross-Discipline Team Leader (CDTL)	William Boyd, MD		Y
Clinical	Reviewer:	Jennifer Harris, MD	Y
	TL:	William Boyd, MD	Y
Social Scientist Review (*for OTC products*)	Reviewer:	n/a	
	TL:	n/a	
OTC Labeling Review (*for OTC products*)	Reviewer:	n/a	
	TL:	n/a	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	n/a	
	TL:	n/a	

Clinical Pharmacology	Reviewer:	Kimberly Bergman, PharmD	N
	TL:	Charles Bonapace, PharmD	Y
Biostatistics	Reviewer:	Yunfan Deng, PhD	Y
	TL:	Yan Wang, PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Conrad Chen, PhD	Y
	TL:	Wendelyn Schmidt, PhD	Y
Statistics (carcinogenicity)	Reviewer:	n/a	
	TL:	n/a	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	n/a	
	TL:	n/a	
Product Quality (CMC)	Reviewer:	Libaniel Rodriguez, PhD	Y
	TL:	Swapan De, PhD	N
Quality Microbiology *(for sterile products)*	Reviewer:	n/a	
	TL:	n/a	
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	n/a	
	TL:	n/a	
Facility Review/Inspection	Reviewer:	n/a	
	TL:	n/a	
OSE/DMEPA (proprietary name)	Reviewer:	Raichell Brown	Y
	TL:	Kellie Taylor	Y
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	Y
	TL:	n/a	
Bioresearch Monitoring (DSI)	Reviewer:	Kassa Ayalew	Y
	TL:	Jean Mulinde, MD	N

DDMAC	Sharon Watson	N
OSE Project Manager	Brantley Dorch	Y
REMS (DCRMSRMP)		
DMPQ (CDER DMPQ PM TRACK)	n/a	
Additional attendees	Wiley Chambers, MD, Acting Director, DAIOP Lucious Lim, MD, Clinical Reviewer, DAIOP Martin Nevitt, MD, Clinical Reviewer, DAIOP Sonal Wadhwa, MD, Clinical Reviewer, DAIOP Fariba Izadi, PharmD, Project Manager, DAIOP Sophie Lang-Bradford, OBPS	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO ☐ To be determined

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public	☒ Not Applicable ☐ YES ☐ NO

health significance?	
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: Information request for 95% confidence intervals of treatment differences and corresponding SAS codes	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Wiley A. Chambers, MD **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

JANE A DEAN
05/11/2010

DSI CONSULT: Request for Clinical Inspections

Date: April 19, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Kassa Ayalew
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Jennifer Harris, MD, Clinical Reviewer
Division of Anti-Infective and Ophthalmology Products
William Boyd, MD, Cross Discipline Team Leader
Division of Anti-Infective and Ophthalmology Products

From: Jane A. Dean, RN, MSN, Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application# NDA 021664, Supplement # 013
Applicant/ Applicant contact information (to include phone/email): ISTA Pharmaceuticals, Inc.
Paul Nowacki, Directory, Regulatory Affairs, (949) 789-3109, pnowacki@istavision.com
Drug Proprietary Name: bromfenac sodium (b) (4) ophthalmic solution, (b) (4)
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): This supplement adds QD dosing to the currently approved BID dosing regimen following cataract extraction

PDUFA: October 16, 2010
Action Goal Date: August 16, 2010
Inspection Summary Goal Date: August 16, 2010

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Sall Research Medical Center 11423 187th Street, Suite 200 Artesia, CA 90701			

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

New Information received by the Division concerning falsified data submitted to a previous NDA from this investigative site. (See attached.)

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

  *See*** at end of consult template for DSI's thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
__X__ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites*.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Name of RPM* at *301-796-xxxx or Name of Medical Officer* at 301-796-XXXX.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

***Things to consider in decision to submit request for DSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
    - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

JANE A DEAN
04/21/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	August 23, 2010
Application Type/Number:	NDA 021664/S-013
Through:	Zachary Oleszczuk, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis
From:	Yelena Maslov, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Bromday (Bromfenac) Ophthalmic Solution 0.09%
Applicant:	ISTA Pharmaceuticals
OSE RCM #:	2010-1220

***** This document contains proprietary and confidential information that should not be released to the public.*****

CONTENTS

EXECUTIVE SUMMARY

This review summarizes the Division of Medication Error Prevention and Analysis (DMEPA) proprietary name risk assessment for Bromday (Bromfenac) Ophthalmic Solution 0.09% (NDA 021644/S-013), which is currently marketed under the proprietary name Xibrom. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Bromday, acceptable for this product (See Section 4 for full discussion).

The proposed proprietary name must be re-reviewed 90 days before approval of the NDA. Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from ISTA pharmaceuticals, dated May 25, 2010, for assessment of the proposed proprietary name, Bromday, regarding potential name confusion with other proprietary or established drug names in the usual practice setting.

1.2 REGULATORY HISTORY

NDA 021664 was approved on March 24, 2005 for Xibrom (Bromfenac) Ophthalmic Solution 0.09% for postoperative inflammation following cataract surgery. On December 18, 2009, the Applicant submitted a Supplemental New Drug Application (sNDA) requesting a new proprietary name Xiday (Bromfenac Sodium (b) (4) Ophthalmic Solution with (b) (4) and a once-a-day dosing regimen for Xiday to the currently approved twice-a-day dosing regimen for Xibrom. Subsequently, the proposed proprietary name Xiday was found unacceptable on April 21, 2010 and the Proprietary Name Request Denial Letter was mailed to the Applicant on April 23, 2010. DMEPA objected to the proposed proprietary name Xiday for the following reasons:

1. The proposal to use different proprietary and established name for the same product is confusing and misleading. DMEPA objected to the Applicant's intent to express the established name (b) (4) (b) (4) the active moiety itself. We concluded that this naming approach increases the potential for confusion.
2. DMEPA found that the proposed proprietary name Xiday is vulnerable to confusion with the medical abbreviation for "times one day" (i.e., x 1 day).

Subsequently, the Applicant submitted a new Proprietary Name Request on May 25, 2010 (NDA 021664/S 013) requesting assessment of the alternate proposed proprietary name Bromday (Bromfenac Sodium (b) (4) Ophthalmic Solution (b) (4) In a cover letter, also dated May 25, 2010, the Applicant stated the intent to discontinue marketing the existing product, Xibrom, in order to alleviate the confusion between proposed product Bromday and marketed product Xibrom.

- *To alleviate confusion- ISTA plans to discontinue the existing product (Xibrom), (b) (4) The naming should alleviate confusion on the part of the prescriber, the dispenser (pharmacist), and the end-user (patient).*

DMEPA requested ISTA submit their plans regarding the Xibrom marketing cessation and projection of the time period both products will be on the market. The Applicant submitted the cessation plans for Xibrom on July 09, 2010 stating that the discontinuation of the Xibrom (b) (4) once Bromday is approved. (b) (4) up to the point that all existing Xibrom products expire.

Additionally, per consensus with Chemistry, Manufacturing, and Control (CMC), DMEPA, and the Review Division the Applicant was informed that the proposed product, Bromday, must express the established name (b) (4) in terms of the active moiety since the new proposed drug product is the same as the existing product Xibrom (Bromfenac) Ophthalmic Solution 0.09%.

1.3 PRODUCT INFORMATION

Bromday (Bromfenac) Ophthalmic Solution 0.09% is a topical ophthalmic solution for treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction. Bromday will be administered once daily into the affected eye beginning the day before cataract surgery, continued on the day of surgery, and for 14 days after surgery (*i.e.,* a total of 16 days of therapy). It will be available as single strength product, packaged in a white plastic squeeze bottle with a dropper tip. Bromday will need to be stored at USP controlled room temperature 15° to 25° C (59° to 77° F).

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2, and 2.3 identify specific information associated with the methodology for the proposed proprietary name, Bromday.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'B' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[1,2]

To identify drug names that may look similar to Bromday, the DMEPA safety evaluators considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (7 letters), upstrokes (2, capital letter 'B' and lower case letter 'd'), and down strokes (one, letter 'y'). Additionally, some letters in the proprietary name Bromday may be vulnerable to ambiguity when scripted (see Appendix B). The DMEPA safety evaluators also considers these alternate appearances when identifying drug names that may look similar to Bromday.

