CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203168Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	203168
Supporting document/s:	000
Applicant's letter date:	6/5/2012
CDER stamp date:	6/7/2012
Product:	Prolensa™: bromfenac ophthalmic solution, 0.07%
Indication:	Treatment of inflammation and pain associated with cataract extraction
Applicant:	ISTA Pharmaceuticals, Inc
Review Division:	CDER/OAP/Division of Transplant and Ophthalmology Products
Reviewer:	Robeena Aziz, MPH, PhD
Supervisor/Team Leader:	Lori Kotch, PhD, DABT
Division Director:	Renata Albrecht, MD
Project Manager:	Michael Puglisi

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203168 are owned by ISTA Pharmaceuticals, Inc or are data for which ISTA Pharmaceuticals, Inc has obtained a written right of reference. Any information or data necessary for approval of NDA 203168 that ISTA Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203168.

TABLE OF CONTENTS

Table of Tables

1 Executive Summary

1.1 Introduction

The sponsor (ISTA Pharmaceuticals, Inc) is submitting this NDA application for bromfenac ophthalmic solution, 0.07% (also referred to bromfenac sodium, or bromfenac in this review). Bromfenac ophthalmic solution 0.07% is a topical, nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of inflammation and pain associated with cataract extraction. Patients will apply one drop to affected eye(s) once daily beginning one day prior to cataract surgery, on the day of surgery, and through 14 days post surgery.

The indication is the same as the currently marketed product, Bromday™ (bromfenac ophthalmic solution) 0.09%, administered once daily (sNDA 021664 for Bromday™ FDA approval on 10/2010) and Xibrom™ administered twice daily (NDA 21644 FDA approval 3/2005). The bromfenac ophthalmic solution 0.07% formulation in the current submission differs from the currently marketed bromfenac 0.09% product in the amounts of bromfenac sodium and its target pH. (b) (4) The same manufacturer, Regis Technologies, will continue to supply the bromfenac sodium solution.

The oral formulation of bromfenac (Duract capsules) was developed by Wyeth-Ayerst and was approved for marketing under NDA 20 535 in 1997. However, due to 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 in Japan (Bronuck®; bromfenac sodium ophthalmic solution, 0.1% dosed BID). The Japanese formulation is identical to the US product, with the concentration of the active shown as the salt form (0.1% bromfenac sodium) rather than the free acid (0.09% bromfenac), respectively. Bronuck was approved in Japan in July 2000, and is indicated for the treatment of blepharitis, conjunctivitis, scleritis (including episcleritis) and post-operative inflammation.

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. The nonclinical studies to support this NDA application are referenced to the approved products mentioned above.

This indication in the current submission is supported by two clinical trials (Studies Nos. S00124-ER and S00124-WR) to evaluate the efficacy and safety of bromfenac ophthalmic solution 0.07% vs. placebo for the treatment of ocular inflammation and pain associated with cataract surgery.

1.2 Brief Discussion of Nonclinical Findings

The sponsor referred to the nonclinical information submitted to NDAs 21 644 (bromfenac solution, 0.09%) and 20 535 (bromfenac sodium capsules) for nonclinical support for the current NDA application. NDA 21 644 was reviewed by Dr. Conrad H. Chen, PhD.

No additional nonclinical studies were required for this current NDA. However, in a pre-NDA meeting held on 8/29/2011, FDA requested a comparison of the excipients in the new formulation and the previously approved 0.09% formulation. This comparison consists of three pharmacokinetic distribution studies, as well as a toxicology study conducted with a higher concentration of bromfenac (0.18%) at the same pH and with similar excipients as the proposed formulation. All studies were conducted in rabbits. Table 1 outlines the studies.

Table 1: List of nonclinical studies conducted supporting bromfenac ophthalmic solution, 0.07%

Type of study	Description of study	Route of administration	Study No.
Pharmacokinetics			
Distribution [1] *(rabbits)*	12-hour aqueous humor pharmacokinetics with Xibrom – 0.09% and 0.08% Bromfenac	topical ocular instillation	NP050905
	12-hour aqueous humor pharmacokinetics with Xibrom QD – 0.18% and 0.20% Bromfenac	topical ocular instillation	NP051001
	12-hour aqueous humor pharmacokinetics with Xibrom QD – 0.18%, Bromfenac, (b) (4) Tyloxapol, (b) (4) Sodium Sulfite and (Xibrom QD - 0.18% Bromfenac, (b) (4) Tyloxapol, (b) (4) Sodium Sulfite)	topical ocular instillation	NP060702
Toxicology			
Topical instillation studies[2] *(rabbits)*	Toxicity of different formulations of bromfenac ophthalmic solutions when administered at varying frequencies daily for 28 days	topical ocular instillation	POS00004

