

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-664**

**PHARMACOLOGY REVIEW**



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## ***EXECUTIVE SUMMARY***

### **I. Recommendations**

#### **A. Recommendation on approvability**

The approval of this NDA is recommended.

#### **B. Recommendation for nonclinical studies**

None

#### **C. Recommendations on labeling**

The proposed labeling is acceptable, except that the Pregnancy Category should be changed from B to C. However, it is recommended that 50  $\mu$ L be used as the volume of one drop (unless a measured volume of a drop is available) in the calculation of ratio of animal dose vs. human dose in the labeling. It is also recommended that 60 kg be used as the average human body weight.

The recommended labeling is as follows.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (360 times the recommended human ophthalmic dose [RHOD] of 1.67  $\mu$ g/kg in a 60 kg person on a mg/kg/basis, assuming 100% absorbed) and 5.0 mg/kg/day (3,000 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 (4,500 times RHOD) revealed no evidence of teratogenicity due to bromfenac. However, 0.9 mg/kg/day in rats caused embryo-fetal lethality, ~~and~~ reduced postnatal growth. Pregnant rabbits treated with 7.5 mg/kg/day caused increased post-implantation loss.

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

**Note:** The ratios of animal dose and human ocular dose in the labeling are calculated using 1.67 µg/kg/day as the human clinical dose.

## II. Summary of nonclinical findings

### A. Brief overview of nonclinical findings

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

### B. Pharmacologic activity

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

### C. Non-clinical safety issues relevant to clinical use

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

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## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 21-664

**Review number:** No.1

**Sequence number/date/type of submission:** SN000/May 24, 2004/ 505 (b)(1), Original Application

**Information to sponsor:** Yes (x) No ( )

**Sponsor and/or agent:** ISTA Pharmaceuticals, Inc.

**Manufacturer for drug substance:** Regis Technologies, Inc., Morton Grove, Illinois

**Reviewer name:** Conrad H. Chen, Ph.D.

**Division name:** Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

**HFD #:** 550

**Review completion date:** January 14, 2005

**Drug:**

Trade name: Xibrom™

Generic name: Bromfenac Sodium Ophthalmic Solution 0.1%

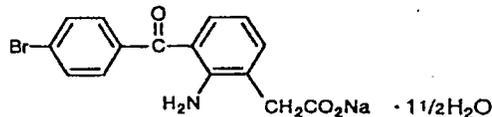
Code name: AHR-10282B

Chemical name: Sodium 2-[amino-3-(4-bromobenzoyl) phenyl] acetate sesquihydrate

CAS registry number: 120638-55-3

Molecular formula/molecular weight: C<sub>15</sub>H<sub>11</sub>BrNNaO<sub>3</sub>·1.5 H<sub>2</sub>O

Structure:



**Relevant INDs/NDAs/DMFs:** IND 60,295 (bromfenac sodium ophthalmic solution) / NDA 20-535 (Duract, bromfenac sodium capsules) / DMF #16414

**Drug class:** NSAID

**Indication:** For the treatment of postoperative inflammation in patients who have undergone cataract extraction

**Clinical formulation:**

**Drug product quantitative composition**

Components	Function	Amount/mL	%
Bromfenac sodium hydrate	Active ingredient	0.001035 g	0.1035*
Boric acid			
Sodium borate			
Sodium sulfite, anhydrous			
Disodium edetate			
Povidone			
Polysorbate 80			
Benzalkonium chloride solution		0.5 g	
Sodium hydroxide			
Purified water			

**Route of administration:** Ophthalmic instillation

**Proposed use:** 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.

**Disclaimer:** Tabular and graphical information are mostly constructed by the sponsor.

**Studies reviewed within this submission:** The non-clinical studies by ocular administration are reviewed in details. The non-clinical studies by oral route, that were submitted previously under NDA 20-535 (Duract capsules), are cross-referenced in this review.

**Studies not reviewed within this submission:** The non-clinical studies previously reviewed under NDA 20-535 are not reviewed but are cross-referenced.