---

[1] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[2] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

When searching to identify potential names that may sound similar to Bromday, the DMEPA safety evaluators searches for names with similar number of syllables (2), stresses (BROM-day or brom-DAY), and placement of vowel and consonant sounds. Additionally, the DMEPA safety evaluators considers that pronunciation of the parts of the name can very such as 'Brom' may sound like 'Prom' and '-ay' may sound like 'ā' or 'ey'. The Applicant did not provide intended pronunciation of the proprietary name in the proposed name submission. Nevertheless, drug names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name were also considered.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following verbal prescription and two inpatient medication orders and were communicated during the FDA prescription studies.

Figure 1: Bromday Rx Study (Conducted on July 6, 2010):

HANDWRITTEN PRESCRIPTION MEDICATION ORDER	VERBAL PRESCRIPTION
Medication Order from 06/10/2010: Bromday 1 drop to affected eye OD	Bromday #1 Use as directed
Outpatient Prescription from 06/10/2010: Bromday #1 bottle use directed	

2.3 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The primary safety evaluator noted that the prefix 'Brom-' is commonly used for products that contain brompheniramine or bromide salt. However, the use 'Brom-' in a proposed proprietary name, Bromday, and currently marketed proprietary name, Xibrom refers to bromfenac. Thus, to evaluate this difference and to determine if the proposed proprietary name, Bromday could be misleading, a search of Adverse Event Reporting System (AERS) database was conducted to identify any medication error cases involving the misinterpretation of the syllable 'Brom' between Xibrom and bromphineramine/bromide salt-containing products.

A search was conducted on July 19, 2010 using the MedDRA high level group term (HLGT) "Medication Error" along with active ingredient name of Bromfenac, the trade name Xibrom, and the verbatim names "Xibr%" and "Bromfen%" with no dates limitations.

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The safety evaluators searches yielded a total of fifteen (n=15) names having some similarity to the name Bromday.

Eleven (n=11) of the fifteen names were thought to look like Bromday by the safety evaluators. These names are Brovana, Pataday, Bromatap, Bromanate/Bromanate DM/Bromanate DC, Bromfenex/Bromfenex PD, Bromadine DM, Bromatane DX, Bromaline/Bromaline DM, Bromatan DM/Bromatan Plus, Bromplex DM/Bromplex HD, and Bromfed DM.

The remaining four (n=4) were thought to look and sound like Bromday by the safety evaluators. These names are Brimonidine, Bromtapp/Bromtapp DM, Bromdec/Bromdec DM, and Brontex.

Additionally, DMEPA's safety evaluators did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of July 21, 2010.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA's safety evaluators (See Section 3.1 above) and did not find additional names thought to have orthographic or phonetic similarity to Bromday.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of thirty one (n=31) practitioners responded to the outpatient and voice mail prescription analysis studies. Due to an administrative error responses for the inpatient were not captured during our prescription analysis studies. For the responses that were captured, none of the practitioners responded to the inpatient prescription analysis study. Twenty-two (n=22) respondents interpreted the name correctly as 'Bromday', with correct interpretation occurring with outpatient prescriptions (n=10) and voice prescription studies (n=12). The most common misinterpretation of the remaining 9 prescriptions occurred with misinterpretation of the letter 'o' in the letter string 'Brom-' as a lower case letter 'a' associated with outpatient prescription study (n=8). Additionally, one interpretation (n=1) involved misinterpretation of the name Bromday as the name (b) (4) associated with a voice prescription study.

3.4 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The search of the Adverse Events Reporting System (AERS) database did not identify any cases of medication errors reports involving Xibrom.

3.5 COMMENTS FROM THE DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS

DMEPA notified the Division via email that we do not object to the use of proprietary name, Bromday, on July 28, 2010. Per e-mail correspondence, the Division of Anti-Infective and Ophthalmology Products indicated that they concur with our assessment regarding the use of the proprietary name, Bromday, stating, "The review team is in concurrence with DMEPA."

3.6 SAFETY EVALUATOR RISK ASSESSMENT OF PROPOSED PROPRIETARY NAME

Primary safety evaluator identified ten additional names (n=10), which were thought to look or sound similar to Bromday and represent a potential source of drug name confusion.

Eight (n=8) of the ten names were thought to look like Bromday. These names are Promit, Bromcomp HC, Bromtuss DM, Prometa, [redacted]**, Promacta, Percedex, and Bromdex D.

The remaining two names (n=2) were thought to sound like Bromday. These names are [redacted] and Bron-tuss.

Additionally, attempts to identify product characteristics associated with the name Bromatap were unsuccessful. We determined that this name was misspelled during the search process (i.e. Bromatap for Bromatapp).

Thus, a total of twenty-four names (n=24) were evaluated for the potential similarity to the proposed name Bromday.

4 DISCUSSION

The proposed proprietary name, Bromday, was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly.

4.1 BROMFENAC PRODUCT LINE EXTENSION

The Applicant intends to discontinue the production of Xibrom as soon as Bromday is approved. The Applicant stated that the discontinuation of the Xibrom will take [redacted] once Bromday is approved. [redacted]

However, although the two products [redacted] we believe the risk of medication error is minimized since both products contain the same active ingredient and the same strength, they can be used interchangeably. Thus, even if the prescriber confuses Bromday and Xibrom and prescribes Bromday with twice-a-day regimen or Xibrom with once-a day regimen, the efficacy of either product remains the same.

Additionally, in the submission sequence S- 013, on July 9, 2010, [redacted]

4.2 BROMDAY ASSESSMENT OF RISK OUTSIDE THE BROMFENAC PRODUCT LINE

4.2.1 Promotional Assessment

DDMAC had no concerns regarding the proposed name from a promotional perspective. The Division of Anti-Infective and Ophthalmology Products and the Division of Medication Error Prevention and Analysis concurred with this assessment.

4.2.2 Safety Assessment

In total, DMEPA evaluated twenty-four names (n=24). Seventeen (n=17) of the 24 names were eliminated from further analysis for the following reasons: five names (n=5) lack orthographic and/or phonetic similarity (See Appendix D), eleven names (n=11) are withdrawn from the U.S. market with no generic equivalent available (See Appendix E), and one name (n=1) withdrawn by the Applicant prior to the product's approval (See Appendix F).

*** This document contains proprietary and confidential information that should not be released to the public.

Failure Mode and Effect Analysis (FMEA) was then applied to determine of the proposed proprietary name could potentially be confused with the remaining seven names (n=7) and, thereby, lead to medication errors. This analysis determined that the name similarity between Bromday was unlikely to result in medication errors with all seven of the remaining products for the reasons presented in Appendices G though I.

Additionally, the Failure Mode and Effect Analysis (FMEA) determined that the prefix 'Brom' would not misleadingly lead practitioners to think that Bromday is a brompheniramine or bromide salt containing product because the prefix 'Brom-' is used for other established names (e.g., bromocriptine and pipobroman). Thus, the prefix 'Brom-' does not have an established meaning for one only product. Additionally, our search of the Adverse Events Reporting System (AERS) database did not identify any cases of medication errors reports involving Xibrom. However, we note that medication errors are known to be under reported and negative, our AERS result can not guarantee that errors are not occurring, only perhaps that errors are not being reported.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment indicates that the proprietary name, Bromday, is not vulnerable to name confusion that could lead to medication errors, nor is the name considered promotional. Thus, DMEPA has no objection to the proposed name, Bromday, for this product at this time.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. Furthermore, if the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be re-reviewed.

The proposed proprietary name must be re-reviewed 90 days before approval of the NDA. If you have further questions or need clarifications, please contact Brantley Dorch, OSE Project Manager, at 301-796-0150.

6 REFERENCES

1. Micromedex Integrated Index (http://csi.micromedex.com)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. The Document Archiving, Reporting, and Regulatory Tracking System (DARRTS)

DARRTS is a government database used to track individual submissions and assignments in review divisions.

5. Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. Electronic online version of the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. U.S. Patent and Trademark Office (http://www.uspto.gov)

USPTO provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (www.statref.com)

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [3]

For the proposed proprietary name, DMEPA safety evaluators search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA safety evaluators also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

[3] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [4] DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its safety evaluators to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA safety evaluators considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA safety evaluators considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[5] DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly in spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA safety evaluators also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA safety evaluators applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA safety evaluators compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice.

[4] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[5] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	**Considerations when searching the databases**		
	Potential causes of drug name similarity	*Attributes examined to identify similar drug names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA safety evaluators also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error safety evaluators provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA safety evaluators conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA safety evaluators use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA safety evaluators review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) safety evaluators and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA safety evaluators to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

4. Comments from the OND review Division or Generic drugs

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND or OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to concur/not concur with DMEPA's final decision.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

[6] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Sponsor. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. . (See Section 4 for limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Bromday	**Scripted may appear as**	**Spoken may be interpreted as**
Capital 'B'	'D', 'Pr', 'Pe', 'R'	'D', 'P', 'V'
Lower case 'b'	'l', 'h', 'k'	'd', 'p', 'v'
Letter String 'Br'	'M', 'Nu'	
Lower case 'r'	'c', 'e', 'n', 's', 't', 'x', or 'z'	
Lower case 'o'	'0', 'Q', 'a'	Any vowel
Lower case 'm'	'rn', 'nc', 'nz', 'nn', 'n', 'v', 'w', or 'wi'	'n'
Lower case 'd'	'cl', 't', 'a', 'b', 'h', 'l'	't', 'b'
Lower case 'a'	'e', 'o', 'u'	'e'
Lower case 'y'	g', 'j', 's', 'v', 'x', 'z', 'p'	
Letter string 'ay'		'a', 'ae', 'ai', 'ey'

Appendix C: FDA Prescription study for Bromday from June 10, 2010

Figure 1: Bromday study samples:

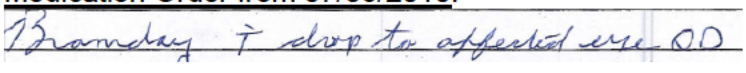
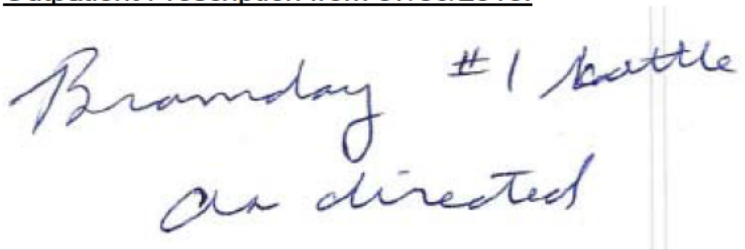
HANDWRITTEN PRESCRIPTION MEDICATION ORDER	VERBAL PRESCRIPTION
Medication Order from 07/06/2010: 	
Outpatient Prescription from 07/06/2010: 	Bromday #1 Use as directed

Table 1: Responses to prescription study

Outpatient Prescription 07/06/2010	Voice Prescription from 07/06/2010
Bromday	Bromday
Bromday	Bromday
Bramday	Brahmday
Bramday	Bromday
Bromday	Bromday
Bromday	Bromday
Bramday	Bromday
Bramday	Bromday
Bramday	Bromday
Bromday	Bromday
Bromday	Bromday
Bramday	Bromday
Bramday	Bromday
Bramday	
Bromday	
Bromday	
Bromday	
Bromday	

Appendix D: Names of products that lack convincing orthographic and/or phonetic similarity

Drug Product Name
Brimonidine
Brovana
Pataday
Promit
(b) (4)

Appendix E: Proprietary names for discontinued products with no generic equivalents available

Name	Similarity to Bromday	Product Description
Bromanate (Brompheniramine Maleate and Pseudoephedrine HCl) Elixir 1mg/15 mg per 5mL **Bromanate DM** (Brompheniramine Maleate , Dextromethorphan HBr, and Pseudoephedrine HCl) Elixir 1 mg/5 mg/15 mg per 5 mL **Bromanate DC** (Brompheniramine Maleate, Codeine PO4, and Phenylpropanolamine HCl) Syrup 2 mg/10 mg/12.5 mg per 5 mL	Look alike	Discontinued
Bromfenex (Brompheniramine Maleate and Pseudoephedrine HCl) Extended-Release Capsules 12 mg/120 mg **Bromfenex PD** ((Brompheniramine Maleate and Pseudoephedrine HCl) Extended-Release Capsules 6 mg/60 mg	Look alike	Discontinued
Bromadine DM (Brompheniramine Maleate , Dextromethorphan HBr, and Pseudoephedrine HCl) Syrup 2 mg/10 mg/30 mg per 5 mL	Look alike	Discontinued
Bromatane DX (Brompheniramine Maleate , Dextromethorphan HBr, and Pseudoephedrine HCl) Syrup 2 mg/10 mg/30 mg per 5 mL	Look alike	Discontinued
Bromcomp HC (Brompheniramine Maleate , Hydrocodone Bitartrate, and Pseudoephedrine HCl) Solution 3 mg/2.5 mg/30 mg per 5 mL	Look alike	Discontinued
Bromtuss DM (Brompheniramine Maleate , Dextromethorphan HBr, and Phenylephrine HCl) Solution 2 mg/15 mg/7.5 mg per 5 mL	Look alike	Discontinued
Prometa (Metaproterenol Sulfate) Syrup 10 mg per 5 mL	Look alike	Discontinued
Bron-Tuss (Codeine PO4 and Guaifenesin) Syrup 2.5 mg/75 mg per 5 mL	Sound alike	Discontinued
Bromtapp (Brompheniramine Maleate and Pseudoephedrine HCl) Elixir 1mg/15 mg per 5mL **Bromtapp** (Brompheniramine Maleate and Phenylpropanolamine HCl) Tablet 4 mg/25 mg **Bromtapp DM** (Brompheniramine Maleate , Dextromethorphan HBr, and Pseudoephedrine HCl) Elixir 1 mg/5 mg/15 mg per 5 mL	Look and sound alike	Discontinued
Bromdec (Brompheniramine Maleate and Pseudoephedrine HCl) Syrup 4 mg/45 mg per 5mL **Bromdec DM** (Brompheniramine Maleate , Dextromethorphan HBr, and Pseudoephedrine HCl) Syrup 4 mg/15 mg/45 mg per 5 mL	Look and sound alike	Discontinued
Brontex (Codeine PO4 and Guaifenesin) Solution 2.5 mg/75 mg per 5 mL **Brontex** (Codeine PO4 and Guaifenesin) Tablets 10mg/300 mg	Look and sound alike	Discontinued

Appendix F: Proprietary Name withdrawn by the Applicant

Proprietary Name	Similarity to Bromday	Status
(b) (4) (Telmisartan/Amlodipine)	Look alike	Approved NDA 022401 under the proprietary name Twynsta

Appendix G: Products with no overlap in strength or dose

Product name with potential for confusion	Similarity to proposed proprietary name	Strength	Usual dose (if applicable)
Bromday (Bromfenac) Ophthalmic Solution	**N/A**	**0.09%**	**1 drop to affected eye(s) once daily for 1 day prior to cataract surgery, continued on the day of surgery and through first 14 days of the postoperative period**
Promacta (Eltrombopag) tablets	Look alike	25 mg, 50 mg, 75 mg	Start with 25 mg by mouth daily, and adjust according to platelet response. Maximum of 75 mg daily. The product has restricted distribution: Distribution limited to only specially certified institutional/hospital pharmacies and physician clinics.