[1] *The distribution studies were not GLP compliant.*

[2]*The toxicology study was GLP compliant.*

Summary of pharmacokinetics distribution studies:
The sponsor submitted three individual distribution studies using multiple formulations and concentrations of bromfenac ophthalmic solutions containing ^{14}C-labeled bromfenac (See Table 1 for Study Nos.). The solutions were administered by ocular instillation to rabbits, and the aqueous humor levels of radioactivity were measured at 1, 2, 4, 8, and 12 hours following instillation. The results of these studies showed that after 8 and 12 hours, the 0.18% bromfenac ophthalmic solution achieved twice the aqueous humor bromfenac concentration of the currently approved 0.09% formulation (see specific study reviews for details). The increased aqueous humor levels was attributed to the increased concentration of active ingredient, and the lower pH of the formula [pH=7.8 (in 0.18% formulation) vs. pH=8.3 (in 0.09% formulation)].

Summary of toxicology studies (topical instillation study):
In the toxicology study, two formulations of bromfenac ophthalmic solution (0.18% and 0.08%) were administered at varying frequencies for 28 days by ocular administration to rabbits (See Table 1 for Study No.). The 0.08% formulation differed from the 0.18% formulation in that it contained (b) (4) sodium sulfite, and was formulated at a pH of 8.3 (as compared to pH 7.8 in 0.18% formulation). Sodium sulfite has been used in the approved 0.09% formulation at a (b) (4) and the same amount will be used in the current 0.07% formulation. For each formulation, there were 3 study groups of rabbits (N=4/sex/dose) with instillation frequencies of 1, 2 and 4 times per day, respectively, for the three 0.18% bromfenac study groups; and instillation frequencies of 2, 4 and 8 times per day, respectively, for the three 0.08% bromfenac study groups. At each instillation, a 50 µL drop of test article were administered into the right eye, and 50 µL of saline solution was administered into the left eye.

There was no mortality during the study. Clinical abnormalities included a slight ocular discharge on 2 occasions during the study at 2 instillation time points (once following a test article instillation, and once following a saline control instillation). These observations, however, were not considered to be drug related. There were no ocular abnormalities in any of the rabbits during ophthalmic examinations. All animals exceeded their initial body weight at study termination (Day 29). Furthermore, there were no remarkable changes and/or findings in gross necropsy or histopathological examination at study termination (Day 29). Therefore, the bromfenac ophthalmic solutions were considered to be non-toxic and nonirritating to the rabbit eye when administered for 28 consecutive days at a concentration of 0.08% (8 times per day at approximate 1-hour intervals) or at a concentration of 0.18% (4 times per day at approximate 2-hour intervals).

1.3 Recommendations

1.3.1 Approvability

From a pharmacology/toxicology perspective, approval is recommended.

1.3.2 Additional Non Clinical Recommendations

Labeling changes:

For all nonclinical sections of the label (i.e. 8.1, 8.3, 12.1 and 13.1) the proposed labeling is similar to that of Bromday® and Xibrom™ 0.09% (NDA 21 664). The recommended reviewer's changes to the sponsor-proposed label were made to adjust for mg/m^2 scaling in systemic studies, ensure correct use of terminology (teratogen-), and to include effects that were omitted in the sponsor's proposed label (i.e. dystocia and delayed parturition).

Italics and blue = additions
Strikethrough and red = deletions

8.1 Pregnancy

(b) (4)

(b) (4) *Treatment of rats at oral doses up to 0.9 mg/kg/day* (b) (4) *and rabbits at oral doses up to 7.5 mg/kg/day* (b) (4) *produced no treatment-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3mg/kg/day* (b) (4) *and dystocia, increased neonatal mortality and reduced postnatal growth at 0.9mg/kg/day.*

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.

(b) (4)

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

8.3 Nursing Mothers

Caution should be exercised when Prolensa ophthalmic solution is administered to a nursing woman

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.

13 NONCLINICAL TOXICOLOGY

13.1 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 (b) (4) and 5 mg/kg/day (b) (4) 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 (b) (4)

2 Drug Information

2.1 Drug: Bromfenac sodium, 0.07%

CAS Registry Number (Optional): 120638-55-3

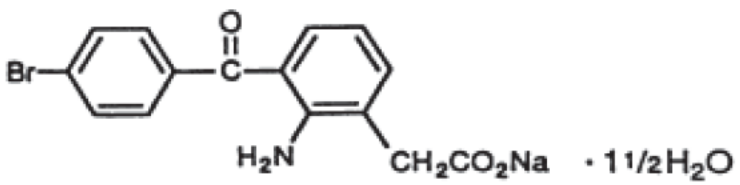
Generic Name: bromfenac sodium, bromfenac