**2.6.2 PHARMACOLOGY**

**2.6.2.1 Brief summary:** Bromfenac sodium, AHR-10282b, is a cyclooxygenase inhibitor possessing analgesic, anti-inflammatory, and antipyretic activities in various animal experimental models. It belongs to a non-steroidal anti-inflammatory drug class (NSAID) without any narcotic-like activity. Bromfenac did not possess any significant effects on the central nervous system and cardiovascular function.

The oral formulation of bromfenac (Duract capsules) was developed by Wyeth-Ayerst and was approved for marketing under NDA 20-535 in 1997. However, because of the clinical findings of hepatotoxicity after marketing, Duract was withdrawn from the market in June 1998.

Bromfenac sodium was licensed to Senju Pharmaceutical Co., Ltd, Osaka, Japan for development as an ophthalmic solution. Senju conducted non-clinical and clinical studies for bromfenac ophthalmic solution and obtained approval for marketing in Japan in 2000.

Senju recently sublicensed bromfenac for ophthalmic use in the United States to ISTA Pharmaceuticals, Inc. The non-clinical studies submitted in this NDA were mostly conducted by Wyeth-Ayerst and Senju Pharmaceuticals.

**2.6.2.2 Primary pharmacodynamics:**

Bromfenac sodium inhibited both arachidonic acid and carrageenan-induced conjunctival edema in a dose-dependent manner, and the increase of aqueous humor protein typically seen in response to paracentesis and laser energy application. Bromfenac sodium demonstrated greater inhibition of acute chemosis in comparison with pranoprofen ophthalmic solution (PPF), an ophthalmic solution marketed in Japan. Further, the inhibition of increased aqueous humor protein induced by paracentesis was 8 to 10 times greater than that seen with PPF. Bromfenac sodium ophthalmic solution instilled QID demonstrated significant inhibition in the experimental uveitis rabbit model (a chronic ocular inflammation model), and its effect was maintained when the frequency of instillation was reduced to BID. In the same model, PPF demonstrated significant inhibition when instilled QID but not BID.

**Table 2.6.2.1-1: Pharmacodynamic Studies for Bromfenac Sodium (AHR-10282B)**

	Study Items (Study Number)	Animal Species	Dose or Administration Method (% - concentration)	Test Result		
				AHR-10282B	Pranoprofen	Dexamethasone
Action against local ocular inflammation	Conjunctival edema induced by arachidonic acid (E-01)	Rat	Topical instillation of AHR-10282B (0.02 - 0.2%) Pranoprofen (0.02 - 0.1%) Dexamethasone (0.02 - 0.1%)	Inhibition rate of 44% with 0.1% BROM, and 18% with 0.02% BROM, p<0.01 compared to control group	Inhibition rate of 40% with 0.1% PPF, and 29% with 0.02% PPF, p<0.01 compared to control group	Inhibition rate of 31% with 0.1% DEX, and 16% with 0.02% DEX, p<0.01 compared to control group
	Conjunctival edema induced by carrageenan (E-01)	Rat	Topical instillation of AHR-10282B (0.02 - 0.2%) Pranoprofen (0.02 - 0.1%) Dexamethasone (0.02 - 0.1%)	Inhibition rate of 45% with 0.05, 0.1 and 0.2% BROM, p<0.01 compared to control group	Inhibition rate of 31% at 0.1%, p<0.01 compared to control group	Inhibition rate of 45% with 0.1% DEX, p<0.01 compared to control group
	Aqueous humor protein concentration after paracentesis (E-01)	Rabbit	Topical instillation of AHR-10282B (0.0025% - 0.2%) Pranoprofen (0.02% - 0.1%)	Dependent on concentration, significant inhibition of protein concentration at ≥0.0025% BROM (inhibition of 93% with 0.1% BROM), ED <sub>50</sub> : 0.0054%	Inhibitory action was noted (79% inhibition with 0.1% PPF), ED <sub>50</sub> : 0.0437%	Not used
	Aqueous humor protein after laser irradiation to iris (E-01)	Rabbit	Topical instillation of AHR-10282B (0.005% - 0.2%), Pranoprofen (0.1%)	Dependent on concentration, significant inhibition at ≥0.01% BROM (inhibition rate of 88% with 0.1% BROM)	Inhibitory action was noted (48% inhibition with 0.1% PPF)	Not used
	BSA-induced uveitis (E-02)	Rabbit	Topical instillation of AHR-10282B (0.02% - 0.2%) Pranoprofen (0.02% - 0.1%) Dexamethasone (0.02% - 0.1%) 1) BID 2) QID	1) Concentration dependent, significant inhibition of 49, 56, 59, and 72% for concentrations of 0.02, 0.05, 0.1, and 0.2% BROM, respectively, 2) Concentration independent, significant inhibition with 0.02 - 0.2% BROM (inhibition of 55 - 59%)	1) No inhibitory effect with 0.02% PPF, and 26% inhibition with 0.1% PPF, 2) Inhibitory activity was noted (46% inhibition with 0.1% PPF)	1) Significant inhibition of 41 and 73% with concentrations of 0.02 and 0.1% DEX, respectively.