*** This document contains proprietary and confidential information that should not be released to the public.

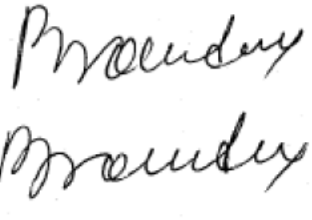
Appendix H: Single strength products with differentiating product characteristics

Product name with potential for confusion	**Similarity to product name**	**Strength**	**Usual Dose**	**Other differentiating product characteristics**
Bromday (Bromfenac) Ophthalmic Solution	**N/A**	**0.09%**	**1 drop to affected eye(s) once daily for 1 day prior to cataract surgery, continued on the day of surgery and through first 14 days of the postoperative period**	**N/A**
Bromaline (Brompheniramine Maleate and Pseudoephedrine HCl) Solution; **Bromaline DM** (Brompheniramine Maleate, Dextromethorphan HBr, and Pseudoephedrine HCl) Solution	Look	**Bromaline**: 1 mg/15 mg per 5mL **Bromaline DM**: 1 mg/5 mg/5 mg per 5mL	**Bromaline**: 10 mL to 20 mL by mouth every 4 hours, up to 4 doses per day **Bromaline DM**: 10 mL to 20 mL by mouth every 4 hours as needed, up to 4 doses per day	Dosage Form Ophthalmic solution vs. oral solution Route of Administration Ophthalmic vs. oral Usual Dose 1 drop vs. 10 mL to 20 mL (or 2 to 4 teaspoonfuls) Frequency of Administration Once every day vs. every 4 hours as needed, up to 4 times a day

Bromatan DM (Brompheniramine Maleate, Dextromethor-phan Tannate, and Phenylephrine Tannate) Suspension **Bromatan Plus** (Dexchlor-pheniramine Tannate, Dextromethorphan Tannate, and Pseudoephedrine Tannate) Suspensionn	Look	**Bromatan DM**: 8 mg/20 mg/20 mg per 5 mL **Bromatan Plus**: 3.5 mg/30 mg/ 45 mg per 5mL	**Bromatan DM**: 5 mL by mouth every 4 hours as needed up to 4 doses per day **Bromatan Plus**: 1.25 mL to 15 mL by mouth every 12 hours as needed	<u>Dosage Form</u> Ophthalmic Solution vs. oral suspension <u>Route of Administration</u> Ophthalmic vs. oral <u>Usual Dose</u> **Bromatatan DM:** 1 drop vs. 5 mL (or 1 teaspoonful) **Bromatan Plus:** 1 drop vs. 1.25 mL to 15 mL (or ¼ teaspoonful to 3 teaspoonfuls) <u>Frequency of Administration</u> **Bromatatan DM**: Every day vs. every 4 hours as needed, up to 4 times a day **Bromatan Plus:** Every day vs. every 12 hours as needed
Bromplex DM (Brompheniramine Maleate, Dextromethorphan Hydriodide, and Pseudoephedrine HCl) Solution **Bromplex HD** (Brompheniramine Maleate, Hydrocodone Bitartratre, and Pseudoephedrine HCl) Solution	Look	**Bromplex DM**: 4mg/30 mg/60 mg per 5 mL **Bromplex HD**: 2mg/1.7 mg/30 mg per 5 mL	**Bromplex DM**: 1.25 mL to 5 mL by mouth every 4 to 6 hours as needed up to 3 doses to 4 doses per day **Bromplex HD**: 5 mL to 10 mL by mouth every 4 to 6 hours as needed up to 3 to 4 doses per day	<u>Dosage Form</u> Ophthalmic solution vs. oral solution <u>Route of Administration</u> Ophthalmic vs. oral <u>Usual Dose</u> **Bromplex DM**: 1 drop vs. 1.25 mL to 5mL (or ¼ to 1 teaspoonful) **Bromplex HD**: 1 drop vs. 5mL to 10 mL (or 1 to 2 teaspoonfuls) <u>Frequency of Administration</u> Every day vs. every 4-6 hours as needed, up to 3-4 times a day

Bromfed DM (Brompheniramine Maleate, Dextromethorphan HBr, Pseudoephedrine HCl) Syrup	Look	2 mg/30 mg/10 mg per 5 mL	10 mL to 20 mL by mouth every 4 hours as needed up to 4 doses per day	Dosage Form Ophthalmic solution vs. oral syrup Route of Administration Ophthalmic vs. oral Usual Dose 1 drop vs. 10 mL to 20 mL (or 2 to 4 teaspoonfuls) Frequency of Administration Every day vs. every 4 hours as needed, up to 4 times a day
Precedex (Dexmedetomidine HCl) Injection	Look	100 mcg/mL (200 mcg/2 mL)	1 mcg/kg IV loading dose infusion over 10 minutes, followed by maintenance infusion of 0.2 to 0.7 mcg/kg/hr IV up to 24 hours.	Dosage Form Ophthalmic solution vs. injection Route of Administration Ophthalmic vs. intravenous Usual Dose 1 drop vs. 1 mcg/kg, followed by 0.2 mcg to 0.7 mcg/kg/hr up to 24 hours Frequency of Administration Every day vs. one time loading dose, followed by continuous infusion lasting no longer than 24 hours.

Appendix I: Potential confusing names with Bromday due to orthographic similarity

Failure Mode: Name confusion	**Causes (can be multiple)**	**Rationale for Failure Mode Prevention**
Proposed Name:	**Strength:**	**Usual Dose and Administration:**
Bromdex D (Brompheniramine Maleate, Dextromethorphan HBr, and Pseudoephedrine HCl) Syrup 3mg/30mg/50 mg per 5 mL <u>Route of Administration</u> Orally <u>Usual Dose</u> 2.5 mL to 5 mL by mouth <u>Frequency</u> every 6 hours up to 4 doses	If the modifier D is dropped, Bromdex can look like Bromday when scripted. The beginning letter strings 'Bromd-' are identical in both names. Additionally, the Letter string '-ex' can be scripted to look like the letter string '-ay'  <u>Overlap in dosing intructions</u> Often Bromday prescription can be written with directions of "use as directed" due to the fact that ordinarily patient receives several medications before and after cataract surgery. Since no additional information may not be written on Bromday prescription, it is easier to misread the name of the medication	<u>Distribution</u> Sponsor of Bromdex D is in the process of discontinuing the product. Although limited amount of the stock with expiration date of 05/2011 is still available, the sponsor is no longer manufacturing new batches. Additionally, we have post-marketing evidence, which shows that Bromdex D is not widely distributed, which further lowers the potential for confusion between Bromday and Bromdex D. <u>Route of the Administration, Dose, and Frequency</u> Bromday is administered ophthalmically vs. Bromdex D is administered orally <u>Usual Dose</u> Bromday is administered as one drop to affected eye vs. Bromdex D is administered as ½ teaspoonful to1 teaspoonful <u>Frequency of Administration</u> Bromday is administered once daily vs. Bromdex D is administered every 6 hours as needed up to 4 times a day

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

YELENA L MASLOV
08/23/2010

ZACHARY A OLESZCZUK
08/23/2010

DENISE P TOYER
08/23/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 19, 2010
To:	Wiley Chambers, MD, Director Division of Anti-Infective and Ophthalmology Products
Through:	Laura Pincock Pharm.D., Acting Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Raichell Brown, Pharm.D., J.D., Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name:	Xiday (Bromfenac Sodium) Ophthalmic Solution, (b) (4)
Application Type/Number:	IND 60295 and NDA 21664/s13
Sponsor:	ISTA Pharmaceuticals
OSE RCM #:	2009-2058

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

EXECUTIVE SUMMARY

Xiday is the proposed proprietary name for Bromfenac Sodium Ophthalmic Solution, (b) (4) (IND 60295/NDA 021644/s013), which is equivalent to Bromfenac Ophthalmic Solution, 0.09%. Bromfenac Ophthalmic Solution, 0.09% is currently marketed under the proprietary name Xibrom. The proposed name Xiday was evaluated from a safety and promotional perspective based on the product characteristics provided by the Sponsor. We sought input from pertinent disciplines involved with the review of this application, considered it accordingly, and we find that the use of a dual tradename for this product is misleading and vulnerable to confusion that may lead to medication errors. We also find the proposed proprietary name Xiday vulnerable to confusion with the medical abbreviation for "times one day" (*i.e.,* x 1 day).

