CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-664

MEDICAL REVIEW

Deputy Division Director's Review of NDA 21-664

Original New Drug Application

Submission Date: May 24, 2004
Review Completed: March 23, 2005

Deputy Division Director: Wiley A. Chambers, MD

Established Name: bromfenac sodium ophthalmic solution

Applicant: Ista Pharmaceuticals
15295 Alton Parkway
Irvine, CA 92618
(949) 788-6000

Pharmacologic Category: Non-steroidal anti-inflammatory (NSAID)

Proposed Indication: Cataract postoperative inflammation
Dosage Form: Ophthalmic solution
Route of Administration: Topical ocular
NDA Drug Classification: 3S

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I. Recommendations

A. Recommendation on Approvability

NDA 21-664 is recommended for approval for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

B. Recommendation on Postmarketing Studies and/or Risk Management Steps

No postmarketing studies are recommended. No risk management steps are recommended.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Oral bromfenac sodium (Duract) (NDA 20-535) was approved for marketing in the United States in 1997 for the treatment of short term management of pain. Duract was withdrawn from the United States market following reports of liver toxicity when the drug was administered for periods of time exceeding the package insert recommended dosing maximum of 10 days. Bronuck, the topical ophthalmic form of bromfenac sodium, was developed by Senju Pharmaceuticals and was approved for marketing in Japan in May 2000 for the symptomatic therapy of external or anterior ocular inflammatory diseases (blepharitis, conjunctivitis, scleritis (including episcleritis) and post-operative inflammation). Since that time, Bronuck has been prescribed to approximately 2.8 million patients. Xibrom is the same drug product as Bronuck marketed in Japan.

ISTA conducted two phase 3 trials for the marketing application for Xibrom. The trials were well-controlled, randomized, double-masked, safety and efficacy clinical trials conducted under a single protocol

B. Efficacy

Bromfenac has demonstrated superiority over vehicle in replicative trials in the primary efficacy endpoint, as well as patients with a score of zero "0" on the anterior chamber cell and flare scales. The trials were designed to evaluate the clearance of post-operative inflammation following cataract surgery. Evaluation of clearance in these studies however, was not true clearance because evaluations demonstrating 1-5 cells per high power field (normally called trace inflammation) were counted as cleared. While this is potentially problematic for demonstrating efficacy, a one unit difference in mean inflammation score between the bromfenac group and the vehicle group was also demonstrated. A one unit difference is consistent with the therapeutic effect demonstrated by other NSAIDs with an approved indication for reducing postoperative inflammation.

Senju's clinical study reports that supported approval of Bronuck in Japan were also provided as supportive data to the Xibrom NDA. Post-marketing information for Bronuck has also been provided.

C. Safety

The safety profile of Xibrom (bromfenac sodium ophthalmic solution) is consistent with other products in the topical non-steroidal anti-inflammatory drug (NSAID) class. There are no new unexpected adverse events associated with the use of this product. The drug product has demonstrated low levels of systemic absorption [redacted]. This level is orders of magnitude below the levels demonstrating systemic adverse events with the oral administration.

D. Dosing, Regimen, and Administration
In the clinical studies evaluating safety and efficacy, one drop of bromfenac ophthalmic solution was administered twice daily to the affected eye for 14 days.

III. Reviews from Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

Reviews have been completed from Chemistry/Manufacturing, Non-clinical Pharmacology/Toxicology, Microbiology (sterility assurance), Clinical Pharmacology, and the Division of Drug Marketing, Advertising and Communications (DDMAC). There are no outstanding or unresolved issues from any of the reviews.

IV. Labeling

Labeling is based on the labeling of other non-steroidal anti-inflammatory drug products with respect to warnings and precautions. The efficacy information listed in the labeling is based on the submitted clinical studies. The drug product contains a demulcent and the sponsor could have elected to perform contribution of component studies to demonstrate a "comfort" claim, but did not elect to perform them. The product can not therefore make any "comfort" or "relief of pain" claims. The revised draft labeling submitted on March 17, 2005, was considered acceptable by the review team.

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/s/

Wiley Chambers
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MEDICAL OFFICER

Medical Officer's Label Review of NDA 21-664
Label Review #3

NDA 21-664 Label Review #3	**Submission Date:** March 17, 2005 **Received Date:** March 18, 2005 **Review Date:** March 18, 2005
Sponsor:	ISTA Pharmaceuticals 15295 Alton Parkway Irvine, CA 92618 Marvin J. Garrett (949) 788-5303
Drug:	bromfenac ophthalmic soln. 0.09%
Pharmacologic Category:	non-steroidal anti-inflammatory
Dosage Form and Route of Administration:	Topical
Submitted:	Requested changes to the divisions draft labeling based on the telecon with the sponsor on 3/17/05.

The sponsor has requested the following changes to the division's draft labeling:

ANNOTATION

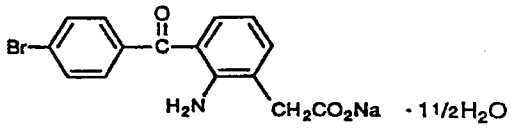
XIBROM™
(bromfenac [redacted] ophthalmic solution) 0.09%

Sterile

Description:

XIBROM (bromfenac [redacted] ophthalmic solution) 0.09% is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each mL of Xibrom 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 $C_{15}H_{11}BrNNaO_3 \bullet 1\frac{1}{2}H_2O$. The structural formula of bromfenac sodium is



Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. XIBROM ophthalmic solution is supplied as a sterile aqueous [2]0.09% solution, with a pH of 8.3. The osmolality of XIBROM ophthalmic solution is approximately 300 mOsmol/kg. Each mL of XIBROM ophthalmic solution contains: **Active**: bromfenac sodium hydrate 0.1035%. **Inactives**: benzalkonium chloride (0.05 mg/mL), 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 the pH, and purified water, USP.

Clinical Pharmacology:
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.

Pharmacokinetics:
The plasma concentration of bromfenac following ocular administration of [2]0.09% XIBROM (bromfenac [redacted] ophthalmic solution) in humans is unknown. Based on the maximum [redacted] proposed dose of one drop to each eye ([3]0.09mg) 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.

Clinical Trials:
Clinical efficacy was evaluated in two randomized, double-masked, placebo-controlled U.S. trials in which subjects with a summed ocular inflammation score ≥3 after cataract surgery were assigned to XIBROM or placebo in a 2:1 ratio following surgery. One drop of XIBROM or vehicle was self-instilled in the study eye twice a day for 14 days, beginning the day after surgery. The primary endpoint was reduction of ocular inflammation (to trace inflammation or

clearing) assessed 14 days post-surgery using a slit lamp binocular microscope. 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%).

Indications and Usage:
XIBROM ophthalmic solution is indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

Contraindications:
XIBROM ophthalmic solution is contraindicated in patients with known hypersensitivity to any ingredient in the formulation.

Warnings:
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 nonasthmatic people.

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.

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.

Precautions:
General:
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.

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.

Postmarketing 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.

Postmarketing 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.

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

Information for Patients:
XIBROM ophthalmic solution should not be administered while wearing contact lenses.

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 (360 times the recommended human ophthalmic dose [RHOD] of 1.67 µg/kg in 60 kg person on a mg/kg/basis, assuming 100% absorbed) and 5.0 mg/kg/day (3000 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 (540 and 180 times RHOD, respectively.

Pregnancy: Teratogenic Effects: Pregnancy Category C.
Reproduction studies performed in rats at oral doses up to 0.9 mg/kg/day (540 times RHOD) and in rabbits at oral doses up to 7.5 mg/kg/day (4500 times RHOD) revealed no evidence of teratogenicity due to bromfenac. However, 0.9mg/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.

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

Nursing Mothers:
Caution should be exercised when XIBROM ophthalmic solution is administered to a nursing woman.

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

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

Adverse Reactions:

The most commonly reported adverse experiences reported following use of XIBROM 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.

Clinical Practice: The following events have been identified during postmarketing use of bromfenac ophthalmic solution ^{2}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 ^{2}0.09%, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown (see PRECAUTIONS, General).

Dosage and Administration:
For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of XIBROM ophthalmic solution should be applied 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.

How Supplied:
XIBROM™ (bromfenac ophthalmic solution) ^{2}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:

NDC 67425-004-50 5 mL in 10 cc container

Storage
Store at 15-25°C (59-77°F)

Rx Only

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

by: Bausch & Lomb Incorporated
Tampa, FL 33637

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

Issued Date (to be determined)
Printed in USA

REFERENCES

Conclusions/Recommendations:
The division agrees with the changes proposed by the sponsor. The label is acceptable as written.

Jennifer D. Harris, M.D.
Medical Officer

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/s/

Jennifer Harris
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Wiley Chambers
3/18/05 05:13:25 PM
MEDICAL OFFICER

Medical Officer's Label Review of NDA 21-664
Label Review #2

NDA 21-664 Label Review #2	**Submission Date:** March 15, 2005 **Received Date:** March 16, 2005 **Review Date:** March 16, 2005
Sponsor:	ISTA Pharmaceuticals 15295 Alton Parkway Irvine, CA 92618 Marvin J. Garrett (949) 788-5303
Drug:	bromfenac sodium ophthalmic soln. 0.1035%
Pharmacologic Category:	non-steroidal anti-inflammatory
Dosage Form and Route of Administration:	Topical
Submitted:	Requested changes to the divisions draft labeling.

The sponsor has requested the following changes other division's draft labeling:

1. The presentation of the Tradename "XIBROM" in all caps should be consistent throughout the package insert.

   Reviewer's comments: *Agree. This is consistent with regulatory policy.*

2. Our calculations show 1.035 mg of bromfenac sodium [redacted] is equivalent to [redacted] mg of bromfenac free acid, not [redacted] mg as the Agency noted. Technically, the active ingredient is bromfenac sodium [redacted].