Code Name: AHR-10282B, WAX-121165A

Chemical Name: sodium [2-amino-3-(4-bromobenzoyl) phenyl] acetate sesquihydrate or benzeneacetic acid, 2-amino-3-(4-brombobenzoyl)-, monosodium salt, sesquihydrate

Molecular Formula/Molecular Weight: $C_{15}H_{11}BrNNaO_3$/383 g/mole

Structure or Biochemical Description



Pharmacologic Class: non-steroidal anti-inflammatory drug

2.2 Relevant INDs and NDAs

IND/NDA number	Description of submission	Indication	Approval date if applicable
INDs			
60 295	Bromfenac sodium hydrate ophthalmic solution	Treatment of post-operative ocular inflammation in patients who have undergone cataract extraction with posterior chamber intraocular lens implantation	N/A
NDAs			
sNDA 21 664 – Bromday™ 0.09% **QD dosing**	bromfenac sodium hydrate ophthalmic solution drops	Treatment of postoperative inflammation in patients who have undergone cataract extraction beginning 1 day prior to cataract surgery, continue on the day of surgery, and for 14 days after cataract surgery	10/2010
NDA 21 664 – Xibrom™ 0.09% **BID dosing**	bromfenac sodium hydrate ophthalmic solution drops	Treatment of postoperative inflammation in patients who have undergone cataract extraction beginning 1 day prior to cataract surgery, continue on the day of surgery, and for 14 days after cataract surgery	03/2005
NDA 20 535 – Duract® (Letter of Authorization provided – Pfizer)	bromfenac sodium capsules	short-term management of acute and chronic pain	Withdrawn in 6/1998

2.3 Drug Formulation

The drug substance, bromfenac sodium, formulated as an ophthalmic solution was approved March 2005. Regis Technologies will continue to supply bromfenac sodium manufactured according to Senju Pharmaceutical's DMF 16414. The DMF was updated in August 2011. Table 2 lists the qualitative and quantitative composition of the 0.07% formulation.

Table 2: Qualitative and quantitative composition of bromfenac ophthalmic solution, 0.07%

Component	Function	Bromfenac ophthalmic solution 0.07% (b) (4) (b) (4)
Bromfenac sodium sesquihydrate	Active ingredient	0.0805[1]
Boric acid	(b) (4)	
Sodium borate		
Sodium sulfite		
Edetate disodium (EDTA)		
Tyloxapol		
Benzalkonium chloride	Preservative	0.005
Povidone (b) (4)	(b) (4)	
Sodium hydroxide[2]	pH adjuster	q.s. to pH 7.8
(b) (4)		

[1] Equivalent to 0.07 bromfenac free acid

[2] Only if necessary to adjust pH to 7.8

(b) (4)

2.4 Comments on Novel Excipients

All excipients meet current USP/NF criteria and are within the limits of the previously previous approved ophthalmic product, bromfenac ophthalmic solution, 0.09% (NDA 21664- Xibrom™ 0.09%), with the following exceptions (see Table 3):

- the 0.07% formulation differs in the drug (API) concentration (b) (4)
- differs in pH
- differs in use of tyloxapol, rather than (b) (4)

Sodium sulfite (at proposed (b) (4) was not included in the 0.18% nonclinical batch used for nonclinical toxicology study, but was included in the 0.08% batch (Study No. POS00004 – a topical ocular instillation study). Additionally, the current 0.07% formulation will contain the same concentration of sodium sulfite as that contained in the currently approved bromfenac 0.09% formulation (NDA 21644- Xibrom™ 0.09%), No serious adverse events attributed to (b) (4) have been reported to date. As such, this amount of sodium sulfite to be added to the 0.07% formulation is considered qualified by existing clinical data, as well as provided nonclinical data.

Table 3: Comparison Table of proposed, approved and nonclinical toxicology study formulation

Ingredient	0.07% Bromfenac [1] %w/v	Bromday®/Xibrom™ 0.09% %w/v	0.18% Formula %w/v
Bromfenac Sodium Sesquihydrate	0.0805	(b) (4)	(b) (4)
Boric Acid	(b) (4)		
Sodium Borate (decahydrate)			
(b) (4)			
Sodium sulfite			
EDTA			
(b) (4)			
Tyloxapol			
BAK	0.005		
Povidone	(b) (4)		
NaOH	pH to 7.8		

[1] All excipients in the 0.07% formulation can be found in other approved ophthalmic drug products.

2.5 Comments on Impurities/Degradants of Concern

There are no pharmacology/toxicology concerns regarding impurities. Table 4 lists the impurities presented in the 0.07% formulation. The acceptance criteria for the specified impurities are set at or lower than (b) (4) which is the identification threshold according ICH Q3B.