Thus, DMEPA finds the proposed proprietary name Xiday unacceptable for this product. Moreover, DMEPA finds use of a second proprietary name (*i.e.,* a dual tradename) for this product unacceptable (see Section 4 for full discussion).

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Sponsor, dated October 30, 2009, for an assessment of the proposed proprietary name Xiday regarding potential name confusion in the usual practice settings.

1.2 REGULATORY HISTORY

NDA 021664 was approved on March 24, 2005 for Xibrom (Bromfenac 0.09%) for postoperative inflammation following cataract surgery. On December 18, 2009, the Applicant submitted a Supplemental New Drug Application (sNDA) for Xiday (Bromfenac Sodium (b) (4) to add a once-a-day dosing regimen to the currently approved twice-a-day dosing regimen for Xibrom

According to our discussions with Chemistry, Manufacturing, and Controls (CMC) and the Review Division, Bromfenac Sodium (b) (4) is equivalent to active Bromfenac 0.09% (see insert labeling for Xibrom). There is no difference in the formulation, indication for use, or strength of active drug between the proposed "product" Xiday and the marketed product Xibrom. Rather, the only difference between the proposed product Xiday and the approved product Xibrom proposed by the sNDA is that clinical data now supports a once-a-day dosing regimen for the already approved product (*i.e.,* Xibrom).

In a cover letter submitted for this sNDA dated December 18, 2009, the Applicant explained its rationale for expressing the established name (b) (4) of this sNDA differently than it expresses the established name and strength in the original NDA:

> *As portions of the sNDA protocols and reports have been completed prior to the selection of the tradename XiDay, the product has been referred to as bromfenac ophthalmic solution 0.09%. We have chosen the established name of the new product to be bromfenac sodoim (b) (4) ophthalmic solution (b) (4) for the following reasons:*
>
> - *to differentiate from the existing product (Xibrom) which has significantly different dosing instructions. This should alleviate any confusion on the part of the prescriber, the dispenser (pharmacist) and the end-use (patient).*
> - (b) (4) (b) (4)

1.3 PRODUCT INFORMATION

Xiday is a topical ophthalmic solution for treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction. Xiday will be available in a single strength of Bromfenac Sodium, (b) (4) which is equivalent to active Bromfenac, 0.09%.

Xiday will be packaged in a white plastic squeeze bottle with a dropper tip. Xiday is administered once daily into the affected eye beginning the day before cataract surgery, continued on the day of surgery, and for 14 days after surgery (*i.e.,* a total of 16 days of therapy).

Xiday should be stored at USP controlled room temperature 15º to 25º C (59º to 77º F).

The proposed product Xiday will be administered once daily.

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2, and 2.3 identify specific information associated with the methodology for the proposed proprietary name, Xiday.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'X' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[1,2]

To identify drug names that may look similar to Xiday, the DMEPA staff considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (five letters), upstrokes (two, capital letter 'X' and letter 'd'), down strokes (one, letter 'y'), cross strokes (one, letter 'X'), and dotted letters (one, letter 'i'). Additionally, some letters in Xiday may be vulnerable to ambiguity when scripted (see Appendix B). The DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Xiday.

When searching to identify potential names that may sound similar to Xiday, the DMEPA staff search for names with similar number of syllables (two), stresses (XI day or XID ay), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary such as 'Xi-' may sound like 'Zi-', 'Zy-', or 'Xy-' and '-ay' may sound like 'ā' or 'ey'. The Sponsor provided its intended pronunciation of the proprietary name in the proposed name submission, *Zī•dā*. The Sponsor's intended pronunciation was considered. However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name were also considered.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following verbal prescription and two inpatient medication orders and were communicated during the FDA prescription studies.

---

[1] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[2] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

Figure 1. Xiday Rx Study (conducted on November 16, 2009)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order #1: x iday instill one drop to affected eye QD	Xiday Instill one drop to affected eye once daily
Outpatient Prescription: Xiday #1 bottle i gtt to affected eye QD x 16 days beginning the day before cataract surgery	

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The searches yielded a total of ten (n=10) names as having some similarity to the name Xiday.

Nine of the 10 names were thought to look like Xiday. These names are [(b) (4)] Today, Vidaza, Videx, [(b) (4)], Xibrom, [(b) (4)], [(b) (4)] and Xolox.

One of the 10 names, Zydone, was thought to sound like Xiday.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of January 13, 2010.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (see Section 3.1.1 above) and identified one additional name, Zydis (*i.e.,* Zyprexa Zydis)[3], thought to sound similar to the proposed proprietary name Xiday.

In addition, the Expert Panel identified that the proposed proprietary name Xiday is spelled the same as the medical abbreviation 'x i day' which is commonly used to communicate the duration of therapy "times one day" on prescriptions/physician orders.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

[3] The full proprietary name is 'Zyprexa Zydis' but DMEPA notes that, in practice healthcare practitioners have been known to shorten the name to simply Zydis.

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 21 practitioners responded to the prescription analysis studies. Five (n=5) respondents interpreted the name correctly as Xiday. Misinterpretation in the written studies included interpreting 'i' in Xiday as 'e', 'u', 'r' or 'y'. All four respondents in the verbal study misinterpreted the 'X' in Xiday as 'Z' or 'S'. However, none of the misinterpretations in the written or verbal studies overlapped with names of currently marketed medications. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator did not result in identification of any additional names (n=0) thought to look or sound similar to Xiday and, thereby, represent a potential source of drug name confusion.

3.5 COMMENTS FROM THE OFFICE OF NEW DRUGS DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS

3.5.1 Initial Point of Review

In response to the OSE email on November 5, 2009, Division of Anti-Infective and Ophthalmology Products did not have any comments and/or concerns on the proposed name at the initial phase of the name review.

3.5.2 Mid-point of Review

DMEPA notified the Division of Anti-Infective and Ophthalmology Products via e-mail, on February 24, 2010, that we object to the use of the proposed proprietary name Xiday. Per e-mail correspondence on the same day, the Division of Anti-Infective and Ophthalmology Products indicated that they had no additional comments regarding our assessment of the proposed proprietary name Xiday.

4 DISCUSSION

The proposed name was evaluated from both a promotional and safety perspective. Furthermore, input from pertinent disciplines involved in the review of this application was considered accordingly.

4.1 PROMOTIONAL REVIEW

DDMAC had no concerns regarding the proposed name from a promotional perspective. The Division of Anti-Infective and Ophthalmology Products and the Division of Medication Error Prevention and Analysis concurred with this assessment.

4.2 SAFETY REVIEW OF THE PROPRIETARY NAME

DMEPA evaluated the proposed name and identified concerns with orthographic similarity of the name and the use of the actual name for this product.

4.2.1 Confusion Involving the Proposed Proprietary Name Xiday

We identified and evaluated a total of eleven (n=11) names for their potential similarity to the proposed name, Xiday. Six (n=6) of the 10 names were eliminated from further analysis because they lacked convincing orthographic and/or phonetic similarity to the proposed proprietary name Xiday (see Appendix D). One name (n=1) was eliminated from further analysis because it is not marketed in the

United States and, thus, represents minimal risk for medication error in the United States (see Appendix E).

Failure mode and effects analysis (FMEA) was then applied to determine if the proposed proprietary name could potentially be confused with the remaining four (n=4) names and, thereby, lead to medication errors. This analysis determined that the name similarity between Xiday was unlikely to result in medication errors with these four products for the reasons presented in Appendices F and G.

However, DMEPA identified the medical abbreviation for the duration of therapy "times one day" which is spelled exactly the same as the proposed proprietary name Xiday (i.e., x i day). FMEA determined that the proposed proprietary name Xiday is vulnerable to confusion with the medical abbreviation for the duration of therapy "x i day" (*i.e.*, times one day), and may lead to medication errors. Medication errors can occur if the proposed proprietary name Xiday is misinterpreted as "times one day" when written on a prescription/physician order with another medication, such as another eye drop. For example,

Antibiotic i drop in both eyes qid xiday i drop in both eyes qday.