   Reviewer comments: *Agree; however, recalculation of the bromfenac free acid is* [redacted]

3. This appears to be a typographical error in that the label claim and actual concentration of bromfenac sodium hydrate is 0.1035% [redacted]

   Reviewer Comments: *Agree.*

4. Under Clinical Pharmacology, Mechanism of Action, we desire this statement to be included: " Bromfenac sodium is a non-steroidal anti-inflammatory [redacted]

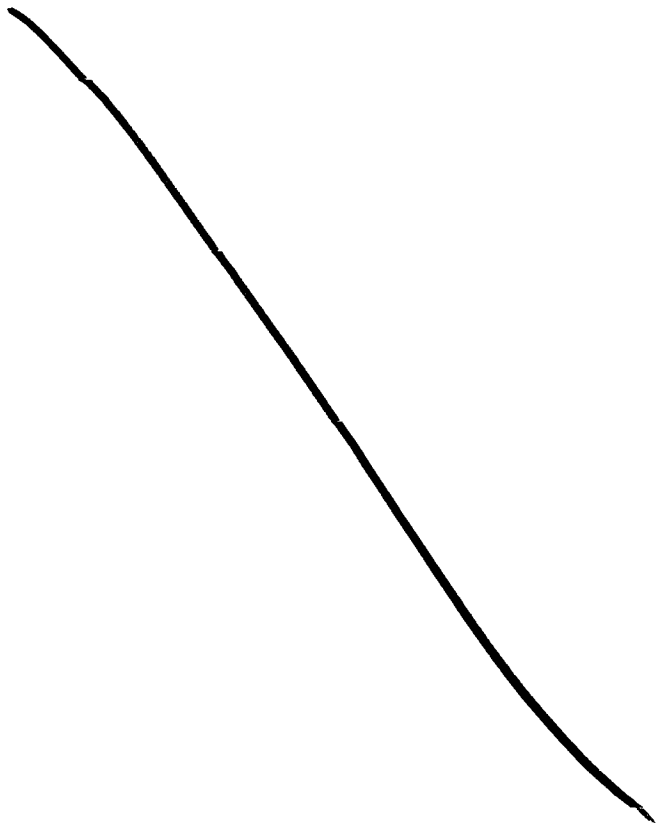
5 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical-1



Jennifer D. Harris, M.D.
Medical Officer

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/s/

Jennifer Harris
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Wiley Chambers
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CLINICAL REVIEW

Application Type	NDA 21-664
Submission Number	000
Submission Code	N
Letter Date	May 24,2004
Stamp Date	May 26, 2004
PDUFA Goal Date	March 26, 2005
Reviewer Name	Jennifer D. Harris, M.D.
Review Completion Date	February 9, 2005
Established Name	bromfenac sodium ophthalmic solution
(Proposed) Trade Name	Xibrom
Therapeutic Class	non-steroidal anti-inflammatory
Applicant	ISTA Pharmaceuticals
Priority Designation	S
Formulation	bromfenac sodium 0.1%
Dosing Regimen	one drop B.I.D.
Indication	treatment of ocular inflammation following cataract surgery
Intended Population	Patients who have undergone cataract surgery

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

NDA 21-664 is recommended for approval after labeling revisions are made consistent with the recommendations listed in this review. There are no unresolved regulatory issues.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no postmarketing risk management activities recommended for this drug product.

1.2.2 Required Phase 4 Commitments

There are no phase 4 commitments recommended for this drug product.

1.2.3 Other Phase 4 Requests

N/A – see section 1.2.2.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Oral Bromfenac sodium (Duract) (NDA 20-535) was approved for marketing in the U.S. in 1997 for the treatment of short term management of pain. Duract was withdrawn from the U.S. market following reports of liver toxicity when the drug was administered for periods of time exceeding the package insert recommended dosing maximum of 10 days. Bronuck, the topical ophthalmic form of bromfenac sodium, was developed by Senju Pharmaceuticals and was approved for marketing in Japan in May 2000 for the symptomatic therapy of external or anterior ocular inflammatory diseases (blepharitis, conjunctivitis, scleritis (including episcleritis) and post-operative inflammation). Since that time, Bronuck has been prescribed to approximately [redacted] patients.

ISTA Pharmaceuticals submitted the original IND 60,295 for Xibrom (bromfenac ophthalmic solution) on March 8, 2003. Xibrom is the same drug product as Bronuck marketed in Japan. A pre-NDA teleconference was held on August 12, 2003. The FDA and ISTA agreed that additional phase 3 trials would need to be conducted due to issues with the design of the trials conducted by Senju.

ISTA conducted two phase 3 trials for the marketing application for Xibrom. The trials were well-controlled, randomized, double-masked, safety and efficacy clinical trials conducted under a single protocol. The trials were designed to evaluate the clearance of post-operative inflammation following cataract surgery.

Senju's clinical study reports that supported approval of Bronuck in Japan were also provided as supportive data to the Xibrom NDA. Post-marketing information for Bronuck has also been provided.

1.3.2 Efficacy

The grading scale used by ISTA to evaluate the clearance of inflammatory cells (component of the primary efficacy endpoint) is not the Division's recommended grading scale. Using the sponsors scale can lead to misleading results since patients who are graded as having "cleared ocular inflammation" may in fact still have trace inflammatory cells in the anterior chamber. This may or may not have had any clinical relevance based on the types of cells that were present.

However, based on the totality of the data presented in this NDA, the submitted studies are sufficient to establish efficacy for the use of bromfenac sodium ophthalmic solution (0.1%) for the treatment of ocular inflammation following cataract extraction. Bromfenac has demonstrated superiority over vehicle in replicative trials in the primary efficacy endpoint, as well as patients with a score of zero "0" on the anterior chamber cell and flare scales.

1.3.3 Safety

The safety profile of Xibrom (bromfenac sodium ophthalmic solution) is consistent with other products in the topical non-steroidal anti-inflammatory drug (NSAID) class. There are no new unexpected adverse events associated with the use of this product.

1.3.4 Dosing Regimen and Administration

The recommended dosing of bromfenac sodium (one drop twice daily for 14 days following cataract surgery) is appropriate based on the clinical data provided. Efficacy for this product was demonstrated, and there was an acceptable safety profile when dosed at this level. There are no recommended dose modifications for special populations.

1.3.5 Drug-Drug Interactions

N/A – drug-drug interactions were not conducted.

1.3.6 Special Populations

There are no dosing modifications needed for any of the special populations (e.g. demographics, hepatic, renal insufficiency, etc). This is common for topical ophthalmic drops due to the concentrations, dosing amounts and the limited systemic availability.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Proprietary Name:	Xibrom
Tradename:	bromfenac sodium 0.1%
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 following cataract surgery
Dosage Form and Route of Administration:	topical drops

2.2 Currently Available Treatment for Indications

There are currently two topical nonsteroidal anti-inflammatory drugs (NSAIDs) and two topical ophthalmic steroids approved for the treatment of postoperative inflammation: Acular (ketorolac tromethamine ophthalmic solution) 0.5%, Voltaren (diclofenac sodium ophthalmic solution) 0.1%, Lotemax (loteprednol etabonate ophthalmic solution) 0.5%, and Vexol (rimexolone ophthalmic suspension) 1%.

2.3 Availability of Proposed Active Ingredient in the United States

Oral Bromfenac sodium (Duract) (NDA 20-535) was approved for marketing in the U.S. in 1997 for the treatment of short term management of pain. Duract was withdrawn from the U.S. market following reports of liver toxicity when the drug was administered for periods of time exceeding the package insert recommended dosing maximum of 10 days. The topical ophthalmic form of bromfenac has never been marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

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 Presubmission Regulatory Activity

The original IND 60,295 for Xibrom (bromfenac ophthalmic solution) was submitted on March 8, 2003. A pre-NDA teleconference was held on August 12, 2003. Agreements reached between the FDA and ISTA concerning the content of the NDA were as follows:

- The basic design and analysis plan of the two phase 3 studies were agreed upon
- A minimum of 300 patients were to be treated with Xibrom under a single protocol analyzed as two vehicle-controlled, double masked studies
- Senju's clinical studies that supported approval of Bronuck (bromfenac sodium hydrate) in Japan were to be provided as supportive data to the Xibrom NDA.

2.6 Other Relevant Background Information

Bronuck (bromfenac sodium hydrate ophthalmic solution) which is the same drug product as Xibrom (bromfenac sodium ophthalmic solution) was approved in Japan in May 2000. Bronuck was approved to treat symptomatic therapy for external or anterior ocular inflammatory diseases (blepharitis, conjunctivitis, scleritis (including episcleritis) and post-operative inflammation.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

There are no clinically relevant CMC issues at this time based on a preliminary evaluation from the chemistry reviewer.

Drug product quantitative composition

Components	Function	U.S. Commercial (Amount/mL)	%	Japanese Commercial (Amount/mL)
Bromfenac sodium hydrate	Active ingredient		0.1035*	
Boric acid				
Sodium borate				
Sodium sulfite, anhydrous				
Disodium edetate				
Povidone				
Polysorbate 80				
Benzalokonium chloride				
Sodium hydroxide				
Purified water				

Specification for Bromfenac Sodium

Test Description	Release Specifications
Description: solution	Yellow, Clear Solution
Description: container	A white plastic bottle with dropper tip and gray cap, with not significant discoloration or physical deformation
Bromfenac Identification (HPLC)	Presence of bromfenac
Bromfenac Identification (UV)	Presence of Bromfenac
Bromfenac Assay	of labeled amount
Total U-II Unknown Impurity	NMT
Total Impurities Excluding U-II	NMT
Total Impurities	NMT
pH	8.1-8.5
Osmolality	mOsM
Assay for Benzalkonium chloride	of labeled amount
Assay for EDTA	of labeled amount

Test Description	Release Specifications
Assay for Sodium sulfite	Report Only
Sterility	Sterile (conforms to current USP)
Antimicrobial Effectiveness Test	N/A
Particulate Matter (microscopic evaluation)	NMT [redacted] NMT [redacted] NMT

3.2 Animal Pharmacology/Toxicology

There are no clinically relevant findings in any of the ocular pharmacology/toxicology studies.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data for this NDA include two phase 3 trials conducted by the applicant. The trials were well-controlled, randomized, double-masked, safety and efficacy clinical trials conducted under a single protocol. Senju's clinical study reports that supported approval of Bronuck in Japan was also provided as supportive data to the Xibrom NDA. Post-marketing information for Bronuck has also been provided.

4.2 Tables of Clinical Studies

Study	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	No. Sites	No. Patients Randomized
ISTA-BR-CS001-ER	Double-masked, randomized, vehicle-controlled	14 days	Post cataract surgery with IOL implantation	bromfenac 0.1% vehicle	BID	20	296
ISTA-BR-CS001-WR	Double-masked, randomized, vehicle-controlled	14 days	Post cataract surgery with IOL implantation	bromfenac 0.1% vehicle	BID	19	231

4.3 Review Strategy

The sources of clinical data for safety and efficacy for this NDA include two phase 3 trials conducted by the applicant. Each of the phase 3 trials 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. Senju's clinical study reports that supported approval of Bronuck in Japan were used only as supportive data for this NDA. Data from the phase 3 trials, the Senju's study reports for Bronuck and postmarketing data from Japan were used to determine the safety of this product.

A clinical pharmacology review was conducted by the biopharmacology reviewer and integrated into the clinical review.

4.4 Data Quality and Integrity

The Division did not request site inspections for this NDA. There were no concerns raised about the integrity of the data contained in phase 3 trials. The primary efficacy results were tested for a site-by-treatment interaction. This analysis was carried out on 16 individual sites and one grouped site due to small enrollment numbers. There was no site by treatment interaction identified in this analysis (p=0.53).

4.5 Compliance with Good Clinical Practices

The studies were conducted in accordance with current Good Clinical Practice (cGCP). Prior to initiation of the studies, the protocol and the informed consent form (ICF) were reviewed by either a central Institutional Review board (IRB) or site specific local IRB. The ICF was reviewed and approved by the Investigator's IRB prior to initiation of the study. Written informed consent was obtained by the patients prior to initiation of the study.