Table 4: List of impurities present in bromfenac ophthalmic solution, 0.07%

Compound Identification	Chemical Name
(b) (4)	

2.6 Proposed Clinical Population and Dosing Regimen

- Proposed clinical population: patients who have undergone cataract extraction
- Dosing regimen: Apply one drop to affected eye(s) once daily beginning one day prior to cataract surgery, on the day of surgery, and through 14 days post surgery.

2.7 Regulatory Background

- A Type B meeting (pre-NDA) was held with FDA on 8/29/11

3 Studies Submitted

3.1 Studies Reviewed

Three pharmacokinetic distribution studies and one toxicology study was reviewed in the current submission (see below). All other studies were reviewed under previous NDAs listed in Section 2.2 – Relevant INDs and NDAs.

Pharmacokinetics - Distribution

Study Title	Study No.	Module
12-hour evaluation of the aqueous humor pharmacokinetics of two formulations of ^{14}C labeled bromfenac following topical instillation into the eyes of New Zealand White Rabbits	NP050905	4.2.2.3
12-hour evaluation of the aqueous humor pharmacokinetics of two formulations of ^{14}C labeled bromfenac following topical instillation into the eyes of New Zealand White Rabbits	NP051001	4.2.2.3
12-hour evaluation of the aqueous humor pharmacokinetics of two formulations of ^{14}C labeled bromfenac following topical instillation into the eyes of New Zealand White Rabbits	NP050905	4.2.2.3

Toxicology

Study Title	Study No.	Module
A 28-day toxicity study of bromfenac ophthalmic solutions administered by the ocular route to rabbits	POS00004	4.2.2.2

3.2 Studies Not Reviewed

All were reviewed under the relevant INDs and NDAs.

3.3 Previous Reviews Referenced

Please see Section 2.2 - Relevant INDs and NDAs above

4 Pharmacology

4.1 Primary Pharmacology

No additional studies were needed to support the current submission. Secondary pharmacology studies using bromfenac sodium was evaluated by Wyeth-Ayerst under NDA 20 535. The completed primary and secondary pharmacology studies were intended to provide proof of-concept for the drug.

4.2 Secondary Pharmacology

No additional studies were needed to support the current submission. Secondary pharmacology studies using bromfenac sodium was evaluated by Wyeth-Ayerst under NDA 20 535.

.

4.3 Safety Pharmacology

No additional studies were needed to support the current submission. A battery of safety pharmacology studies following oral and IV dosing in several species using bromfenac sodium was evaluated by Wyeth-Ayerst under NDA 20 535.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Early studies conducted by Wyeth-Ayerst (NDA 20 535) established the bioavailability, general pharmacokinetics, excretion routes and rates, protein binding, and metabolic pathway of bromfenac sodium when given both oral and IV routes. Senju Pharmaceuticals conducted studies examining the distribution and metabolism of radio-labeled bromfenac sodium in ocular tissues following topical ocular instillation of an ophthalmic solution in rabbits. For the current submission, three additional studies were conducted by the Sponsor to measure bromfenac levels of various formulations in the aqueous humor of rabbits. All pharmacokinetic studies are listed in Table 1 and are reviewed below.

.

NP050905: 12-hour evaluation of the aqueous humor pharmacokinetics of two formulations of ^{14}C labeled bromfenac following topical instillation into the eyes of New Zealand White Rabbits

Key Study Findings:

- The currently approved 0.09% formulation achieved peak levels of 0.064 ppm bromfenac in the aqueous humor at two hours, with levels decreasing to 0.009 ppm at 12 hours.
- The new 0.08% formulation achieved peak levels of 0.093 ppm bromfenac in the aqueous humor at two hours, with levels decreasing to 0.005 ppm at 12 hours.
- Thus the 0.08% formulation showed a somewhat higher level of mean bromfenac concentration in the aqueous humor. The clinical formulation in the current submission is similar in composition to the new 0.08% formulation.
- Summary of findings are listed in Table 5.

Table 5: Mean ppm of bromfenac in aqueous humor at indicated time after instillation (mean of 2 rabbits at each time-point)

Ophthalmic Solution	1 hr	2 hr	4 hr	8 hr	12 hr
0.09% bromfenac solution	0.032	0.064	0.039	0.022	0.009
0.08% bromfenac solution	0.064	0.093	0.036	0.011	0.005

(b) (4) NaOH, Water: q.s. both formulations

Report #:	NP050905
Study report location:	Module 4.2.3.3
Conducting Laboratory and Location:	(b) (4)
Date of Study Initiation	9/28/2005
GLP Compliance	No

QA Report: No

Drug and lot #:
- ^{14}C bromfenac sodium; CP-2301
- Formula 1 - Xibrom 0.09% vehicle; Lot No. 0250-45-2
- Formula 2 - New Xibrom 0.08% vehicle; Lot No. 0250-44-2

Doses: Single dose on Day 1(50 µL or 0.046 mg) using a calibrated pipette, into the right eye of each animal