In the above example, if the name Xiday is misinterpreted as part of the direction for use rather than a product name, the antibiotic may be administered four times a day for only one day and then once a day after the first day. In addition, the anti-inflammatory therapy, Xiday, may be omitted altogether.

A secondary safety concern regarding the proposed proprietary name Xiday is the name may communicate that the drug is used for only one day if the name is interpreted literally. This interpretation, which is suggested on the face of the proposed name, conflicts with the recommended duration of therapy which is a total of 16 days.

4.2.2 Confusion Involving Use of a Dual Tradename

DMEPA sought input from the Review Division and CMC to evaluate the differences and similarities between the proposed "product" Xiday (Bromfenac Sodum (b) (4) and the approved product Xibrom (Bromfenac), 0.09% and concluded that no differences exist, except the Applicant's proposal for a different frequency of administration (*i.e.,* once-a-day vs. twice-a-day). In fact, Bromfenac Sodium (b) (4) Ophthalmic Solution, (b) (4) is Bromfenac Ophthalmic Solution, 0.09% bu (b) (4) (b) (4) the active moiety.

In the December 18, 2009 cover letter for the sNDA, the Applicant stated that it expresses the established name (b) (4) of this product (b) (4) the active moiety itself, to "alleviate any confusion" created by marketed two different proprietary names for the same product. However, DMEPA believes that the Applicant's naming actually increases the potential for confusion.

The Applicant's naming approach is misleading because it suggests that Xiday (Bromfenac Sodium (b) (4) Ophthalmic Solution, (b) (4) is somehow different from Xibrom (Bromfenac) Ophthalmic Solution, 0.09%, when, in fact, these products are the same. In addition to the same active ingredient and strength, the formulation, indication for use, patient/prescriber population, setting of use, and Applicant are the same for both products.

This misleading naming approach can lead to medication errors by implying that Xiday (Bromfenac Sodium (b) (4) Ophthalmic Solution, (b) (4) Xibrom (Bromfenac) Ophthalmic Solution, 0.09% (b) (4)

5 CONCLUSIONS AND RECOMMENDATIONS

The findings of the Proprietary Name Risk Assessment indicate that although the proposed name Xiday is not promotional, it is vulnerable to name confusion with the medical abbreviation for the duration of therapy "times one day" (*i.e.,* x 1 day). In addition, the use of a dual tradename for this product is misleading and vulnerable to confusion that may lead to medication errors. Accordingly, the proposed name Xiday is unacceptable for this product.

5.1 COMMENTS TO THE SPONSOR

We have completed our review of the proposed proprietary name Xiday and have concluded that it is unacceptable because the use of a dual tradename for this product is misleading and vulnerable to confusion that may lead to medication errors. We also find the proposed proprietary name Xiday vulnerable to confusion with the medical abbreviation for "times one day" (*i.e.,* x 1 day).

The use of a dual tradename for this product is misleading and vulnerable to confusion that may lead to medication errors. In your December 18, 2009 cover letter for the supplemental NDA, you stated that you intend to express the established name (b) (4) (b) (4) the active moiety itself, to "alleviate any confusion" created by marketed two different proprietary names for the same product. However, DMEPA believes that this naming approach actually increases the potential for confusion.

This naming approach is confusing and misleading because it implies that Xiday (Bromfenac Sodium (b) (4) Ophthalmic Solution, (b) (4) Xibrom (Bromfenac) Ophthalmic Solution, 0.09% (b) (4) .

In addition, if the proposed proprietary name Xiday is misinterpreted as "times one day" when written on the same prescription/physician order with another medication (*i.e.,* another eye drop), medication errors can occur. For example,

Antibiotic i drop in both eyes qid xiday i drop in both eyes qday.

In the above example, if the name Xiday is misinterpreted as part of the direction for use rather than a product name, the antibiotic may be administered four times a day for only one day and then once a day after the first day. In addition, the anti-inflammatory therapy, Xiday, may be omitted altogether.

Another safety concern is that the name Xiday may communicate that the drug is used for only one day if the name is interpreted literally. This interpretation, which is suggested on the face of the proposed name, conflicts with the recommended duration of therapy which is a total of 16 days.

For the all of the before-stated reasons, our analysis has determined that the proposed proprietary name Xiday is unacceptable.

If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names,* HTTP://www.fda.gov/cder/guidance/7935dft.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

6 REFERENCES

1. Micromedex Integrated Index (http://csi.micromedex.com)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. Electronic online version of the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. U.S. Patent and Trademark Office (http://www.uspto.gov)

USPTO provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (www.statref.com)

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [4]

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [5] DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[6] DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products

---

[4] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[5] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[6] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

because similarly in spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	**Considerations when searching the databases**		
	Potential causes of drug name similarity	*Attributes examined to identify similar drug names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a

variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

4. Comments from the OND Review Division

DMEPA requests the Office of New Drugs (OND) responsible for the application for its comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests

concurrence/non-concurrence with DDMAC's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the Safety Evaluator's assessment.

The OND is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys its decision to accept or reject the name. OND is requested to concur/not concur with DMEPA's final decision.

5. External Proprietary Name Risk Assessment

DMEPA conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's risk assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the safety evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of the overall risk assessment to the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the DMEPA staff's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the DMEPA staff provides a detailed explanation of these differences.

6. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[7] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that

[7] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Sponsor. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint

Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Xiday	Scripted may appear as	Spoken may be interpreted as
'X'	K, T, V , Y, **or** an abbreviation for the word "times"	Z
Lower case 'i'	'e', 'o', 'l' **or** an abbreviation for the number "one"	'e', 'y', or 'eye'
Lower case 'd'	'b', 'h', 'l'	'b', 't'
Lower case 'a'	'e', 'o', 'u'	'e'
Lower case 'y'	'g', 'j', 's', 'v', 'x', 'z'	
'ay'		'a', 'ae', 'ai', 'ey'

Appendix C: FDA Prescription Study Responses (conducted November 16, 2009).

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
Xeday	Xdewy	Sideday
Xiday	Xiday	Ziday
Xiday	Xideng	zyday
Xiday	Xidexy	Zyday
Xiday	Xidey	
Xrday	Xilday	
	Xildewg	
	Xrdewy	
	Xudery	
	Xudry	
	Xyday	

Appendix D: Names Lacking Orthographic and/or Phonetic Similarity.

Name	Name
(b) (4)	Xibrom*
Vidaza	(b) (4)
(b) (4)	Zydone

*Xibrom is tradename for Bromfenac Sodium 0.09% eye drop and is also marketed by ISTA Pharmaceutical.

Appendix E: Proprietary Name Not Marketed in the U.S.

Proprietary Name	Similarity to (b) (4)	Status and Source	Description
(b) (4) ***	orthographic	ND (b) (4) (See DARRTS)	(b) (4)

*** This document contains proprietary and confidential information that should not be released to the public.***

Appendix F: Products with strengths or doses which are numerically dissimilar to the strength or dose of Xiday.

Product name with potential for confusion	Similarity to Xiday	Strength	Usual Dose
Xiday **(Bromfenac)** **Ophthalmic Solution**	**N/A**	(b) (4)	**One drop in affected eye once daily for 16 days, beginning the day before surgery.**
Videx (Didanosine) Oral Solution, Capsule, and Tablet	orthographic	Oral Solution 10 mg/mL Chewable Tablet 100 mg, 150 mg. 200 mg Extended Release Capsule 200 mg, 250 mg, 400 mg	Oral Solution & Chewable Tablets (Patient weight of 60 kg or less) 125 mg twice daily or 250 mg once daily (Patient weight greater than 60 kg) 200 mg twice daily or 400mg once daily Extended Release Capsule (Patient weight less than 25 kg) 200 mg once daily (Patient weight of 25 kg to 60 kg) 250 mg once daily (Patient weight greater than 60 kg) 400mg once daily
Zydis* (Olanzapine) Orally Disintegrating Tablet *The full proprietary name is 'Zyprexa Zydis' but DMEPA notes that in practice practitioners sometimes shorten it to simply Zydis.	phonetic	5 mg, 10 mg, 15 mg, 20 mg	Schizophrenia: 5 mg to 10 mg per day (in one or divided doses) Bipolar I Disorder: 10 mg to 15 mg per day

<u>Appendix G:</u> Product with strength or dose that is numerically similar to the strength or dose of Xiday.