4.6 Financial Disclosures

The sponsor has certified that no investigators in the US Phase 3 clinical study had financial arrangements requiring disclosure.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There is extensive PK data available in NDA 20-535 for the oral formulation of bromfenac sodium. Based on the known volume of distribution from the oral studies, the dose administered topically would result in undetectable plasma concentrations. This is consistent with a PK study conducted in Japan in healthy Japanese volunteers which

showed no detectable plasma concentrations after administration of bromfenac 0.1% for 28 days. The lower limit of quantification was [redacted] The applicant should develop a method with a lower limit of quantification.

5.2 Pharmacodynamics

N/A – see section 5.1

5.3 Exposure-Response Relationships

N/A – the sponsor has not conducted exposure-response studies. Only one concentration has been evaluated for this NDA.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication sought for bromfenac sodium 0.1% is for the treatment of post-operative ocular inflammation in subjects who have undergone cataract extraction [redacted]

6.1.1 Methods

See sections 4.1 and 4.2. 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. Senju's clinical study reports that supported approval of Bronuck in Japan was used as supportive data for this NDA.

6.1.2 General Discussion of Endpoints

The original primary efficacy endpoint for the phase 3 trials proposed by the sponsor was defined as a summed ocular inflammation score (i.e. cell+ flare) ≤ 1 within the 14-day treatment period. This is not considered an acceptable endpoint for the treatment of ocular inflammation since rebound is a common occurrence after anti-inflammatory drugs are discontinued. This endpoint did not address this concern or the sustainability of the effect after the active-treatment period.

The agency requires a more rigorous definition of efficacy which required bromfenac to demonstrate both statistical and clinical significance in the reduction of summed ocular inflammation score, or reduction in anterior cells, as compared to vehicle. A decision was made to redefine the primary efficacy endpoint. The primary efficacy endpoint is defined as the sum of anterior chamber cell and flare equal to zero (based on a five-point scale for each) at Visit 4 (Day 15).

6.1.3 Study Design

This was a Phase 3, multicenter, repeat-dose, double-masked, parallel-group study for bromfenac ophthalmic solution 0.1% versus vehicle in subjects who had undergone uncomplicated unilateral cataract extraction (by phacoemulsification or extracapsular cataract extraction) with posterior chamber intraocular lens implantation. The data for this study were collected under a common protocol (ISTA-BR-CS001), but analyzed as two studies (ISTA-BR-CS001-ER and ISTA-BR-CS001-WR) based on site enrollment (i.e. Eastern Region or Western Region respectively).

The primary objective of this study was to investigate the efficacy of bromfenac sodium ophthalmic solution 0.1% in the treatment of post-operative ocular inflammation in subjects who had undergone cataract extraction with posterior chamber intraocular lens implantation.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria

1. Male or female subjects at least 18 years of age scheduled for unilateral cataract surgery (phacoemulsification or extracapsular extraction) with posterior chamber intraocular lens implantation
2. No topical, systemic or inhaled NSAIDs within one week of cataract surgery
3. No topical, inhaled or oral corticosteroids within 15 days of cataract surgery and no depo-corticosteroids within 45 days of cataract surgery
4. No concurrent use of anti-inflammatory drugs, topical or systemic, during the study (treatment and follow-up stages) and no use of preserved artificial tears
5. A best corrected visual acuity of at least 20/200 in the fellow eye (non-study eye)
6. A summed score of > 3 (without rounding) for anterior chamber cells (scale 0-4) and flare (scale 0-4) at the baseline examination (Visit 1, Study Day 1)
7. Willing/able to return for all required study visits
8. Willing/able to follow instructions from the study Investigator and his/her staff
9. Able to self-administer test agent (or have a caregiver available to instill all doses of test agent)
10. Agreed to avoid disallowed medications (including the anticipated or regular use of preserved artificial tears) throughout the duration of the study
11. For women capable of becoming pregnant: must agree to have urine pregnancy testing performed at screening (must be negative) and at the end of the study, and must agree to use a medically acceptable form of birth control throughout the study duration and for at least one week prior to and after completion of the study.
12. Signed informed consent approved by Ethics Committee or Institutional Review Board
13. An intraocular pressure (IOP) of > 5 mm Hg and ≤ 22 mm Hg (in study eye) with or without anti-glaucoma therapy at the pre-operative screening visit

Exclusion Criteria

1. A known hypersensitivity to bromfenac sodium, tobramycin sulfate, or any component of the test agents (including "procedural" medications such as anesthetic and/or fluorescein drops, dilating drops, etc.)
2. A known hypersensitivity to salicylates (aspirin) or other non-steroidal antiinflammatory drugs (NSAIDs)
3. Any active or chronic/recurrent ocular or systemic disease that was uncontrolled and was likely to affect wound healing (eg, diabetes mellitus, systemic connective tissue disease, severe atopic disease)
4. A known blood dyscrasia or bone marrow suppression; a diagnosis of uncontrolled/unstable peptic ulcer disease; inflammatory bowel disease; or ulcerative colitis; or any uncontrolled/unstable pulmonary, cardiac, vascular, autoimmune,
5. Need for anticoagulant therapy during the study (including aspirin at doses of more than 165 mg/day), or any known or suspected bleeding tendencies
6. Use of any ocular, topical, or systemic medication that could have interfered with normal lacrimation, wound healing, the test agent, or the interpretation of study results, within one week prior to Study Visit 1 (eg, NSAIDs/aspirin, antihistamines, mast cell stabilizers, regular use of preserved artificial tears)
7. Any active corneal pathology or corneal scarring noted in either eye at the screening visit (except punctate keratopathy, which was allowable in the nonoperative eye if mild)
8. Any extraocular/intraocular inflammation in either eye noted at the screening visit (blepharitis was allowed if scurf only, and no concurrent conjunctivitis or lid erythema/edema) or ongoing, unresolved uveitis
9. Rupture of the posterior capsule; disruption of the vitreous or anterior hyaloid face; or inability to undergo capsular bag or sulcus-fixated intraocular lens placement during the operative procedure
10. Hyphema, hypopyon, or a plasmoid-appearing aqueous humor in the operative eye at the baseline examination at post-surgery Day 1
11. Radial keratopathy, corneal transplant, or LASIK within the last two years
12. Need for refractive corneal incisions in the study eye during the operative procedure
13. History of abuse of alcohol/drugs within six months prior to the screening visit
14. Pregnancy or nursing/lactating
15. Participation in any other study of an investigational drug or device within 30 days prior to enrollment
16. Clinically significant liver function tests at the screening visit

Primary Efficacy Variable

The primary efficacy outcome was the proportion of subjects in the ITT population with cleared ocular inflammation in the study eye at Visit 4 (Day 15 visit). Cleared ocular inflammation was defined as a summed ocular inflammation score (anterior chamber cell score plus flare score, each measured on a five-point scale) of zero. The anterior chamber cell and flare score was determined as follows:

Anterior Chamber Cells		Anterior Chamber Flare	
Grade	Cell Count	Grade	Flare
0	None-5 (trace)	0	Complete absence
1	6-15	1	Very slight
2	16-25	2	Moderate
3	26-50	3	Marked
4	>50	4	Intense

Reviewer's Comments: *The definition of Grade 0 on the anterior chamber cell scale is not acceptable. Grade 0 should be defined as a cell count of zero (complete absence of cells). Any cells in the anterior chamber could be indicative of an inflammatory process and should not be graded as zero.*

Secondary Efficacy Measurements

The secondary measures of efficacy include the following:

- Cleared ocular inflammation at Visit 4, ITT population with censored data - subjects who discontinued masked test agent treatment prior to Visit 4 and received an alternative anti-inflammatory medication were censored at the visit closest to (on or before) receipt of the alternative medication.
- Treatment success, ITT population, LOCF, no censoring – defined as occurrence of a summed ocular inflammation score of one or less within the period the subject was receiving masked test agent.
- Mean anterior chamber cell score at Visit 4
- Mean change from baseline in summed ocular inflammation score at each follow-up visit
- Mean percent improvement in summed ocular inflammation score at each follow-up visit
- Mean change from baseline in anterior chamber cell and anterior chamber flare scores at each follow-up visit.
- Proportion of subjects who achieved a summed ocular inflammation score, anterior chamber cell score, and anterior chamber flare score improvement of at least 20% over baseline, by treatment group, at each visit.
- Proportion of subjects with summed ocular inflammation score, anterior chamber cell score, and anterior chamber flare score of zero at each follow-up visit
- Shifts from baseline to each follow-up visit for anterior chamber cell score and anterior chamber flare score
- Proportion of subjects who were prematurely discontinued from the study or the masked test agent
- Proportion of subjects using any rescue medications
- Time to resolution of inflammation
- Time to resolution of ocular pain
- Changes from baseline to each follow-up visit for anterior chamber cell and flare scores, ITT population, LOCF

- Investigator's Global Assessment

Safety Measurements

Safety outcomes included ocular adverse events (incidence, frequency, severity and relationship to test agent), systemic adverse events reported by the Investigator, evidence of liver toxicity based on laboratory analysis (AST, ALT, GGT, total and direct bilirubin, and alkaline phosphatase), and evaluation of tolerability of the test agents by assessment of scores of ocular test agent discomfort.

Study Schedule

Procedures	Screening visit (Day-7 to-1	Day of Surgery	Day 1[a] Baseline Visit 1		Day 3±1 Visit 2	Day 8±1 Visit 3	Day 15±24[h] Visit 4	Day 22±2 Visit 5	Early D/C of Test Agent[j]	Day 29±2 Visit 6 or Early D/C from Study[b]
			Post Surgery Screening	Post Enrollment						
Treatment Days			1 – 14							
Informed Consent	X									
Medical History/Demographics	X									
Inclusion/Exclusion Criteria	X	X	X							
Ocular Inflammation Grade for Entry			X							
Physical Examination	X									
Visual Acuity (best correctable)	X									X
Visual Acuity (uncorrected)			X		X	X	X	X	X	
Pupillary Exam	X								X	X
Biomicroscopy[c]	X		X		X	X	X	X	X	X
Intraocular Pressure[d]	X		X		X	X	X	X	X	X
Funduscopic Exam (dilated)	X								X	X
Laboratory Tests[e]	X								X	X
Urine Pregnancy Test[f]	X								X	X
Dispense Test agent/Dosing Instructions[g]				X						
Subject Diary				X	X	X	X		X	X[k]
Record Concomitant Medication	X	X	X		X	X	X	X	X	X
Record subject Discomfort Score				X	X	X	X		X	
Assess Adverse Events				X	X	X	X	X	X	X
Assess Treatment Compliance				X	X	X	X		X	X
Discharge from the Study										X
Investigator's Global Assessment										X

[a] 16-32 hours after surgery
[b] if a subject prematurely discontinued from the study , the subjects was seen at the study site for a final visit. All visit 6 assessments were performed.
[c] Included evaluation of external adnexa, conjunctiva, ciliary flush, cornea, anterior chamber, iris, lens and capsular bag
[d] Goldmann tonometry preferred
[e] Included liver function test
[f] Applied only to females capable of becoming pregnant
[g] Test agent was self-administered by subjects, one drop every 12 hours, from Visit 1 though Day 14
[h] Visit 4 occurred after the completion of dosing with test agent on day 14. The visit occurred within 24-48 hours after instillation of the last dose of test agent
[i] Assessed adverse events only after test agent administration commences

[j] after completing test agent discontinuation assessments, subjects completed all remaining protocol visits until they reached the visit 6 completion visit. At each of the remaining protocol visits, the following assessments were completed: VA (uncorrected), biomicroscopy, IOP, concomitant medications and adverse events.
[k] Only when the subject was prematurely discontinued from the study, treatment compliance was assessed.