BROM: bromfenac  
PPF: pranoprofen  
DEX: dexamethasone  
BID: twice daily  
QID: four times daily

**Mechanism of action:** In a series of animal studies, bromfenac sodium was effective in inhibiting both cyclooxygenase 1 and 2, thereby inhibiting the inflammatory reactions induced by mediators such as prostaglandins.

Table 2.6.2.1-1: Pharmacodynamic Studies for Bromfenac Sodium (AHR-10282B) (continued)

Study Items (Study Number)	Animal Species	Dose or Administration Method	Test Result		
			AHR-10282B	Pranoprofen	Dexamethasone
Inhibition of prostaglandin production of ciliary body of iris (E-01)	Rabbit	~10 <sup>-3</sup> M	Concentration-dependent inhibition, IC <sub>50</sub> : 1.1x10 <sup>-6</sup> M	IC <sub>50</sub> : 11.9x10 <sup>-6</sup> M	Not used
Inhibition of cyclooxygenase obtained from bovine seminal vesicles (E-03)	Cow	~10 <sup>-7</sup> M	IC <sub>50</sub> : 7.5x10 <sup>-6</sup> M	Not conducted	Not used
Selective inhibition of cyclooxygenase (E-04)	rCOX derived from human monocytes	~10 <sup>-8</sup> M	COX1 IC <sub>50</sub> : 5.1x10 <sup>-9</sup> M COX2 IC <sub>50</sub> : 4.0x10 <sup>-9</sup> M	Not conducted	Not used
Platelet aggregation inhibition (E-05)	Rabbit's plasma				Not used
1) Collagen aggregation		1) ~1.0 μM	1) Concentration-dependent, IC <sub>50</sub> : 4.1x 10 <sup>-7</sup> M	1) Concentration-dependent, IC <sub>50</sub> : 3.9 x 10 <sup>-6</sup> M	
2) Arachidonic acid aggregation		2) ~0.6 μM	2) Concentration-dependent, IC <sub>50</sub> : 3.8x 10 <sup>-7</sup> M	2) Concentration-dependent, IC <sub>50</sub> : 3.7 x 10 <sup>-6</sup> M	
3) ADP aggregation		3) ~1000 μM	3) No action	3) No action	
PGE <sub>1</sub> antagonism, p.o., Abdominal constriction (E-06)	Mouse	3.16 mg/kg	No action	Not conducted	Not used
Histamine, 5-HT, Acetylcholine antagonism (Magnus method) (E-06)	Guinea Pig's ileum	~10 <sup>-5</sup> M	No action	Not conducted	Not used
Slow reacting substance of anaphylaxis production inhibition (E-07)	Sensitized guinea pig's lung tissue	~10 <sup>3</sup> M	Concentration-dependent inhibition, (Inhibition: 53.4% at 10 <sup>3</sup> M)	Not conducted (However, inhibition rate of 74.2% by amlexanox at 10 <sup>-4</sup> M)	Not used

**Drug activity related to proposed indication:** The effects of bromfenac sodium on acute ocular inflammation described under the primary pharmacodynamics were the basis for its proposed ophthalmic indications.