Species/strain: Rabbits / New Zealand White

Number/sex/group or time point: 20 females assigned to 10 study groups (2 females/dose)

Group	No.	Test Article (Right Eye)	Route	Dose Volume	Necropsy (Time Post-Dose)
A	2	Formula 1 (Xibrom – 0.09%)	Topical ocular instillation	50 µL	1 hour ± 5 minutes
B	2	Formula 1 (Xibrom – 0.09%)	Topical ocular instillation	50 µL	2 hours ± 15 minutes
C	2	Formula 1 (Xibrom – 0.09%)	Topical ocular instillation	50 µL	4 hours ± 15 minutes
D	2	Formula 1 (Xibrom – 0.09%)	Topical ocular instillation	50 µL	8 hours ± 15 minutes
E	2	Formula 1 (Xibrom – 0.09%)	Topical ocular instillation	50 µL	12 hours ± 15 minutes
F	2	Formula 2 (New Xibrom – 0.08%)	Topical ocular instillation	50 µL	1 hour ± 5 minutes
G	2	Formula 2 (New Xibrom – 0.08%)	Topical ocular instillation	50 µL	2 hours ± 15 minutes
H	2	Formula 2 (New Xibrom – 0.08%)	Topical ocular instillation	50 µL	4 hours ± 15 minutes
I	2	Formula 2 (New Xibrom – 0.08%)	Topical ocular instillation	50 µL	8 hours ± 15 minutes
J	2	Formula 2 (New Xibrom – 0.08%)	Topical ocular instillation	50 µL	12 hours ± 15 minutes

Route: Topical ocular instillation into the conjunctival sac

Vehicle Formulation:

Ophthalmic Solution	Bromfenac	Boric acid	Sodium borate	(b) (4)	Sodium sulfite	Disodium edetate	Tyloxapol	Benzalkonium chloride	Povidone
0.09% Formulation Concentration (currently approved under NDA 021664)	0.09%	(b) (4)							
0.08% Formulation Concentration (developmental formulation)	0.08%								

Age: 12 weeks

Weight: 2.5 to 3 kg

Parameters measured:
- Body weights
- Mortality/morbidity
- Aqueous humor sample was collected from the dosed eye of each animal at necropsy.
- Radioactivity for ^{14}C bromfenac present in the aqueous humor samples was determined by LSC.
- Sampling time 1 to 12 hours

NP051001: 12-hour evaluation of the aqueous humor pharmacokinetics of two formulations of ^{14}C labeled bromfenac following topical instillation into the eyes of New Zealand White Rabbits

Key Study Findings:

- The new 0.18% formulation achieved peak levels of 0.567 ppm bromfenac in the aqueous humor at two hours, with levels decreasing to 0.017 ppm at 12 hours.
- The new 0.20% formulation achieved peak levels of 0.265 ppm bromfenac in the aqueous humor at two hours, with levels decreasing to 0.012 ppm at 12 hours.
- Thus, compared to Study No. NP050905, the bromfenac concentration for the 0.18% formulation was approximately twice that for the 0.09% formulation.
- Summary of findings are listed in Table 6.

Table 6: Mean ppm of bromfenac in aqueous humor at indicated time after instillation (mean of 2 rabbits at each time-point)

Ophthalmic Solution	1 hr	2 hr	4 hr	8 hr	12 hr
0.18% bromfenac solution	0.234	0.567	0.176	0.043	0.017
0.20% bromfenac solution	0.414	0.265	0.137	0.058	0.012

(b) (4) NaOH, Water: q.s. both formulations

Report #:	NP051001
Study report location:	Module 4.2.3.3
Conducting Laboratory and Location:	(b) (4)
Date of Study Initiation	9/28/2005
GLP Compliance	No
QA Report	No
Drug and lot #	▪ ^{14}C bromfenac sodium; CP-2301 ▪ Formula 1 - New Xibrom 0.18%; Lot No. ISTA-R-05-0252-12-A ▪ Formula 2 - New Xibrom 0.20% Lot No. ISTA-R-05-0252-12-B
Doses	Single dose on Day 1 (0.060 - 0.090 mg/animal for 0.18% formula; and 0.055 - 0.099 mg/animal for the 0.20% formula) using a calibrated pipette into the right eye of each animal
Species/ strain	Rabbits / New Zealand White
NUMBER/ SEX/ GROUP OR TIMEPOINT	20 females assigned to 10 study groups (2 females/dose)
Route	Topical ocular instillation into the conjunctival sac

Vehicle Formulation

Ophthalmic Solution	Bromfenac	Boric acid	Sodium borate	(b) (4)	Sodium sulfite	Disodium edetate	Tyloxapol	Benzalkonium chloride	Povidone
0.18% Formulation Concentration (developmental formulation)	(b) (4)								
0.20% Formulation Concentration (developmental formulation)									