6.1.4 Efficacy Findings

Data Sets Analyzed

Intent to Treat (ITT) Population – defined as all subjects who were randomly assigned to test agent.

Per Protocol Population – *The sponsor's definition of per-protocol allowed for patients to have protocol violations concerning visits, missed doses and use of disallowed concomitant medications. The data present in the following section is based on a redefined per-protocol population which consists of protocol compliant patients and excludes for following categories of subjects: those with eligibility violations, those with missing study visits or out-of-window visits, those with test agent administration errors of any type, and those who received disallowed medication before Visit 4 (Day 15).*

Primary Efficacy Analysis

The primary efficacy endpoint was the proportion of subjects with cleared ocular inflammation in the study eye at Visit 4. For the primary efficacy analysis data were not censored if the subject discontinued test agent treatment early and was given alternative anti-inflammatory medication.

Based on the interim monitoring plan, an alpha level of 0.049 was required to show statistical significance at the 0.05 level on the final analysis for the primary efficacy endpoint. For the by-visit analyses of secondary efficacy endpoints, a Bonferoni adjustment for multiple comparisons was made. Thus, alpha = 0.01 (alpha = 0.05/5 timepoints) was used to determine statistical significance at each timepoint.

Study ER

	Bromfenac	Vehicle
	N=198	N=98
ITT Population, LOCF Cleared Ocular Inflammation	124 (62.6%)	39 (39.8%)
	p-value = 0.0002	
	N=84	N=43
Protocol-Compliant Cleared Ocular Inflammation	53 (63.1%)	19 (44.2%)
	p-value = 0.042	

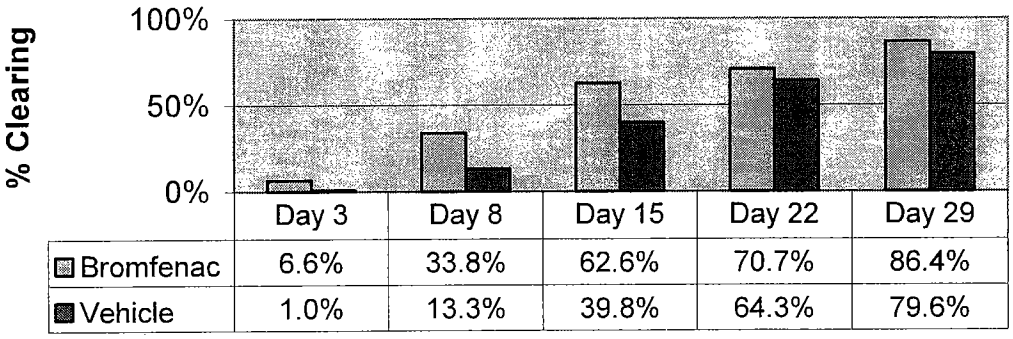
(NDA amendment 000, BM 8/13/04)

Study WR

	Brofenac	Vehicle
	N=158	N=73
ITT Population, LOCF Cleared Ocular Inflammation	104 (65.8%)	35 (47.9%)
	p-value = 0.01	
	N=76	N=44
Protocol-Compliant Cleared Ocular Inflammation	50 (65.8%)	22 (50%)
	p-value = 0.09	

(NDA amendment 000, BM 8/13/04)

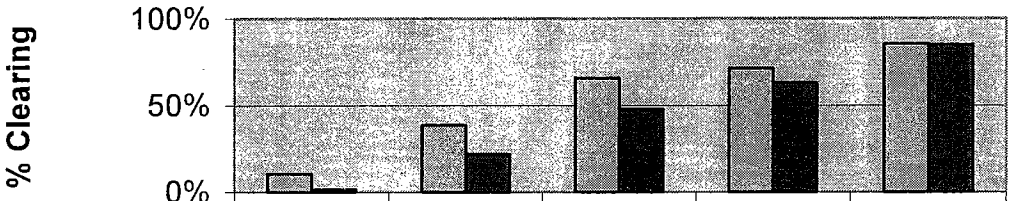
Total Clearing of Inflammation, ITT LOCF - Study ER



	Day 3	Day 8	Day 15	Day 22	Day 29
Bromfenac	6.6%	33.8%	62.6%	70.7%	86.4%
Vehicle	1.0%	13.3%	39.8%	64.3%	79.6%

(mod 5, vol 3, section 14.2, table 38)

Total Clearing of Inflammation, ITT LOCF - Study WR



	Day 3	Day 8	Day 15	Day 22	Day 29
Bromfenac	10.8%	38.6%	65.8%	71.5%	85.4%
Vehicle	1.4%	21.9%	47.9%	63.0%	84.9%

(mod 5, vol 17, section 14.2, table 38)

Reviewer's Comments: *There is a statistically significant difference between bromfenac and vehicle in replicated trials for the primary efficacy endpoint. Patients in the active treatment group also appear to clear inflammation earlier than vehicle treated patients. It is important to note that the protocol definition of "clearing" included patients that may have had up to five (5) cells present in the anterior chamber. This is not an acceptable definition of clearing unless the cells present were non-inflammatory (i.e. pigmented). The database, however does not allow for re-evaluation of the data based on patients with a cell score of "zero (0)" or on the type of cells present in the anterior chamber (i.e. inflammatory vs. non-inflammatory). Based on the scales used, bromfenac appears to be efficacious for the reduction of inflammation following cataract extraction.*

Site-by-Site Interaction

The primary efficacy results were tested for a site-by-treatment interaction and a stratified analysis. This analysis was carried out on 16 individual sites and one grouped site due to small enrollment numbers. There was no site by treatment interaction identified in this analysis (p=0.53).

Secondary Endpoint

An identical analysis to the primary efficacy analysis was carried out with the exception that subjects who discontinued masked test agent treatment prior to Visit 4 and received an

alternative anti-inflammatory medication were censored at the visit closest to (on or before) receipt of the alternative medication. If a subject discontinued test agent early and did not receive alternative medication, data were not censored. These results reflect the treatment effect with bromfenac or vehicle alone, in the absence of any other treatment for inflammation.

Cleared Ocular Inflammation at Visit 4, ITT Population, Censored Data – Study ER

	Bromfenac N = 198	Vehicle N = 98
Cleared ocular inflammation at Visit 4 or discontinued of test agent, LOCF	113 (57.1%)	23 (23.5%)
	P - value = <0.0001	

(mod. 5, vol. 3, section 14.2, table 18)

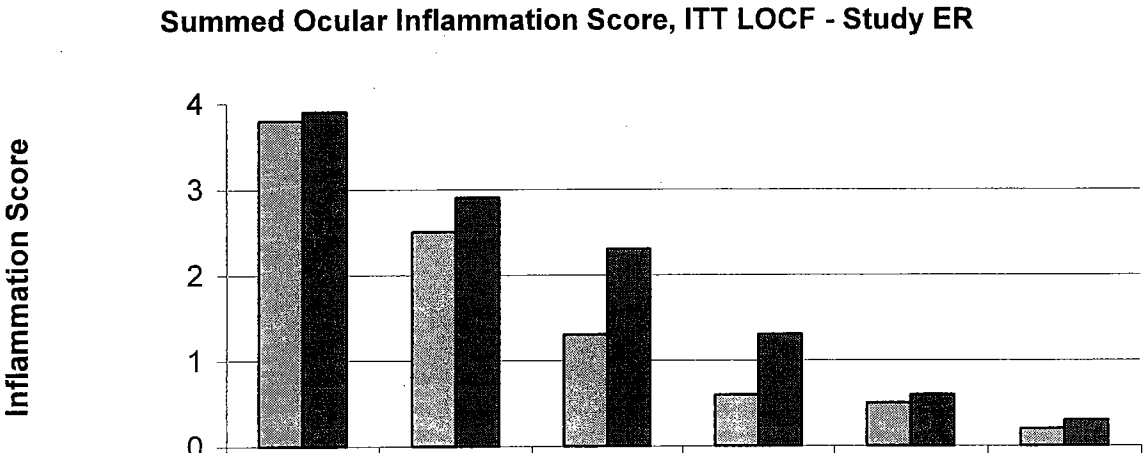
Cleared Ocular Inflammation at Visit 4, ITT Population, Censored Data – Study WR

	Bromfenac N = 158	Vehicle N = 73
Cleared ocular inflammation at Visit 4 or discontinued of test agent, LOCF	98 (62%)	23 (31.5%)
	P - value = <0.0001	

(mod. 5, vol. 17, section 14.2, table 18)

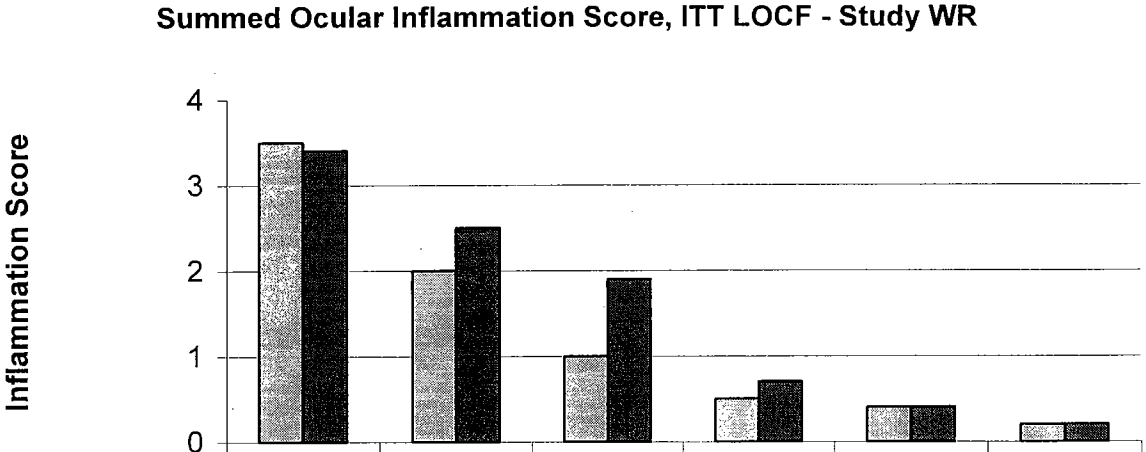
Reviewer's Comments: *These data show replicated results demonstrating the efficacy of bromfenac in the absence of requiring additional anti-inflammatory agents to treat the ocular inflammation. This gives a better indication of the effect of bromfenac alone. This represents those patients who were able to discontinue meds early because of cleared inflammation along with patients who had cleared inflammation at visit 4. These results are supportive of the primary efficacy analysis.*