Xiday **(Bromfenac)** **Ophthalmic Solution** (b) (4)	**Similarities Between the Proposed Name, Xiday, and the Product Name Listed.**	**Rationale for Why Medication Errors are Unlikely to Occur Involving the Proposed Name, Xiday and the Product Name Listed.**
Today (Nonoxynol-9) Vaginal Sponge, 1,000 mg	**Orthographic Similarities:** Both names begin with a cross-stroke ('*X*' and '*T*') Both names end with '*-day*' Both names contain 5 letters. **<u>Ex.</u>**  **Overlap in Dose:** Both products are single strength products and therefore no indication of numerical strength is required to complete a prescription or physician order.	The proposed proprietary name Xiday is orthographically similar to the existing proprietary name Today. However, one orthographic difference between the two names is that Xiday has a dotted letter and Today does not. Additionally, differences in the dosage forms, routes of administration, and settings of use differentiate the two products. Xiday is a prescription eye drop and Today is an over-the-counter vaginal sponge. Because Xiday is an eye drop, some indication of which eye(s) to apply the drops is needed to complete a prescription/physician order. The additional direction(s) for use (*e.g.*, X drops in Y eye) for Xiday will help to differentiate the names. Likewise, if a prescriber writes a prescription for Today, the directions for use may describe the vaginal route of administration. In addition, the setting/context of use of Today will reduce the occurrence of medication errors involving these products. Today is an over-the-counter contraceptive that is placed vaginally only in the context of imminent sexual intercourse and removed within 24 hours.
Xolox (Oxycodone/ Acetaminophen) Tablet, 10 mg/500 mg	**Orthographic Similarities:** Both names begin with the letter '*X*' Both names contain upstrokes in the middle of the names	The proposed proprietary name Xiday is orthographically similar to the existing proprietary name Xolex. However, one orthographic difference between the two names is that Xiday has a dotted letter and Xolox does not. Additionally, differences in the dosage forms, routes of administration, and frequencies of administration differentiate the two products. Xiday is an eye drop and Xolex is an oral tablet. Because

	(*-d-* and *-l-*) The last letter of each name (*-y* and-*x*) can appear similar when scripted Both names contain 5 letters. **Ex.**  **Overlap in Dose:** Both products are single strength products and therefore no indication of numerical strength is required to complete a prescription or physician order.	Xiday is an eye drop, some indication of which eye(s) to apply the drops is needed to complete a prescription/physician order. The additional direction(s) for use (*e.g.*, X drops in Y eye) for Xiday will help to differentiate the names. Also Xiday is administered once daily, but Xolex is administered every 6 hours on an as needed basis. This difference in the frequencies of administrations will also help to differentiate these products.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-60295	ORIG-1	ISTA PHARMS	BROMFENAC SODIUM (b) (4) OPHTHALMIC SOLU
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

LAURA L PINCOCK
04/20/2010

DENISE P TOYER
04/21/2010

CAROL A HOLQUIST
04/21/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664/S013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is not likely to be used in a substantial number of pediatric patients. The waiver is based on the fact that cataract surgery is not performed on a substantial number of pediatric patients, the use of topical anti-inflammatory agents in pediatrics patients undergoing strabismus surgery and nasolacrimal duct probing is not a standard of practice in medicine and the standard of care for pediatric and adult patiens with anterior uveitis is topical steroids.

Pediatric Research and Equity Act Waivers

NDA #: **021664** Supplement Type: **SE2** Supplement Number: **013**

Product name and active ingredient/dosage form: **bromfenac sodium** [redacted] **ophthalmic solution** [redacted]

Sponsor: **ISTA Pharmaceuticals, Inc.**

Indications(s): **treatment of postoperative inflammation in patients who have undergone cataract extraction.**

PREA is triggered for this supplement because it is adding a new dosing regimen to an approved product.

1. Pediatric age group(s) to be waived. **16 years and under**

2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

    a. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested. The waiver is based on the fact that cataract surgery is not performed on a substantial number of pediatric patients, the use of topical anti-inflammatory agents in pediatrics patients undergoing strabismus surgery and nasolacrimal duct probing is not a standard of practice in medicine and the standard of care for pediatric and adult patiens with anterior uveitis is topical steroids.

Attachment I

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver
These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration
Alzheimer's disease
Amyotrophic lateral sclerosis
Atherosclerotic cardiovascular disease
Benign prostatic hypertrophy
Chronic Obstructive Pulmonary Disease
Erectile Dysfunction
Infertility
Menopausal and perimenopausal disorders
Organic amnesic syndrome
(not caused by alcohol or other psychoactive substances)
Osteoarthritis
Parkinson's disease
Postmenopausal Osteoporosis
Vascular dementia/ Vascular cognitive disorder/impairment

Cancer:
- Basal cell
- Bladder
- Breast
- Cervical
- Colorectal
- Endometrial
- Gastric
- Hairy cell leukemia
- Lung (small & non-small cell)
- Multiple myeloma
- Oropharynx (squamous cell)
- Ovarian (non-germ cell)
- Pancreatic
- Prostate
- Renal cell
- Uterine

EXCLUSIVITY SUMMARY

NDA # 021664 SUPPL # 013 HFD # 520

Trade Name: Bromday

Generic Name: bromfenac ophthalmic solution, 0.09%

Applicant Name ISTA Pharmaceuticals, Inc.

Approval Date, If Known October 16, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1), SE-2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21664 Xibrom (bromfenac ophthalmic solution) 0.09%

NDA# 20535 Duract (bromfenac sodium capsules)

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer

to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1	CL-S&E- 0802071-P [BromCom]
Investigation #2	CL-S&E-0415081-P-ER [QD-ER]
Investigation #3	CL-S&E-0415081- P-WR [QD-WR]
Investigation #4	CL-S&E-1205081-P [QDII]

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

Investigation #3	YES ☐	NO ☒
Investigation #4	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒
Investigation #4	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1	CL-S&E- 0802071-P [BromCom]
Investigation #2	CL-S&E-0415081-P-ER [QD-ER]
Investigation #3	CL-S&E-0415081- P-WR [QD-WR]
Investigation #4	CL-S&E-1205081-P [QDII]

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 60295	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND # 60295	YES ☒	! NO ☐
		! Explain:
Investigation #3		!
		!
IND # 60295	YES ☒	! NO ☐
		! Explain:
Investigation #4		!
		!
IND # 60295	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1		!
		!
YES ☐		! NO ☐
Explain:		! Explain:
Investigation #2		!

YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Jane A. Dean, RN, MSN
Title: Project Manager
Date: 10/29/10

Name of Office/Division Director signing form:
Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

JANE A DEAN
10/29/2010

WILEY A CHAMBERS
10/29/2010

From: Dean, Jane
To: "Nowacki,Paul";
cc: "Garrett, Marvin";
Subject: NDA 21-664/S-013 (bromfenac) - 10/8/10 label changes
Date: Friday, October 08, 2010 1:32:50 PM
Attachments: FDA Bromday 10_8_10.doc

Paul

The following changes were made:

Sec. 6.1 line 2 - Bromday changed to bromfenac
Sec. 11 under inactives list - edentate changed to edetate
Sec. 12.3 line 3 - "…one drop to each eye (b) (4) …" changed to "…one drop to the eye (b) (4) …"

Please submit this revised label to the NDA asap. Thanks.

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

7 Page(s) 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/

JANE A DEAN
10/08/2010

From: Dean, Jane
To: "Nowacki,Paul";
cc: "Garrett, Marvin";
Subject: NDA 21-664/S-013 (bromfenac) - FDA revised version of Bromday label dated 10/7/10
Date: Thursday, October 07, 2010 1:08:55 PM
Attachments: FDA Bromday 10_7_10.doc

Paul, here is the label with the FDA's most current revisions. Please let us know if you accept them and follow up this acceptance with a formal submission to the NDA.