**2.6.2.3 Secondary pharmacodynamics:** See the tabulated summaries under 2.6.2.2. (Primary pharmacodynamics) and 2.6.3 (Pharmacology tabulated summary).

**2.6.2.4 Safety pharmacology:** Studies in cats (from the NDA 20-535 review) revealed that bromfenac sodium did not have effects on central nervous system (behavior and normal spontaneous cerebral activities). Results obtained from the studies in dogs indicated that bromfenac sodium did not have anti-adrenergic and anti-histaminic properties, but it had little or limited effects on cardiovascular function.

As to the respiratory and circulatory organs, a transient increase in the systolic, mean and diastolic blood pressure, as well as an increase in femoral artery blood flow, was observed after intravenous administration at 10 mg/kg. This change was considered to be a common feature of drugs of this class.

With respect to the water and electrolyte metabolism, oral administration of bromfenac sodium at 1 or 3 mg/kg decreased urine volume and urinary electrolyte excretion volumes (Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>). At a dosage of 10 or 100 mg/kg, decreased urine volume and urinary Na<sup>+</sup>

and Cl<sup>-</sup> excretion volume were observed. However, it was reported that the urine volume was decreased in rats due to acute inhibition of Na<sup>+</sup> excretion after administration of various NSAIDs. Accordingly, these changes are considered as common features of NSAIDs. The investigation of the safety pharmacology of bromfenac sodium did not indicate any action that caused a clinical concern.

Table 2.6.2.1-2: Safety Pharmacology for Bromfenac Sodium (AHR-10282B)

	Study Items (Study Number)	Animal Species (N)	Dosing Route	Dose or Concentration (mg/kg)	Results
General Symptoms and Central Nervous System	Effect on general symptoms and behavior: multi-dimensional observation (E-09)	Mouse (6)	p.o.	10, 30, 100	No effect up to 100 mg/kg
	Effect on spontaneous motor activity (E-09)	Mouse (10)	p.o.	10, 30, 100	No effect up to 100 mg/kg
	Effect on normal body temperature (E-09)	Rat (6)	p.o.	10, 30, 100	No effect up to 100 mg/kg
	Action on hexobarbital-induced sleep (E-09)	Mouse (10)	p.o.	10, 30, 100	No effect up to 100 mg/kg
	Anti-convulsive action (pentetrazol method and maximum electric shock-induced convulsion method) (E-09)	Mouse (10)	p.o.	10, 30, 100	No effect up to 100 mg/kg
	Convulsion-inducing action (pentetrazol method and electric shock-induced convulsion method) (E-09)	Mouse (10)	p.o.	10, 30, 100	No action by combination with electric shock below the threshold value or with pentetrazol
	Analgesic action (acetic acid-induced writhing method) (E-09)	Mouse (10)	p.o.	1, 3, 10, 30, 100	Analgesic effect at 3 mg/kg or more
Effect of combination administration with quinolones (E-10)	Mouse (10)	p.o.	AHR-10282B 1000, norfloxacin 500, lomefloxacin 500, ofloxacin 1000	Combination of AHR-10282B and norfloxacin induced clonic convulsions and subsequent death in 5-6/10 animals; AHR-10282B and lomefloxacin induced clonic convulsions and death in 8/10 animals, and tonic convulsions in 4/10; AHR-10282B and ofloxacin induced clonic convulsions and death in 4/10 animals.	
Autonomic Nervous System and Smooth Muscle	Influence on the autonomic movement of extracted ileum (Magnus method) (E-09)	Rabbit (3)	<i>in vitro</i>	10 <sup>-7</sup> , 10 <sup>-5</sup> , 10 <sup>-3</sup> M	No action
	Influence on the constriction of extracted ileum induced by various spasmogens (acetylcholine, histamine, barium chloride) (Magnus method) (E-09)	Guinea Pig (3)	<i>in vitro</i>	10 <sup>-7</sup> , 10 <sup>-5</sup> , 10 <sup>-3</sup> M	No action on the constriction induced by each spasmogen
Respiratory and Circulatory Systems	Influence on mean respiration rate, mean systolic blood pressure and diastolic blood pressure, mean heart rate, mean femoral artery blood flow and ECG (E-09)	Dog (3)	i.v.	1, 3, 10	At 10 mg/kg, an increase in systolic blood pressure (p<0.05), mean blood pressure (p<0.05) and diastolic blood pressure (p<0.01) as well as an increase in femoral artery blood flow (p<0.05) was observed at a single measurement.
Gastrointestinal System	Influence on the small intestine transport function (charcoal powder method) (E-09)	Mouse (10)	p.o.	10, 30, 100	No effect up to 100 mg/kg
Water and Electrolyte Metabolism	Influence on water and electrolyte metabolism (determination of urine volume, and Na <sup>+</sup> , K <sup>+</sup> and Cl <sup>-</sup> excretion volume in urine) (E-09)	Rat (6)	p.o.	0.01, 0.1, 1, 10, 30, 100	No influence was observed at 0.01 and 0.1 mg/kg. A decrease in urine volume and urinary electrolyte excretion volume (Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> ) occurred at 1 and 3 mg/kg. A decrease in urine volume and urinary Na <sup>+</sup> and Cl <sup>-</sup> excretion volume occurred at 10 and 100 mg/kg. No influence on urine volume and urinary electrolyte excretion volume was noted at 30 mg/kg.