Summed Ocular Inflammation Score ITT, LOCF Population



	Baseline	Day 3	Day 8	Day 15	Day 22	Day 29
Bromfenac	3.8	2.5	1.3	0.6	0.5	0.2
Vehicle	3.9	2.9	2.3	1.3	0.6	0.3

(mod. 5, vol 3, section 14.2, table 19)

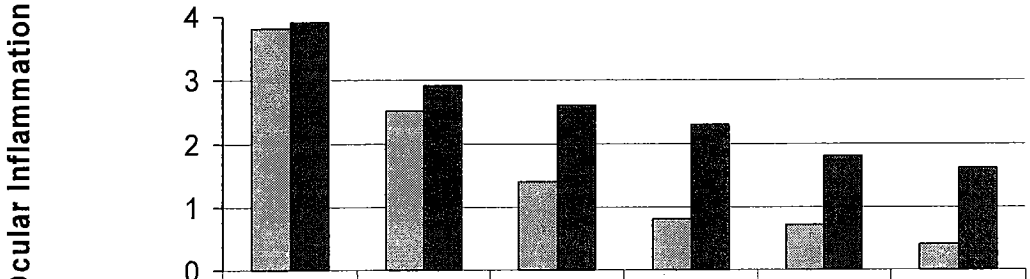


	Baseline	Day 3	Day 8	Day 15	Day 22	Day 29
Bromfenac	3.5	2	1	0.5	0.4	0.2
Vehicle	3.4	2.5	1.9	0.7	0.4	0.2

(mod. 5, vol. 17, section 14.2, table 19)

Reviewer's Comments: *These analyses demonstrate approximately 1 unit difference between bromfenac and vehicle after 1 week of treatment. Differences of this level served as the basis of approval for other products with this indication.*

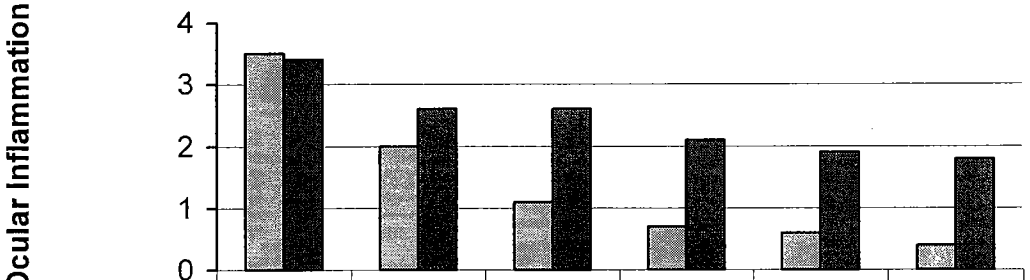
Summed Ocular Inflammation, ITT, Censored Data - Study ER



	Baseline	Day 3	Day 8	Day 15	Day 22	Day 29
Bromfenac	3.8	2.5	1.4	0.8	0.7	0.4
Vehicle	3.9	2.9	2.6	2.3	1.8	1.6

(mod 5, vol 3, section 14.2, table 19a)

Summed Ocular Inflammation, ITT, Censored Data - Study WR



	Baseline	Day 3	Day 8	Day 15	Day 22	Day 29
Bromfenac	3.5	2	1.1	0.7	0.6	0.4
Vehicle	3.4	2.6	2.6	2.1	1.9	1.8

(mod 5, vol 17, section 14.2, table 19a)

Reviewer's Comments: *The mean summed ocular inflammation score at day 15 is less in the bromfenac treated group than in the vehicle group for both studies ER and WR. This difference*

is more pronounced when the censored data set is analyzed which indicates that there was likely greater use of rescue anti-inflammatory agents in the vehicle group. This is confirmed by the table below which shows that there was statistically significant more patients in the vehicle group than in the bromfenac group that received at least one rescue medication.

Rescue Medication Received for Ocular Inflammation

Study ER

	Bromfenac N = 198	Vehicle N = 98
Subjects receiving at least one rescue medication for ocular inflammation	19 (9.6%)	36 (36.7%)
	P - value = <0.0001	

(mod 5, vol 3, section 14.2, table 44)

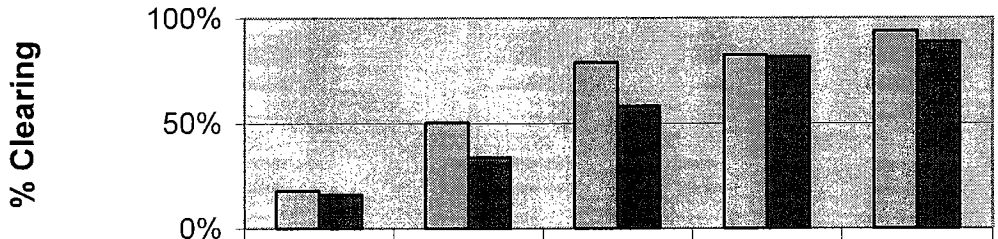
Study WR

	Bromfenac N = 158	Vehicle N = 73
Subjects receiving at least one rescue medication for ocular inflammation	18 (11.4%)	30 (41.1%)
	P - value = <0.0001	

(mod 5, vol 17, section 14.2, table 44)

Cleared Ocular Inflammation Score

Anterior Chamber Cell Clearing, ITT LOCF - Study ER



	Day 3	Day 8	Day 15	Day 22	Day 29
Bromfenac	18.2%	50.5%	78.8%	82.3%	93.9%
Vehicle	16.3%	33.7%	58.2%	81.6%	88.8%

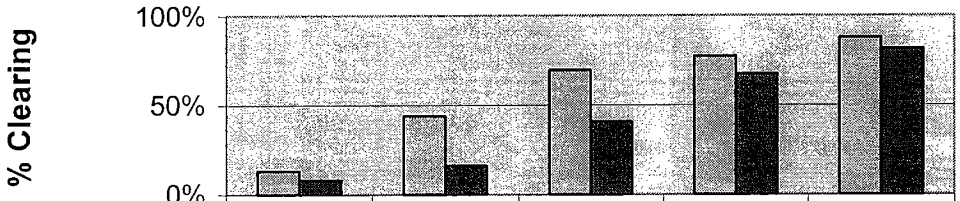
(mod 5, vol 3, section 14.2, table 38)

Anterior Chamber Cell Clearing, ITT LOCF - Study WR

	Day 3	Day 8	Day 15	Day 22	Day 29
Bromfenac	22.2%	58.2%	83.5%	88.6%	96.2%
Vehicle	16.4%	39.7%	76.7%	90.4%	95.9%

(mod 5, vol 17, section 14.2, table 38)

Anterior Chamber Flare Clearing, ITT LOCF - Study ER

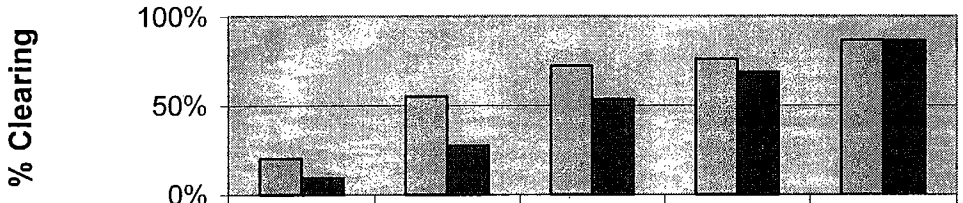


	Day 3	Day 8	Day 15	Day 22	Day 29
Bromfenac	13.1%	43.9%	69.7%	77.3%	87.9%
Vehicle	8.2%	16.3%	40.8%	67.3%	81.6%

(mod 5, vol 3, section 14.2, table 38)

Appears This Way
On Original

Anterior Chamber Flare Clearing, ITT LOCF - Study WR



	Day 3	Day 8	Day 15	Day 22	Day 29
Bromfenac	20.3%	55.1%	72.2%	75.9%	86.7%
Vehicle	9.6%	27.4%	53.4%	68.5%	86.3%

(mod 5, vol 17, section 14.2, table 38)

Reviewer's comments: *It is important to note that the graph showing "anterior chamber cell clearing" is misleading. The protocol definition of "clearing" included patients that may have had up to five (5) cells present in the anterior chamber. However, it can be concluded from the graph that there does not appear to be any rebound of ocular inflammation up to 2 weeks after discontinuation of bromfenac.*

6.1.5 Clinical Microbiology

N/A – This drug product is not an antimicrobial.

6.1.6 Efficacy Conclusions

The grading scale used by the sponsor to evaluate the clearance of inflammatory cells is not the Division's recommended scale. Using the sponsors scale can result in somewhat misleading results since patients who are graded as having "cleared ocular inflammation" may in fact still have trace inflammatory cells in the anterior chamber. This may or may not have had any clinical relevance based on the types of cells that were present.

Based on the totality of the data presented in this NDA, the submitted studies are sufficient to establish efficacy for the use of bromfenac sodium ophthalmic solution (0.1%) for the treatment of ocular inflammation following cataract extraction. Bromfenac has demonstrated superiority over vehicle in replicative trials in the primary efficacy endpoint, as well as patients with a score or zero "0" on the anterior chamber cell and flare scales. Bromfenac also demonstrated a 1 unit mean difference in inflammation compared to its vehicle.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There was one (1) death reported in the 527 subjects evaluated for safety in the two phase 3 studies. Subject 3132-311 died 3 weeks after experiencing a cerebrovascular accident. There were no deaths reported during the clinical studies conducted in Japan to support the marketing application of Bronuck ophthalmic solution. (module 2, vol. 3, sec. 2.7.4)

7.1.2 Other Serious Adverse Events

Serious Adverse Events – Pooled Results CS001

MedDRA preferred Term	Patient #	Bromfenac N= 356	Vehicle N=171
Cardiac Arrest	1042-370	1 (0.3%)	0
Cellulitis	3913-340	1 (0.3%)	0
Cerebrovascular accident/death	3132-311	1 (0.3%)	0
Pyrexia	1024-135	0	1 (0.6%)

(mod 2, vol.3, Sec. 2.7.4, table 2.7.4.2.3:2)

Serious Adverse Events – Postmarketing Data from Japan

Period	Serious Adverse Events
January 15, 2000 – July 14, 2000	0
July 15, 2000 – January 14, 2001	0
January 15, 2001 – July 14, 2002	3 SAE's (3 cases of corneal erosion)
July 15, 2002 – January 14, 2003	0
January 15, 2003 – January 15, 2004	5 SAE's (2 cases o corneal ulcer, 2 cases of corneal perforation, 1 case of conjunctival disorder

(Mod 2, Vol 3, sec 2.7.4.6.2)

Reviewer's Comments: *Corneal ulcer and corneal perforation are known adverse events associated with this class of drugs. These events are contained in the class labeling.*

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Subject Disposition for Randomized Subjects – Study ER

		Bromfenac N=198	**Vehicle N=98**
	p-value [a]		
Number of Subjects			
Randomized		198	98
Completing the Study		193 (97.5%)	93 (95%)
Prematurely Terminating the Study	0.31	5 (2.5%)	5 (5.1%)
Primary Reason for Study Termination			
Withdrawal of Consent/Non-compliance	0.6	2 (1.0%)	2 (2%)
Loss to Follow-up	0.55	1 (0.5%)	1 (1%)
Death	N/A	0	0
Early Discontinuation of Test Agent	0.33	0	1 (1%)
Other Reason[b]	1	2 (1.0%)	1 (1%)

(mod 5, vol. 2, sec. 10, table 10.3.1)

[a] p-value is for bromfenac vs. vehicle based on the chi-square or Fisher's exact test.
[b] "other" reasons for discontinuation of test agent included subject non-compliant with study procedures (bromfenac Subject 1035-303), prolonged hospitalization (bromfenac Subject 1042-370), and subject inadvertently randomized who did not meet entry criteria (vehicle Subject 3403-160)

Subject Disposition for Randomized Subjects – Study WR

		Bromfenac N=158	**Vehicle N=73**
	p-value [a]		
Number of Subjects			
Randomized		158	73
Completing the Study		155 (98.1%)	73 (100%)
Prematurely Terminating the Study	0.55	3 (1.9%)	0
Primary Reason for Study Termination			
Withdrawal of Consent/Non-compliance	1	1 (0.6%)	0
Loss to Follow-up	N/A	0	0
Death	N/A	0	0
Early Discontinuation of Test Agent	N/A	0	0
Other Reason[b]	1	2 (1.3%)	0

(mod 5, vol. 16, sec. 10, table 10.3.1)

[a] p-value is for bromfenac vs. vehicle based on the chi-square or Fisher's exact test.
[b] reasons for premature study termination included subject withdrawal of consent/noncompliance (subject 1613-143), subject hospitalization for stoke (bromfenac subject 2132-311), and subject inadvertently randomized who did not meet entry criteria (bromfenac subject 4920-392).