Age 11 weeks

Weight 1.71-2.55 kg

Parameter measured
- Body weights
- Mortality/morbidity
- Aqueous humor sample was collected from the dosed eye of each animal at necropsy.
- Radioactivity for ^{14}C bromfenac present in the aqueous humor samples was determined by LSC.
- Sampling time 1 to 12 hours

NP060702: 12-hour evaluation of the aqueous humor pharmacokinetics of two formulations of ^{14}C labeled bromfenac following topical instillation into the eyes of New Zealand White Rabbits

Report #:	NP060702
Study report location:	Module 4.2.3.3
Conducting Laboratory and Location:	(b) (4)
Date of Study Initiation	9/18/06
GLP Compliance	No
QA Report	Yes (), No (x)
Drug and lot #	^{14}C bromfenac sodium; CP-2301 Formula 1 and 2 – New Xibrom 0.18%; Lot No. CP-2301

Key Study Findings:
- This study compared two different 0.18% formulations; one with (b) (4) tyloxapol, (b) (4) sodium sulfite (Formula 1) and one with (b) (4) tyloxapol, (b) (4) sodium sulfite (Formula 2).
- *Note the clinical formulation contains tyloxapol at* (b) (4) *and sodium sulfite at*

(b) (4)

- Formula 1 achieved peak levels of 0.225 ppm bromfenac in the aqueous humor at two hours, with levels decreasing to 0.016 ppm at 12 hours.
- Formula 2 achieved peak levels of 0.111 ppm bromfenac in the aqueous humor at two hours, with levels decreasing to 0.008 ppm at 12 hours.
- Thus at 2 hours, an increase in the concentration of tyloxapol and sodium sulfite (Formula 2) resulted in approximately half of mean bromfenac in the aqueous humor when compared to Formula 1 where the levels of tyloxapol and sodium sulfite were lower.
- Summary of findings are listed in Table 7.

Table 7: Mean ppm of bromfenac in aqueous humor at indicated time after instillation (mean of 3 rabbits at each time-point)

Ophthalmic Solution	1 hr	2 hr	4 hr	8 hr	12 hr
Formula #1	0.200	0.225	0.148	0.036	0.016
Formula #2	0.205	0.111	0.082	0.023	0.008

(b) (4) NaOH, Water: q.s. both formulations

Doses: Single dose on Day 1, 0.58 - 0.9 mg/eye using a calibrated pipette into the light eye of each animal

Species/strain: Rabbits / New Zealand White

Number/sex/ Group: 30 females assigned to 10 study groups (3 females/dose)

Route: Topical ocular instillation into the conjunctival sac

Vehicle Formulation

0.18% Ophthalmic Solution	Bromfenac	Boric acid	Sodium borate	(b) (4) Sodium sulfite	Disodium edetate	Tyloxapol	Benzalkonium chloride	Povidone
Formula #1								(b) (4)
Formula #2								

Age: 14-18 weeks

Weight: 2.11-2.73 kg

Parameters measured:

- Body weights
- Mortality/morbidity
- Aqueous humor sample was collected from the dosed eye of each animal at necropsy.
- Radioactivity for ^{14}C bromfenac present in the aqueous humor samples was determined by LSC.
- Sampling time 1 to 12 hours

6 General Toxicology

6.1 Single-Dose Toxicity

No additional studies were needed to support the current submission. Single dose toxicology studies using bromfenac sodium was evaluated by Wyeth-Ayerst under NDA 20 535.

6.2 Repeat-Dose Toxicity

Repeat dose toxicology studies using bromfenac sodium were evaluated by Wyeth-Ayerst under NDA 20 535. The systemic toxicity studies for bromfenac sodium were previously reviewed under NDA 21-535. In the current submission, the sponsor submitted a topical instillation study in rabbits (Study No. POS00004) which tested two formulations of bromfenac ophthalmic solution administered by ocular administration to New Zealand white rabbits (0.18% and 0.08%), at varying frequencies for 28 days. The 0.08% formulation differed from the 0.18% formulation in that it contained sodium sulfite, and was formulated at a pH of 8.3. The current formulation for this NDA submission contains sodium sulfite at the same level that was tested in the toxicology study (b) (4)

POS00004: A 28-Day toxicity study of bromfenac ophthalmic solutions administered by the ocular route to rabbits

Study no.:	POS00004
Study report location:	Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	1/16/06
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and purity,:	▪ 0.08% Bromfenac Ophthalmic Solution;PA-LAB-120505 1-A; 93% ▪ 0.18% Bromfenac Ophthalmic Solution; PA-LAB-1205051-B; 98%

Key Study Findings:

- No mortality was observed throughout the study.
- Clinical observations included a slight ocular discharge on in 1/4 control eyes in Group 2 [0.08% Bromfenac (4x/day)] males on Day 23 and in 1/4 test eyes in Group 6 [0.18% Bromfenac (4x/day)] males on Day 5.
- No ocular abnormalities were observed in any of the rabbits during ophthalmic examinations.
- No remarkable changes in body weight, gross pathology and histopathology on Day 29 (end of study).
- In conclusion, both bromfenac ophthalmic solutions were considered to be non-toxic and non-irritating to the rabbit eye when administered for 28 consecutive days at a concentration of 0.08% (up to 8x/day at approximate one-hour intervals) or at a concentration of 0.18% (4x/day at approximate two-hour intervals). Thus, the NOAEL was established at 0.18% bromfenac ophthalmic solution instilled 1 drop (50µL) per eye, 4x/day for 28 days.

Methods

Doses: 0.08% and 0.18% solution

Frequency of dosing:
- 0.08% solution: 2x, 4x, and 8x/day for 28 days consecutive days
- 0.18% solution: 1x, 2x, and 4x/day for 28 days consecutive days

Route of administration: Topical ocular instillation into the conjunctival sac of the right eye (test article) and left eye (vehicle)

Dose volume: 50 µL

Formulation/Vehicle: 0.9% USP Sterile Saline for Injection

Species/Strain: Rabbits/ New Zealand White

Number/Sex/Group: 4

Age: 8 – 14 weeks

Weight: Approximately 2.0 to 3.5 kg

Satellite groups: none

Parameters measured:
- Mortality/morbidity
- Clinical observations
- Body weights
- Gross pathology
- Histopathology

Deviation from study protocol: None with an impact on the validity of the data

Table 8: Study protocol

Treatment Regimen

Group No.	No. of Animals		Test Material	Dose Volume (µL)[a]	Dosing Frequency	Dosing Intervals	Necropsy Day
	Males	Females					
1	4	4	0. 08% Bromfenac	50	2x	~8 hours	29
2	4	4	0. 08% Bromfenac	50	4x	~2 hours	29
3	4	4	0. 08% Bromfenac	50	8x	~1 hour	29
4	4	4	0. 18% Bromfenac	50	1x	N/A	29
5	4	4	0. 18% Bromfenac	50	2x	~8 hours	29
6	4	4	0. 18% Bromfenac	50	4x	~2 hours	29

Note: N/A = not applicable.
[a]The test article was administered to the right eye. Sterile saline was administered to the left eye at the same dose volume and frequency listed for the test article for each group.

Observations and Results

Observations	**Observations taken**	**Results**
Mortality	Twice daily, in the morning and afternoon	None
Clinical Signs	Day -1 and prior to dosing on Days 1, 8, 15, 22 and 28	Slight ocular discharge on in 1/4 control eyes in Group 2 [0.08% Bromfenac (4x/day)]

		males on Day 23 and in 1/4 test eyes in Group 6 [0.18% Bromfenac (4x/day)] males on Day 5
Body Weights	Days - 1, 1, 8, 15, 22 and 28. In addition, a final fasted body weight was recorded on the day of scheduled euthanasia (Day 29).	Unremarkable
Ophthalmoscopy	Days 1 to 28. The eyes were macroscopically examined with the aid of an auxiliary light source for signs of irritation prior to each initial daily dosing according to the Ocular Grading System, which is based on Draize. A biomicroscopic slit-lamp was also utilized to further clarify ocular lesions	Unremarkable
Gross Pathology	All animals on Day 29	Unremarkable
Histopathology	The eyes were collected from all animals, processed histologically and examined microscopically in all animals on Day 29.	Unremarkable

7 Genetic Toxicology

No additional studies were needed to support the current submission. Genetic toxicology studies using bromfenac sodium were evaluated by Wyeth-Ayerst under NDA 20 535.

7.4 Other Genetic Toxicity Studies

See note regarding genetic toxicology studies.

8 Carcinogenicity

No additional studies were needed to support the current submission. Carcinogenicity studies using bromfenac sodium were evaluated by Wyeth-Ayerst under NDA 20 535.

9 Reproductive and Developmental Toxicology

No additional Reproductive and Developmental Toxicology studies were needed to support the current submission. Reproductive and developmental toxicology studies using bromfenac sodium were evaluated by Wyeth-Ayerst under NDA 20 535 (cross referenced).

10 Special Toxicology Studies

No special toxicology studies were submitted.