**2.6.2.5 Pharmacodynamic drug interactions:**

As a supplementary study to the pharmacological activity of bromfenac sodium, the effect of the combination of bromfenac and one of three quinolones was investigated by oral administration in rats (studies E-09 and E-10). Bromfenac was administered at 100 and 1000 mg/kg orally and was combined with norfloxacin, lomefloxacin, and ofloxacin. When 100 mg/kg bromfenac was combined with 500 mg/kg of norfloxacin or 1000 mg/kg of ofloxacin, no convulsions were induced, but the combination of 100 mg/kg bromfenac with 500 mg/kg of lomefloxacin induced clonic convulsions in 2 of 10 animals.

The combination of bromfenac (1000 mg/kg) with 500 mg/kg of norfloxacin induced clonic convulsions in 5 and subsequent death in 6 of 10 animals. When combined with 500 mg/kg of lomefloxacin, clonic convulsions and death occurred in 8 of 10 animals, and tonic convulsions and death occurred in 4 of 10 animals. When combined with 1000 mg/kg of ofloxacin, clonic convulsions and death occurred in 4 of 10 animals. Bromfenac at 1000 mg/kg plus vehicle caused a fall in skin surface temperature, a decrease in the reactivity to sound stimuli, prone position, respiratory suppression, lateral position, tremor and vocalization but not convulsions.

**2.6.3 PHARMACOLOGY TABULATED SUMMARY**

All the tables presented below and in previous sections under Pharmacology were compiled by the sponsor as a summary of non-clinical pharmacology studies for bromfenac sodium.

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Table 2.6.2.1-1: Pharmacodynamic Studies for Bromfenac Sodium (AHR-10282B) (continued)