Early Discontinuation of Test Agent – Study ER

		Bromfenac N=198	**Vehicle N=98**
	p-value [a]		
Early Discontinuation of Test Agent	< 0.0001	18 (9.1%)	39 (39.8%)
Reason for Discontinuation			
Lack of Tolerability of Test Agent	0.33	0	1 (1%)
Adverse Event	0.0003	6 (3%)	14 (14.3%)
Disallowed concurrent Medication	0.6	2 (1%)	2 (2%)
Lack of Efficacy [b]	< 0.0001	6 (3%)	21 (21.4%)
Other Reason [c]	1	4 (2%)	1 (1%)

(mod 5, vol. 2, sec. 10, table 10.3.2)

[a] p-value is for bromfenac vs. vehicle based on the chi-square or Fisher's exact test.
[b] Per the protocol, subjects with any of the following could have been discontinued from test agent early at the decision of the Investigator due to lack of efficacy: 1)an increase in ocular inflammation score compared with the previous visit, 2) a summed inflammation score that is unchanged for tow consecutive visits after treatment initiation, or 3) any sign or symptom of inflammation sufficiently severe as to require more intensive anti-inflammatory treatment.
[c] "other" reasons for premature study termination: non-compliance (vehicle Subject 1226-174), poor subject reliability and diary documentation (bromfenac Subject 1035-303), subject lost study medication for four days (bromfenac Subject 2301-049), site inadvertently enrolled both subject eyes (bromfenac Subject 3509-476), and subject entered study with a flare/cell grade < 3 (bromfenac Subject 3702-146).

Early Discontinuation of Test Agent – Study WR

		Bromfenac N=158	**Vehicle N=73**
	p-value [a]		
Early Discontinuation of Test Agent	< 0.0001	16 (10.1%)	29 (39.7%)
Reason for Discontinuation			
Lack of Tolerability of Test Agent	1	1 (0.6%)	0
Adverse Event	0.0007	4 (2.5%)	11 (15.1%)
Disallowed concurrent Medication	1	3 (1.9%)	1 (1.4%)
Lack of Efficacy [b]	< 0.0001	5 (3.2%)	16 (21.9%)
Other Reason [c]	1	3 (1.9%)	1 (1.4%)

(mod 5, vol. 16, sec. 10, table 10.3.2)

[a] p-value is for bromfenac vs. vehicle based on the chi-square or Fisher's exact test.
[b] Per the protocol, subjects with any of the following could have been discontinued from test agent early at the decision of the Investigator due to lack of efficacy: 1)an increase in ocular inflammation score compared with the previous visit, 2) a summed inflammation score that is unchanged for tow consecutive visits after treatment initiation, or 3) any sign or symptom of inflammation sufficiently severe as to require more intensive anti-inflammatory treatment.
[c] "other" reasons for premature discontinuation of test agent included: site discovery that subject received a disallowed medication during surgery (vehicle subject 4713-347 and bromfenac subject 4714-346), subject required arthritis medication not permitted by protocol (bromfenac subject 1613-143), and subject entered study with an ineligible Grade 1 GGT liver function test (bromfenac subject 4920-392).

Reviewer's Comments: *Significantly more patients in the vehicle group discontinued the study than in the drug group in both studies. The majority of patients discontinued the vehicle arm due to lack of efficacy and adverse events. The adverse events that lead to discontinuation were*

those events that are commonly seen with ocular inflammation. Therefore, these adverse events could likely have occurred due to lack of efficacy of the vehicle

7.1.3.2 Adverse events associated with dropouts

Discontinued Patients – Study ER

Subject ID	Treatment	Study Day	Reason for Discontinuation
1319-271	Bromfenac	10	Cystoid macular edema
1016-125	Bromfenac	9	Descemet folds
2304-052	Bromfenac	2	Disallowed concurrent medication
5201-290	Bromfenac	9	Disallowed concurrent medication
3511-478	Bromfenac	2	Increased cell and flare
1702-225	Bromfenac	2	Itching and swelling of eyelid
1800-079	Bromfenac	9	Keratic precipitates
1305-011	Bromfenac	7	Lack of efficacy
1307-012	Bromfenac	8	Lack of efficacy
1327-411	Bromfenac	7	Lack of efficacy
2306-053	Bromfenac	8	Lack of efficacy
2309-056	Bromfenac	3	Lack of efficacy
3804-178	Bromfenac	8	Lack of efficacy
1035-303	Bromfenac	4	Poor pt reliability
3702-146	Bromfenac	1	Pt entered incorrectly
2301-049	Bromfenac	15	Pt lost study medication
3413-518	Bromfenac	2	Swelling of eyelids and face
3509-476	Bromfenac	9	Unaware 2nd eye not allowed in the study
5125-442	Vehicle	12	Anterior chamber inflammation
1015-128	Vehicle	9	Conjunctival erythema
1005-005	Vehicle	8	Cystoid macular edema
1205-088	Vehicle	8	Disallowed Concurrent Medication
5202-291	Vehicle	12	Disallowed concurrent medication
1043-369	Vehicle	6	Increased cell/flare, descemet folds, eyelid swelling
1301-007	Vehicle	4	Increased inflammation
1338-491	Vehicle	7	Increased inflammation
3514-480	Vehicle	8	Increased inflammation
1048-372	Vehicle	4	Inflammation, redness, pain, striae
1000-001	Vehicle	9	Lack of efficacy
1017-127	Vehicle	6	Lack of efficacy
1211-163	Vehicle	4	Lack of Efficacy
1215-167	Vehicle	8	Lack of Efficacy
1302-008	Vehicle	8	Lack of efficacy
1317-018	Vehicle	8	Lack of efficacy
1321-409	Vehicle	4	Lack of efficacy
1325-273	Vehicle	8	Lack of efficacy
1331-414	Vehicle	7	Lack of efficacy

Subject ID	Treatment	Study Day	Reason for Discontinuation
1700-223	Vehicle	7	Lack of efficacy
1704-224	Vehicle	8	Lack of efficacy
2015-325	Vehicle	8	Lack of efficacy
2023-423	Vehicle	7	Lack of efficacy
2308-054	Vehicle	2	Lack of efficacy
3408-381	Vehicle	8	Lack of efficacy
3409-383	Vehicle	7	Lack of efficacy
3416-521	Vehicle	8	Lack of efficacy
3806-416	Vehicle	6	Lack of efficacy
3906-209	Vehicle	12	Lack of efficacy
5206-293	Vehicle	9	Lack of efficacy
5211-610	Vehicle	2	Lack of efficacy
1226-174	Vehicle	11	Non-compliance
1803-082	Vehicle	28	Punctate keratopathy, striae, increased cell/flare
5104-187	Vehicle	7	Redness, foreign body sensation
5110-331	Vehicle	9	Redness, pain
5113-192	Vehicle	6	Redness, soreness, burning, erythema/edema
1054-586	Vehicle	7	Striae, erythema, cliliary flush, increased cell/flare
1028-137	Vehicle	4	Uveitis
5119-441	Vehicle	5	Watering eye, photophobia

(mod 5, vol 3, sec 14.2, table 65)

Discontinued Patients – Study WR

Subject ID	Treatment	Study Day	Reason for Discontinuation
1911-036	Bromfenac	8	Disallowed concurrent medication
4002-181	Bromfenac	2	Disallowed concurrent medication
4006-185	Bromfenac	7	Disallowed concurrent medication
1618-470	Bromfenac	16	Fuch's dystrophy worsened
4920-392	Bromfenac	3	Grade 1 liver toxicity (GGT outside normal limits at screening)
2900-433	Bromfenac	3	Hyphema
3142-430	Bromfenac	8	Increased inflammation
3148-432	Bromfenac	3	Increased inflammation
3114-046	Bromfenac	8	Lack of efficacy
3607-535	Bromfenac	2	Lack of efficacy
3613-537	Bromfenac	8	Lack of efficacy
4701-091	Bromfenac	7	Lack of efficacy
4906-288	Bromfenac	8	Lack of efficacy
4027-574	Bromfenac	2	Lid swelling, itching, foreign body sensation
4714-346	Bromfenac	3	Received flurbiprofen (disallowed medication)
1613-143	Bromfenac	6	Withdrew consent, prescribed Vioxx for arthritis
3113-045	Vehicle	8	Conjunctival erythema, increased inflammation
1112-507	Vehicle	6	Corneal edema
4016-324	Vehicle	3	Disallowed concurrent medication

Subject ID	Treatment	Study Day	Reason for Discontinuation
1919-373	Vehicle	8	Increased anterior chamber inflammation
3103-042	Vehicle	3	Increased inflammation
3105-038	Vehicle	3	Increased inflammation
3115-048	Vehicle	13	Increased inflammation
3122-193	Vehicle	3	Increased inflammation
3133-312	Vehicle	3	Increased inflammation
3138-429	Vehicle	4	Increased inflammation
3147-523	Vehicle	8	Increased inflammation
3154-528	Vehicle	6	Increased inflammation
1115-510	Vehicle	11	Lack of efficacy
1617-469	Vehicle	5	Lack of efficacy
1904-033	Vehicle	8	Lack of efficacy
1909-035	Vehicle	8	Lack of efficacy
1923-377	Vehicle	8	Lack of efficacy
2102-112	Vehicle	8	Lack of efficacy
2811-547	Vehicle	6	Lack of efficacy
4030-632	Vehicle	9	Lack of efficacy
4206-298	Vehicle	5	Lack of efficacy
4704-093	Vehicle	8	Lack of efficacy
4706-094	Vehicle	2	Lack of efficacy
4710-344	Vehicle	3	Lack of efficacy
4901-283	Vehicle	8	Lack of efficacy
4904-287	Vehicle	3	Lack of efficacy
4913-353	Vehicle	8	Lack of efficacy
4916-360	Vehicle	8	Lack of efficacy
4713-347	Vehicle	3	Protocol violation-pt received pred forte

(mod 5, vol 17, sec 14.2, table 65)

7.1.3.3 Other significant adverse events

N/A – All adverse events have been addressed in other sections of this review.