Thanks!

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products

Office of Antimicrobial Products

FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881

Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

7 Page(s) 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/

JANE A DEAN
10/07/2010

From: Dean, Jane
To: "Nowacki,Paul";
cc: "Garrett, Marvin";
Subject: NDA 21-664 (bromfenac) - Bromday label (supplement 13, dated December 16, 2009)
Date: Wednesday, September 15, 2010 2:22:12 PM
Attachments: 9-13-10_Bromday_label.doc

Paul, here is the label for Bromday. This is what will go into our action letter as long as you formally indicate agreement. I also just sent to you in a separate email the updated Xibrom label. That, too, will require your formal agreement. Please, when making those formal submissions, put it into two separate submissions – it makes the audit trail a little clearer on our end.

Thanks!

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products

Office of Antimicrobial Products

FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881

Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

JANE A DEAN
09/15/2010

From: Dean, Jane
Sent: Wednesday, September 08, 2010 10:59 AM
To: 'Nowacki,Paul'
Cc: 'Garrett, Marvin'
Subject: Labeling - comments for carton/container and final FDA version of Package Insert

Importance: High

Attachments: FDA-draft-labeling-text9-8-10.doc; Bromday Packaging Comments9-8-10.doc

Paul, attached to this email is our final version of the label that would go with an approval letter.

Also included are comments for your carton and container. A formal submission from you indicating you will incorporate our suggestions will be all that is needed at this point to enable us to proceed with our action letter.

Jane


FDA-draft-lab ng-text9-8-10 | Bromday ing Comment

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

JANE A DEAN
09/08/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 021664/S-013

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

ISTA Pharmaceuticals, Inc.
15295 Alton Parkway
Irvine, California 92618

ATTENTION: Paul Nowacki
Director, Regulatory Affairs

Dear Mr. Nowacki:

Please refer to your Supplemental New Drug Application (sNDA) dated December 18, 2009, received December 18, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bromfenac Sodium Ophthalmic Solution, 0.09%.

We also refer to your May 25, 2010, correspondence, received May 25, 2010, requesting review of your proposed proprietary name, Bromday and to your July 9 and 10, 2010, proprietary name amendments received July 9 and 10, 2010, respectively. We have completed our review of the proposed proprietary name, Bromday and have concluded that it is acceptable.

The proposed proprietary name, Bromday, will be re-reviewed 90 days prior to the approval of the Supplemental NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 25, July 9, and July 10, 2010, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150.

For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Jane Dean, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Denise P. Toyer, PharmD
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

DENISE P TOYER
08/23/2010

From: Dean, Jane
To: "Nowacki,Paul";
Subject: NDA 21664/S-013 (bromfenac) - Information Request
Date: Friday, April 16, 2010 6:38:50 PM

Hi, Paul - the Division has the following information request:

> Please provide a re-analysis of the efficacy and safety data for each clinical trial submitted in the supplement that had the Sall Research Medical Center as one of the investigators. This re-analysis should be done with all data from that site removed from the database.

Can you please give us an approximate turn around time for receiving this re-analysis?

Thanks!

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

JANE A DEAN
04/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021664/S-013

FILING COMMUNICATION

ISTA Pharmaceuticals, Inc.
Attention: Paul Nowacki
Director, Regulatory Affairs
15295 Alton Parkway
Irvine, CA 92618

Dear Mr. Nowacki:

Please refer to your December 16, 2009, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bromfenac sodium ophthalmic solution, 0.09%.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, this supplemental application was considered filed 60 days after the date we received your supplemental application in accordance with 21 CFR 314.101(a). The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is October 16, 2010.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 6, 2010.

During our filing review of your supplemental application, we identified the following potential review issue. As described in 21 CFR 201.10, the labeling of a drug may be misleading if there is featuring in the labeling (b) (4) The established name of this drug product should be listed as bromfenac ophthalmic solution.

We are providing the above comments to give you preliminary notice of a potential review issue. Our filing review is only a preliminary evaluation of the supplemental application and is not

indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application.

In addition, we request that you submit the 95% confidence intervals of the treatment differences for both primary and secondary efficacy endpoints (inflammation and pain) for studies CL-S&E-0802071-P, CL-S&E-0415081-P-ER, CLS&E-0415081-P-WR, and CL-S&E-1205081-P. Please also submit the corresponding SAS codes for generating the 95% confidence intervals.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your application and reasons for the waiver request, we will notify you of our decision.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

WILEY A CHAMBERS
02/26/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Jane A. Dean, RN, MSN, Regulatory Health Project Manager, Division of Anti-Infective and Ophthalmology Products, x61202

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
February 17, 2010		NDA 021664/S-013	(PLEASE CHECK OFF BELOW) New supplement

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Bromfenac sodium (b) (4) ophthalmic solution, (b) (4)	Standard	Ophthalmic – nonsteroidal anti-inflammatory	(Generally 1 week before the wrap-up meeting) July 2, 2010

NAME OF FIRM:

ISTA Pharmaceuticals, Inc.

PDUFA Date: October 16, 2010

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

EDR link to submission:
\\CDSESUB1\EVSPROD\NDA021664

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date]: May 10, 2010, 11am, Conf. Rm. 1309, Bdg. 22

Labeling Meetings: [Insert Dates]:

Wrap-Up Meeting: [Insert Date]: July 12, 2010, 11am, Conf. Rm. 1309, Bdg. 22

SIGNATURE OF REQUESTER
Jane A. Dean, RN, MSN

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL ☐ HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

FARIBA IZADI
02/17/2010
Signed on behalf of Jane Dean

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021664/S-013 **PRIOR APPROVAL SUPPLEMENT**

ISTA Pharmaceuticals, Inc.
Attention: Paul Nowacki
Director, Regulatory Affairs
15295 Alton Parkway
Irvine, CA 92618

Dear Mr. Nowacki:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	bromfenac sodium (b) (4) ophthalmic solution, (b) (4)
NDA Number:	021664
Supplement number:	013
Review Priority Classification:	Standard
Date of supplement:	December 18, 2009
Date of receipt:	December 16, 2009

This supplemental application proposes a change in dosing regimen from twice-a-day (BID) dosing following cataract extraction surgery to once-a-day (QD) dosing beginning one day prior to surgery, continuing on the day of surgery and for 14 days after surgery.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 14, 2010, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 16, 2010.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21664	SUPPL-13	ISTA PHARMACEUTICALS	XIBROM (BROMFENAC SODIUM (b) (4) OPHTH)

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

/s/

MAUREEN P DILLON PARKER
01/15/2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 021664	NDA Supplement # S-013	If NDA, Efficacy Supplement Type: SE-2
Proprietary Name: Bromday Established/Proper Name: bromfenac sodium ophthalmic solution, 0.09% Dosage Form: ophthalmic solution		Applicant: ISTA Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Jane A. Dean, RN, MSN		Division: Division of Anti-Infective and Ophthalmology Products

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is October 16, 2010	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date: AP, 10/16/10
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Sponsor Proposed: 10/8/10
• Original applicant-proposed labeling	12/18/10
• Example of class labeling, if applicable	n/a

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Original proposed labeling: 12/18/09 Proposed labeling from sponsor: 10/8/10
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	Letter: 8/23/10 Reviews: 4/21/10; 8/23/10
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA 8/27/10 ☐ DRISK ☐ DDMAC ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing Review/Memo of Filing Meeting: 5/11/10 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 5/12/10 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	10/19/10
Cross-Discipline Team Leader Review *(indicate date for each review)*	10/16/10
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL memo
• Clinical review(s) *(indicate date for each review)*	7/19/10
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical Review - 7/19/10
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 10/12/10
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 9/3/10
Statistical Review(s) *(indicate date for each review)*	☐ None 8/10/10
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 9/8/10
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 7/12/10
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 7/15/10
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 7/15/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 7/12/10; 9/10/10
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 7/12/10; 9/10/10
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	7/12/10
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

JANE A DEAN
10/21/2010