Study Items (Study Number)	Animal Species	Dose & Administration Method	Methods	Results
Anti-inflammatory action	Evan's blue, carrageenan-induced pleural effusion (E-06)	Rat AHR-10282B 0.03 - 0.4 mg/kg Indomethacin 0.16 - 4.0 mg/kg p.o.	At 1 hour after administration of drug, 5 mL of a mixture of 0.075% Evan's blue and 0.025% carrageenan heated to 37°C was injected into the thoracic cavity. The animal was sacrificed after 5 hours and the exudate in the pleural cavity was determined. The inhibition rate was obtained in comparison with the rate in the control group.	AHR-10282B dose-dependently inhibited the pleural exudate and its action was 7.5 and 20.0 times stronger than that of indomethacin after 5 and 17 hours, respectively.
	Carrageenan-induced foot pad edema (E-06)	Rat AHR-10282B 0.8 mg/kg Indomethacin 4 mg/kg p.o.	At 1 hour after administration of drug, 0.1 mL of 1% carrageenan solution was injected to planta pedis of right hind foot. Foot volume was measured before and 3 hours after injection of carrageenan and the difference was determined as the edema. The inhibition rate was obtained in comparison with the rate in the control group.	AHR-10282B at 0.8 mg/kg achieved the same effect as that obtained with 4.0 mg/kg of indomethacin.
	Adjuvant-induced arthritis (E-06)	Rat AHR-10282B 0.0032 - 0.316 mg/kg Indomethacin 0.0032 - 3.16 mg/kg p.o.	0.05 mL of 1.5% <i>Mycobacterium butyricum</i> suspension in mineral oil was inoculated to the right hind legs of female rats. After 18 days, the animals in which the onset of arthritis was noted were selected and the drug was administered to these animals from Day 18 to 28. For comparison of effect, the difference between the bilateral hind leg volumes before and after inducing inflammation was used.	AHR-10282B dose-dependently inhibited the footpad edema, and its action was about 4 times stronger than that of indomethacin.
Antipyretic action	Pyretic test using Brewer's Yeast (E-06)	Rat AHR-10282B 0.8 mg/kg Indomethacin 4 mg/kg p.o.	As a pyrogen, 10 mL/kg of 15% Brewer's Yeast in aqueous suspension was subcutaneously injected. The drug was administered at 18 hours after injection. Using the value immediately before drug administration, the time course measurement of rectum temperature was conducted.	AHR-10282B at 0.8 mg/kg demonstrated antipyretic action equivalent to that observed with 4.0 mg/kg of indomethacin in a high body temperature rat model but the drug did not decrease the normal body temperature in rats.
Analgesic action	Acetylcholine-induced abdominal constriction (E-06)	Mouse AHR-10282B 0.032 - 3.16 mg/kg zomepirac 0.1 - 3.16 mg/kg suprofen 0.032 - 31.6 p.o.	At 10, 20 or 300 minutes after administration of the drug, 6 mg/kg of acetylcholine bromide was intraperitoneally administered as an inducing agent. The administration site was observed for 3 minutes and the analgesic action was assessed as positive if no abdominal constriction was observed.	When pretreated with AHR-10282B at 10, 20 and 300 minutes, the inhibition observed was 3.7 times, 6.5 times and 2.9 times, respectively, stronger than that of zomepirac, and 3.4 times, 6.6 times and 44.2 times, respectively, stronger than that of suprofen.

Table 2.6.2.1-1: Pharmacodynamic Studies for Bromfenac Sodium (AHR-10282B) (continued)

Study Items (Study Number)	Animal Species	Dose & Administration Method	Methods	Results
Analgesic action	Bradykinin-induced reaction (E-06)	Dog AHR-10282B 0.032 - 0.316 mg/kg zomepirac 0.1 - 3.16 mg/kg p.o.	At 30, 60 and 120 minutes after administration of the drug, bradykinin as a pain producing substance was administered through an indwelling peritoneal catheter. The dose of bradykinin was increased from 0.002 µg by 4 times with an interval of 10 minutes until nociceptive reflex was observed.	AHR-10282B dose-dependently inhibited the reaction to bradykinin. Its action was 5.8 times stronger than that of zomepirac.
	Tail clipping method (E-06)	Mouse 3.16 mg/kg p.o.	At 20 minutes after administration of the drug, the tail of animal was nipped with an arterial clip. If the animal did not bite the clip within 30 seconds, the analgesic action was assessed as positive.	No significant action of AHR-10282B was observed.
	Phenylbenzoquinone-induced abdominal constriction (E-08)	Mouse AHR-10282B 0.01 - 1.0 mg/kg (1) AHR-10240-3 (2) AHR-11665-B (3) AHR-11652-3 (4) WAY-127039-A1 10, 30, 100 mg/kg i.p.	Three (3) mg/kg of phenylbenzoquinone was intraperitoneally administered as an inducing agent. The animal was observed for 15 minutes afterwards and the analgesic action was assessed as positive if no abdominal constriction was observed.	AHR-10282B demonstrated an action 350 to 670 times stronger than that of metabolites (1) - (3). The outcome measure (ED <sub>50</sub> ) could not be calculated for metabolite (4), but its strength was similar to that of metabolite (3).