7.1.4 Other Search Strategies

N/A - no other search strategies are required due to the size of the data base and the rate of adverse events seen.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Identical methods were used to elicit adverse event data for both of the phase 3 clinical trials. Safety outcomes included ocular adverse events (incidence, frequency, severity and relationship

to test agent), systemic adverse events reported by the Investigator, evidence of liver toxicity based on laboratory analysis (AST, ALT, gamma-GTP [GGT], total and direct bilirubin and alkaline phosphatase) and evaluation of tolerability of the test agents by assessment of scores of ocular test agent discomfort.

Ocular discomfort was rated on a four-point scale: 0=none, 1=mild, 2=moderate, and 3=severe. Each subject rated each of seven symptoms: tearing, photophobia, eye discharge, itching, foreign body sensation, haziness and eye pain. Subjects were asked to make these assessments of ocular discomfort within one hour after instillation of the test agent. Ocular discomfort assessments made by the subject in their subject diary were not necessarily reported as adverse events. Ocular adverse events may have been reported for any of these symptoms but were assessed by the Investigator based upon each subject's description.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms used in this study were consistent with the actual adverse events experienced.

7.1.5.3 Incidence of common adverse events

See section 7.1.5.4.

7.1.5.4 Common adverse event tables

Number (%) of Patients with Adverse Events Reported by > 1% of Patients in any Treatment Group in Pooled Study ISTA-BR-CS001

Preferred Term	**Bromfenac N=356**	**Vehicle N=171**
Ocular		
Iritis	25 (7%)	31 (18%)
Abnormal Sensation in eye	23 (6.5%)	14 (8.2%)
Eye Pain	15 (4.2%)	20 (11.7%)
Eye Pruritus	14 (3.9%)	5 (2.9%)
Posterior Capsule Opacification	14 (3.9%)	7 (4.1%)
Eye Irritation	9 (2.5%)	8 (4.7%)
Eye Redness	8 (2.2%)	13 (7.6%)
Conjunctival Hyperemia	8 (2.2%)	19 (11.1%)
Macular Edema	7 (2.0%)	8 (4.7%)
Photophobia	7 (2.0%)	19 (11.1%)
Lacrimation Increased	6 (1.7%)	8 (4.7%)
Visual Acuity Reduced	6 (1.7%)	10 (5.8%)
Conjunctival Edema	5 (1.4%)	9 (5.3%)
Ocular Discomfort	5 (1.4%)	1 (0.6%)
Vision Blurred	5 (1.4%)	6 (3.5%)

Preferred Term	Bromfenac N=356	Vehicle N=171
Hyperemia	4 (1.1%)	1 (0.6%)
Intraocular pressure increased	4 (1.1%)	1 (0.6%)
Corneal Striae	3 (0.8%)	7 (4.1%)
Eye Discharge	3 (0.8%)	3 (1.8%)
Vitreous Floaters	3 (0.8%)	2 (1.2%)
Corneal Edema	2 (0.6%)	5 (2.9%)
Descemet's membrane disorder	2 (0.6%)	4 (2.3%)
Punctate Keratitis	2 (0.6%)	2 (1.2%)
Corneal Edema	1 (0.3%)	5 (2.9%)
Erythema of eyelid	0	2 (1.2%)
Vitreous Detachment	0	2 (1.2%)
Systemic		
Headache	7 (2.0%)	3 (1.8%)
Nasopharyngitis	5 (1.4%)	1 (0.6%)
Back Pain	1 (0.3%)	2 (1.2%)
Pyrexia	1 (0.3%)	2 (1.2%)

(mod 2, vol. 3, sec. 2.7.4, tables 2.7.4.2.1:3, and 2.7.4.2.1:7)
note: *events seen at a higher rate in the bromfenac group then in the vehicle group are highlighted in yellow.*

7.1.5.5 Identifying common and drug-related adverse events

The adverse events that were seen at a higher rate in the bromfenac group than the vehicle group are highlighted in the adverse event table in section 7.1.5.4. The relationship between the drug and the ocular adverse events is questionable since they are events that are commonly seen with intraocular inflammation. Systemically, headache is commonly reported with intraocular inflammation and is usually related to the ocular pain cause by the inflammation or associated increase in intraocular pressure. Reports of nasopharyngitis are common with all topical eye drops due to the anatomical relationship with the sinuses.

7.1.5.6 Additional analyses and explorations

Subgroup analyses of all ocular adverse events were conducted for gender and age (<65 and ≥65). These adverse events were analyzed in totality without distinguishing between "drug related" and "non drug-related" events. (module 2, vol 3, sec 2.7, tables2.7.4.5.1:1 through 2.7.4.5.1:8). There was no indication that the safety profile of bromfenac is related to age or gender. Similar types and incidence of adverse events were seen in both genders and for the age subgroups evaluated.

7.1.6 Less Common Adverse Events

N/A – The size of the database submitted in this NDA is not large enough to adequately evaluate rare adverse events that are seen at a rate of less than 1%.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing of liver function (AST, ALT, GGT, total bilirubin, direct bilirubin and alkaline phosphatase) were evaluated during the course of the phase 3 studies. Assessments of LFT's were made at screening and at the last evaluation visit. LFT's were chosen for evaluation due to the hepatotoxicity observed with off-label use of oral bromfenac (Duract) that was voluntarily removed from the U.S. market.

The overwhelming majority of patients enrolled in the phase 3 trials had baseline LFT measurements and follow-up assessments.

Number of patients exposed to Bromfenac with Baseline and Follow-up Laboratory Assessments – Study ER

	Screening	Termination
AST	195	186
ALT	197	187
GGT	198	189
Total Bilirubin	198	188
Direct Bilirubin	195	186
Alkaline Phosphatase	198	189

(mod 5, vol 2, sec 14.1, table 14 and mod 5, vol 3, sec 14.2, table 74)

Number of patients exposed to Bromfenac with Baseline and Follow-up Laboratory Assessments – Study WR

	Screening	Termination
AST	157	154
ALT	157	155
GGT	158	156
Total Bilirubin	158	155
Direct Bilirubin	157	154
Alkaline Phosphatase	158	156

(mod 5, vol 16, sec 14.1, table 14 and mod 5, vol 17, sec 14.2, table 74)

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The integrated database for study ISTA-BR-CS001 (ER and WR) was used to evaluate the effect of bromfenac on the liver function tests.

7.1.7.3 Standard analyses and explorations of laboratory data

Liver Function Toxicity Grades ≥ 1 at Study Termination – Pooled Database ER and WR

	Bromfenac N (%)	**Vehicle N (%)**
AST	3 (0.9%)	2 (1.3%)
	p=0.65	
ALT	4 (1.2%)	2 (1.3%)
	p=1	
GGT	8 (2.3%)	3 (1.9%)
	p=1	
Total Bilirubin	2 (0.6%)	0
	p=1	
Direct Bilirubin	0	0
Alkaline Phospatase	0	0

(mod 2, vol. 3, sec 2.7.4, table 2.7.4.1:1)
note: grade 1 defined as 1.26 – 2.5x upper limit of normal value of population under study.

Reviewer's Comments: *There is no statistical difference in the liver toxicity grades between bromfenac and vehicle at the end of the study.*

7.1.7.4 Additional analyses and explorations

N/A – additional analyses and explorations are not warranted based on review of the data.

7.1.7.5 Special assessments

N/A – special assessments are not warranted based on review of the data.

7.1.8 Vital Signs

N/A – Vital signs and medical histories were evaluated at screening only. Vital signs and physical exams were not evaluated during treatment due to the fact that this is a topical ophthalmic drug with minimal systemic bioavailability.

7.1.8.1 Overview of vital signs testing in the development program

N/A – see section 7.1.8

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

N/A – see section 7.1.8

7.1.8.3 Standard analyses and explorations of vital signs data

N/A – see section 7.1.8

7.1.8.4 Additional analyses and explorations

N/A – see section 7.1.8

7.1.9 Electrocardiograms (ECGs)

N/A – EKG's were not evaluated at baseline or during treatment due to the fact that this is a topical ophthalmic drug with minimal systemic bioavailability.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

N/A/ - see section 7.1.9

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

N/A/ - see section 7.1.9

7.1.9.3 Standard analyses and explorations of ECG data

N/A/ - see section 7.1.9

7.1.9.4 Additional analyses and explorations

N/A - see section 7.1.9

7.1.10 Immunogenicity

N/A – immunogenicity testing has not been conducted in humans.

7.1.11 Human Carcinogenicity

N/A - there were no tumors reported during the trial. This class of drugs is not known to be genotoxic when administered topically.

7.1.12 Special Safety Studies

N/A – There were no special studies conducted to assess safety. Adequate safety measures were evaluated in the phase 3 trials.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

N/A – There is no withdrawal phenomena or abuse potential associated with this drug or this class of drugs.

7.1.14 Human Reproduction and Pregnancy Data

N/A – no data was collected to analyze the use of this topical drug product in reproduction and pregnancy.

7.1.15 Assessment of Effect on Growth

N/A – there were no pediatric patients enrolled in these trials. Height and weight data were not collected.

7.1.16 Overdose Experience

There have been no overdose experiences with this drug product, however, adverse events associated with overdoses in this class of drugs have been evaluated. In particular, post-marketing experience with non-steroidal products have shown that use 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.

7.1.17 Postmarketing Experience

There is no postmarketing experience with this drug product in the U.S. Bromfenac 0.1% (Bronuck) was approved for marketing in Japan in July, 2000. Since Bronuck marketing began, the product has been prescribed for approximately [redacted] patients. Available post-marketing experience data available from Japan include corneal ulcer, corneal perforation, blepharitis, hyperemia, irritation, eye pain, corneal erosion, corneal epithelial desquamation, diffuse superficial keratitis, and conjunctival disorder.
(mod 2, vol 2, sec 2.5.5)

7.2 Adequacy of Patient Exposure and Safety Assessments

There has been adequate patient exposure and assessments during the developments program for to determine the overall safety profile for this drug. The phase 3 U.S. studies evaluated approximately 500 patients. In Japan, the product has been prescribed for approximately [redacted] patients.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See section 4.1 and 4.2.

7.2.1.1 Study type and design/patient enumeration

See section 4.2.