11 Integrated Summary and Safety Evaluation

In the current submission, the Sponsor (ISTA Pharmaceuticals, Inc) is submitting an application for bromfenac ophthalmic solution, 0.07% (bromfenac sodium or bromfenac). Bromfenac ophthalmic solution 0.07% is a topical, nonsteroidal anti-inflammatory drug (NSAID) that inhibits both cyclooxygenase 1 and 2. Mechanism of action studies showed that bromfenac sodium had anti-inflammatory, anti-pyretic, and analgesic effects. Bromfenac ophthalmic solution, 0.07% is indicated for treatment of inflammation and pain following ocular surgery. The proposed clinical dose is ocular administration of one drop to affected eye(s) once daily beginning one day prior to cataract surgery, on the day of surgery, and through 14 days post surgery.

The indication is the same as the currently marketed product, Bromday™ (bromfenac ophthalmic solution) 0.09%, administered once daily (sNDA 21664 FDA approval on 10/2010) and Xibrom™ administered twice daily (NDA 21644 FDA approval 3/2005). The bromfenac ophthalmic solution 0.07% formulation in the current submission differs from the currently marketed bromfenac 0.09% product in the amounts of bromfenac sodium and its target pH. (b) (4) A nonclinical toxicity study was conducted to qualify all components of the new formulation.

Although topical instillation is the intended dosing route in humans, the toxicity of bromfenac sodium was originally studied using the oral route. Most of the following data were submitted by Wyeth-Ayerst supporting their NDA 20535 for oral bromfenac. Additional nonclinical studies to support this NDA application are referenced to FDA approved products Bromday™ (sNDA 21664), Xibrom™ (NDA 21664). NDA and sNDA 21 644 were reviewed by Dr. Conrad H. Chen, PhD.

No additional nonclinical studies were required for this current NDA. However, FDA requested a comparison of the excipients in the new formulation and the previously approved 0.09% formulation. Therefore to support the development and registration of the 0.07% formulation, the Sponsor submitted three pharmacokinetic distribution studies, as well as a toxicology study conducted at a higher concentration of bromfenac (0.18%) at the same pH. This nonclinical formulation also contained similar excipients to those of the proposed clinical formulation. All studies were conducted in rabbits.

The results from the three ocular PK studies showed that after 8 and 12 hours, the 0.18% bromfenac ophthalmic solution achieved twice the aqueous humor bromfenac concentration of the currently approved 0.09% formulation. The increased aqueous humor levels were attributed to the increased concentration of active ingredient, in conjunction with the lower pH of the formula [pH=7.8 (0.18%) vs. pH=8.3 (0.09%)].

The results of the toxicology study showed that bromfenac ophthalmic solutions were considered to be non-toxic and nonirritating to the rabbit eye when administered for 28 consecutive days at a concentration of 0.08% (8 times per day at approximate 1-hour intervals) or at a concentration of 0.18% (4 times per day at approximate 2-hour

intervals). Thus, a NOAEL was established at 0.18% bromfenac ophthalmic solution instilled at 1 unilaterally administered drop (50μL) 4x/day, for 28 days.

The approval of NDA 203 168, bromfenac ophthalmic solution, 0.07% is recommended from the pharmacology/toxicology perspective.

12 Appendix/Attachments

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

/s/

LORI E KOTCH
03/04/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA 203168

NDA Number: **Applicant:** **Stamp Date:**

Drug Name: Bromfenac ophthalmic solution, 0.07%

NDA Type: 203168

Letter date - June 6, 2012

Receipt date -June 7, 2012

(Proposed trade name - Prolensa)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		None
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		None
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		None
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		All nonclinical studies are referenced under NDA 21644 (bromfenac ophthalmic solution approved 3/2005). Original nonclinical data for bromfenac is also under NDA 20 535 bromfenac sodium capsules.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		Formulation to be marketed includes the following changes: ▪ amount of bromfenac sodium (0.09% to 0.07%) ▪ target pH ▪ use of tyloxapol (b) (4) ▪ (b) (4) (all excipients meet current USP/NF criteria) Toxicology studies submitted contains same formulation proposed in the clinical study
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the	X		None

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA 203 168

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA 203168

	Content Parameter	Yes	No	Comment
	alternative route?			
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		None
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		preNDA meeting on 8/29/2011 – no new nonclinical studies were required, however, a comparison of excipients in new formulation and previously approved 0.09% formulation were requested and are included in this submission. A toxicology study was conducted using a higher concentration of bromfenac (0.18%) – >2x higher concentration.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Since the label has not been reviewed, additional comments may be included at a later time.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	At this time, no additional impurity issues have been identified. PT will defer to CMC for definitive decisions regarding impurities
11	Has the applicant addressed any abuse potential issues in the submission?		NA	None
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		NA	This NDA is not intended to support an OTC product.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.
N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA 203168

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None at this time.

Robeena Aziz, MPH, PhD	7/23/2012
Reviewing Pharmacologist	Date
Lori E. Kotch, PhD	7-23-2012
Team Leader/Supervisor	Date

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

/s/

ROBEENA M AZIZ
07/23/2012

LORI E KOTCH
07/23/2012