## 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

### 2.6.4.1 Brief summary:

Wyeth-Ayerst conducted pharmacokinetic studies for bromfenac sodium in animals using oral and intravenous routes. Senju Pharmaceutical Co. conducted pharmacokinetic studies following ocular instillation of <sup>14</sup>C-bromfenac ophthalmic solution in animals. Bromfenac sodium is absorbed well after oral dosing and is distributed to most tissues after oral or intravenous dosing. Bromfenac is not extensively metabolized, with the parent compound representing the majority of the drug-related material in plasma, whether the drug is administered orally, intravenously, or by topical instillation. The compound is cleared rapidly from all tissues with greater than 90% of the dose being recovered in excreta by 48 hours post dosing. Bromfenac sodium is excreted in both urine and feces, with some enterohepatic recirculation occurring in rats. The compound binds significantly to plasma proteins, but does not have a high affinity to bind to melanin. Topically, the compound is retained for several hours in the cornea, conjunctiva, and lens, and is excreted rapidly from the systemic circulation.

### 2.6.4.2 Methods of Analysis

See under individual study reviews.

### 2.6.4.3 Absorption:

Following instillation of <sup>14</sup>C-bromfenac in the eyes of male rabbits at a dose of 0.1 mg (two 0.05 mL drops of a 0.1% solution), plasma C<sub>max</sub> of 113 ng·eq/mL was observed at 30 minutes following administration. The calculated plasma half-life was 2.2 hours, and

the AUC<sub>0-12</sub> was 156 ng·eq·hr/mL. The plasma radioactivity was below detectable levels (0.4 ng·eq/mL) at 24 hours following a single administration.

Following repeated instillation of <sup>14</sup>C-bromfenac in the eyes of male rabbits at a dose of 0.1 mg/day for 21 days, the plasma concentration of bromfenac at 24 hours following the last dose was measured as 1.3 ± 0.2 ng·eq/mL. At 72 and 168 hours following the last dose, the plasma radioactivity levels were measured to be 0.8 ± 0.0 ng·eq/mL and below detectable levels, respectively.

#### **2.6.4.4 Distribution:**

Instillation of <sup>14</sup>C-bromfenac in both eyes of male rabbits resulted in the highest concentration of radioactivity in the cornea and conjunctiva, the sites where bromfenac indication is targeted. At 24 hours following instillation of bromfenac, the respective remaining radioactivity in the cornea and conjunctiva were 0.3% and 0.8% of the peak radioactivity measured at 15 minutes post dosing. At 72 hours after instillation, concentrations were below the detection limit in all ocular tissue except lens (0.5 ng·eq/g). Maximum concentrations in plasma occurred at 30 minutes and radioactivity disappeared thereafter.

#### **2.6.4.5 Metabolism:**

When metabolites in plasma and anterior aqueous humor were investigated after instillation of <sup>14</sup>C-bromfenac in the eyes of male rabbits, the parent compound accounted for 70-80% of drug-related material in both matrices. Metabolites AHR-11665, WAY-127039, AHR-10240 and AHR-11652 were also detected.

#### **2.6.4.6 Excretion:**

No information of excretion after ocular instillation is available.

#### **2.6.4.7 Pharmacokinetic drug interactions**

No information is available.

#### **2.6.4.8 Other Pharmacokinetic Studies:**

Refer to NDA 20-535 and 2.6.4.1 Brief summary.