7.2.1.2 Demographics

Baseline Demographics – Study ER

		Bromfenac N=198	**Vehicle N=98**
	p-value		
Age (years)	0.34 [a]		
Mean (SD)		69.3 (10.1)	70.4 (9.2)
Range		35-88	40-93
Gender	0.50 [b]		
Male		93 (47%)	42 (42.9%)
Female		105 (53%)	56 (57.1%)
Race	0.53 [b]		
Asian		2 (1%)	1 (1%)
Black		20 (10%)	14 (14.3%)
Caucasian		162 (81.8%)	73 (74.5%)
Hispanic		11 (5.6%)	9 (9.2%)
American Indian		0	0
Other [c]		3 (1.5%)	1 (1%)
Iris Color	0.67		
Brown		85 (43%)	45 (45.9%)
Hazel		33 (16.7%)	10 (10.2%)
Blue		58 (29.3%)	32 (32.7%)
Green		19 (9.6%)	9 (9.2%)
Other [d]		3 (1.5%)	2 (2%)
Type of Cataract Procedure			
Phacoemulsification		198 (100%)	98 (100%)
Extracapsular Cataract Extraction		0	0

(vol. 2,section 14.1 table 7 and 15)

[a] p-value is for bomfenac vs. vehicle based on t-test
[b] p-value is for bromfenac vs. vehicle based on chi-square or Fisher's exact test
[c] "other" included Senegalese, Polish, and Hungarian
[d] "other" included grey, blue-green, and unknown

Baseline Demographics – Study WR

		Bromfenac N= 158	**Vehicle N= 73**
	p-value		
Age (years)	0.32 [a]		
Mean (SD)		70.3	68.8
Range		42-93	32-91
Gender	0.05 [b]		
Male		69 (43.7%)	42 (57.5%)
Female		89 (56.3%)	31 (42.5%)
Race	0.88 [b]		
Asian			
Black		3 (1.9%)	2 (2.7%)
Caucasian		5 (3.2%)	3 (4.1%)
Hispanic		134 (84.8%)	64 (87.7%)
American Indian		1 (0.6%)	0
Other [c]		1 (0.6%)	0
Iris Color	0.03		
Brown		69 (43.7)	27 (37%)
Hazel		17 (10.8%)	17 (23.3%)
Blue		57 (36.1%)	20 (27.4%)
Green		8 (5.1)%	8 (11%)
Other [d]		7 (4.4%)	1 (1.4%)
Type of Cataract Procedure			
Phacoemulsification		157 (99.4%)	73 (100%)
Extracapsular Cataract Extraction		1 (0.6%)	0

(vol. 16, section 14.1 table 7 and 15)

[a] p-value is for bomfenac vs. vehicle based on t-test
[b] p-value is for bromfenac vs. vehicle based on chi-square or Fisher's exact test
[c] "other" included Senegalese, Polish, and Hungarian
[d] "other" included grey, blue-green, and unknown

7.2.1.3 Extent of exposure (dose/duration)

Pooled Results – Study CS001

	Bromfenac	**Vehicle**
Randomized	356	171
Subjects completing treatment	290 (81.5%)	93 (54.4%)
p-value	<0.0001	
Number of doses received		
Mean	26.1	21.2
Median	28	28
S.D.	5.9	8.7
Min, Max	0,31	1,30
p-value	< 0.0001	

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

In addition to the two well-controlled Phase 3 trials in the U.S., the applicant has provided safety data from the phase 1, 2, and 3 clinical trials conducted by Senju Pharmaceuticals in Japan and post-marketing safety surveillance data available since approval of Bronuck (bromfenac ophthalmic solution, 0.1%) in Japan after July 2000.

7.2.2.1 Other studies

Study data from the phase 1, 2, and 3 clinical trials conducted by Senju Pharmaceuticals in Japan to support marketing approval has been supplied by the sponsor. The data are considered supportive to the clinical safety review. This data has not been integrated into the primary source data due to study design issues such as inclusion/exclusion criteria, endpoints, comparator groups,, etc.

7.2.2.2 Postmarketing experience

Post-marketing safety surveillance data available since approval of Bronuck (bromfenac ophthalmic solution, 0.1%) in Japan after July 2000 has been reviewed. This database contains approximately [redacted] patients exposed to Bronuck from January 2000 to January 2004. See sections 7.1.1, 7.1.2 and 7.1.17.

7.2.2.3 Literature

N/A - No literature references are cited in the Clinical Summary.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience has met the ICH guidelines for the extent and duration of exposure needed to assess safety. The sponsor has evaluated bromfenac sodium in two randomized, double-masked, vehicle-controlled clinical trials which enrolled 437 subjects at 39 clinical sites. A total of 356 subjects were treated with bromfenac sodium on a b.i.d schedule for up to 14 days. Senju Pharmaceuticals treated approximately 850 subjects in the clinical trials that lead up to licensure in Japan. Since marketing began in Japan in July, 2000, the product has been prescribed for approximately [redacted] patients.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The results of animal testing with this drug are not predictive of human events. Human exposure data supersedes the results of the pre-clinical program.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of this clinical trial. In addition, the evaluation of liver function tests were adequate to address the hepatotoxicity concerns associated with the systemic use of this drug.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Metabolic, clearance and interaction analyses have not been conducted for topical form of bromfenac sodium due to the low dose administered and the limited systemic availability. A full metabolic work-up including drug-drug interaction studies were conducted for the systemic form of bromfenac. See NDA 20-535.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adequate safety information has been collected for bromfenac sodium during development to determine that events associated with this drug product are consistent with those events expected based on what is known about the topical NSAID class. There are no new unexpected adverse events associated with the use of this product. There are no further safety studies recommended for this product.

7.2.8 Assessment of Quality and Completeness of Data

The overall safety database provided in this NDA submission is complete and adequate to evaluate the safety profile for bromfenac sodium. Appropriate monitoring and documentation of potential adverse events including biomicroscopy, visual acuity testing, and investigation of potential liver toxicity based on laboratory analysis of AST, ALT, gamma-GTP [GGT], and total and direct bilirubin was provided.

The supportive data from the Senju supported trial in Japan which included study reports, and periodic safety update reports were adequate for review with exception of the case report forms and some of the patient profile data due to inability to translate the information provided. However, overall this data was adequate for review.

7.2.9 Additional Submissions, Including Safety Update

Additional safety data for this drug was submitted in the 120-day safety update. All safety data from the phase 3 clinical studies were fully reported in the original NDA submission. This update contains periodic Safety Update Reports (PSURs) available from Senju Pharmaceutical Co. from January 15, 2003 to January 14, 2004. The adverse events reported in the current

PSUR are consistent with the events reported in the original NDA submission. There are not new safety concerns raised after review of this update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The relationship between the drug and the ocular adverse events is questionable since many of the events seen are commonly related to intraocular inflammation (for which this drug is being used to treat), or events that are commonly seen after administration of topical drops.

There are however, several adverse events that are specifically drug related and have been observed with the use of all drugs in the class. These events include: epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration and corneal perforation. These events were observed in the post marketing database from Japan. They were not observed in the phase 3 trials since the events are directly linked to off-label use in terms of dosing duration and frequency.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Pooled and individual data was used in this review to adequately assess the safety profile of bromfenac sodium. The data from ISTA-BR-CS001-ER and ISTA-BR-CS001-WR were pooled to assess safety. These studies were well-controlled studies conducted under an identical protocol. The studies were geographically split between the eastern region and western region of the United States.

The data from the studies conducted by Senju Pharmaceuticals in Japan to support marketing approval was not pooled due to study design issues. The data are considered supportive to the clinical safety review.

7.4.1.2 Combining data

Study ISTA-BR-CS001-ER and ISTA-BR-CS001-WR were pooled by simply combining the numerator events and denominators. No other formal weighting methods were used.

7.4.2 Explorations for Predictive Factors

N/A – this review has not revealed specific drug-related adverse events or demographic effects on the safety profile.

7.4.2.1 Explorations for dose dependency for adverse findings

N/A – see section 7.4.2

7.4.2.2 Explorations for time dependency for adverse findings

N/A – see section 7.4.2

7.4.2.3 Explorations for drug-demographic interactions

N/A – see section 7.4.2

7.4.2.4 Explorations for drug-disease interactions

N/A – see section 7.4.2

7.4.2.5 Explorations for drug-drug interactions

N/A – see section 7.4.2

7.4.3 Causality Determination

See sections 7.1.5.5 and 7.3 for discussion concerning causality.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dosing of bromfenac sodium (one drop twice daily for 14 days following cataract surgery) is appropriate based on the clinical data provided. Efficacy for this product was demonstrated and there was an acceptable safety profile when dosed at this level. There are no recommended dose modifications for special populations.

8.2 Drug-Drug Interactions

N/A - drug – drug interactions were not evaluated.

8.3 Special Populations

There are no dosing modifications needed for any of the special populations (e.g. demographics, hepatic or renal insufficiency, etc). This is common for topical ophthalmic drops due to the concentrations and dosing amounts and the limited systemic availability.

8.4 Pediatrics

The applicant requested a waiver of pediatric studies on the basis that this drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients (age 16 years and under) and is not likely to be used in a substantial number of pediatric patients. The division recommends that a waiver of pediatric studies be granted for this indication. .

8.5 Advisory Committee Meeting

N/A – an advisory committee meeting was not held for this drug product.

8.6 Literature Review

N/A – there are no literature references in this submission.

8.7 Postmarketing Risk Management Plan

N/A - the applicant has not submitted a postmarketing management plan, nor is one recommended.

8.8 Other Relevant Materials

Consult reviews from DDMAC and DMETS have found the proprietary name, Xibrom acceptable. Changes were recommended in the precaution section of the package insert to maintain consistency with other topical NSAID's by DDMAC. Additionally, changes were recommended in the adverse event section. DMETS has also recommended changes in the container and carton labeling to minimize potential errors with the use of Xibrom.

All changes recommended by these consults will be reviewed and implemented in the final label review where appropriate.

9 OVERALL ASSESSMENT

9.1 Conclusions

This NDA supports the use of Xibrom (bromfenac sodium ophthalmic solution) for the treatment of post-cataract surgery inflammation. Bromfenac sodium has demonstrated superiority to vehicle in two adequate and well controlled trials in the ability to clear ocular inflammation following cataract surgery. The safety profile of this drug product is consistent with other products in the topical NSAID class. There are no new unexpected adverse events associated with the use of this product. The benefits of bromfenac sodium outweigh the risks in the treatment of ocular inflammation following cataract surgery.

9.2 Recommendation on Regulatory Action

NDA 21-664 is recommended for approval after labeling revisions are made consistent with the recommendation listed in this review. There are no other unresolved regulatory issues.

9.3 Recommendation on Postmarketing Actions

N/A – there are no recommended postmarketing actions.

9.3.1 Risk Management Activity

N/A – there are no recommended postmarketing risk management activities.

9.3.2 Required Phase 4 Commitments

There are no Phase 4 commitments recommended for this drug product.

9.3.3 Other Phase 4 Requests

N/A – there are no Phase 4 commitments recommended for this drug product.

9.4 Labeling Review

9.5 Comments to Applicant

N/A – There are no deficiencies other than labeling recommendations to be conveyed to the sponsor. The NDA is recommended for approval.

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✓ Trade Secret / Confidential

_____ Draft Labeling

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Withheld Track Number: Medical- ✓

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