#### **2.6.4.9 Discussion and Conclusions:**

Bromfenac sodium is absorbed well after oral dosing and is distributed to most tissues after oral or intravenous dosing. Bromfenac is not extensively metabolized, with the parent compound representing the majority of the drug-related material in plasma, whether the drug is administered orally, intravenously, or by topical instillation. The compound is cleared rapidly from all tissues with greater than 90% of the dose being recovered in excreta by 48 hours post dosing. Bromfenac sodium is excreted in both urine and feces, with some enterohepatic recirculation occurring in rats. The compound binds significantly to plasma proteins, but does not have a high affinity to bind to melanin. Topically, the compound is retained for several hours in the cornea, conjunctiva, and lens, and is excreted rapidly from the systemic circulation.

**2.6.4.10 Tables and figures to include comparative TK summary:**

See the table below.

**2.6.5 PHARMACOKINETICS TABULATED SUMMARY**

The summary of PK/TK of bromfenac as provided by the sponsor is listed in the following table.

**Table 2.6.4.1: Pharmacokinetics and Product Metabolism for Bromfenac Sodium (AHR-10282B)**

Study Items (Study Number)	Species	Dosing Route	Test Substance and Dose	Results
Influence of food (F-07) (F-09)	Rat (male) Cynomolgus monkey (male)	p.o. p.o.	AHR-10282B 1 mg/kg 15 mg/kg	$C_{max}$ and $AUC_{0-\infty}$ were significantly higher (2.4 and 1.7 times, respectively) in fasted rats than in rats fed with standard diet. Similar results were demonstrated in monkeys. Because systemic absorption of AHR-10282B would occur via the nasolacrimal duct following ocular instillation, food would have little influence on disposition of the drug.
Concentrations in organs/tissues (F-10)	Rabbit (male)	Ophthalmic application	$^{14}C$ -AHR-10282B 0.05 mg/eye (as hydrate)	F-10: Following single instillations, radioactivity in ocular tissues was highest in cornea and conjunctiva. At 72 hours, radioactivity was below detection limits in ocular tissue except lens. Elimination of radioactivity following repeated instillations was slower, but retention was not seen in any specific tissue.
(F-10)	Rabbit (male)	Ophthalmic instillation	$^{14}C$ -bromfenac 0.05 mg/eye/day (as hydrate)	Single dose: plasma $C_{max} = 113 \text{ ng}\cdot\text{eq}/\text{mL}$ , $T_{max} = 30 \text{ minutes}$ , $t_{1/2} = 2.2 \text{ hours}$ , $AUC_{0-12} = 156 \text{ ng}\cdot\text{eq}\cdot\text{hr}/\text{mL}$ . The plasma radioactivity was below detectable levels (0.4 ng•eq/mL) at 24 hours. Repeated dose (21 days): The plasma concentration of bromfenac sodium at 24 hours following the last dose was measured at $1.3 \pm 0.2 \text{ ng}\cdot\text{eq}/\text{mL}$ . At 72 and 168 hours following the last dose, the plasma radioactivity levels were measured at $0.8 \pm 0.0 \text{ ng}\cdot\text{eq}/\text{mL}$ and below detectable levels, respectively.
Composition of metabolites (F-10)	Rabbit (male)	Ophthalmic application	$^{14}C$ -AHR-10282B 0.05 mg/eye (as hydrate)	In aqueous humor, the following metabolites were detected: AHR-11665, WAY-127039-A-1, AHR-10240, and AHR-11652.
(D2000J0203) (S2000R1002)	Human liver microsomes and individual Cytochrome p450 enzymes	<i>In-vitro</i>	$^{14}C$ -AHR-10282B 10 $\mu$ M	The major metabolite found was 2-amino-3-(4-bromobenzoyl)-5-hydroxyphenylacetate and was produced by CYP2C9*1 (Arg)

**2.6.6 TOXICOLOGY****2.6.6.1 Overall toxicology summary**

The non-clinical toxicology studies conducted by Wyeth-Ayerst in support of the approval of NDA 20-535 (bromfenac capsules) have been reviewed previously (dated December 18, 1995). The non-clinical toxicology studies conducted by Senju Pharmaceutical Co. in support of bromfenac ophthalmic solution are reviewed in details in section 2.6.6.7 Local tolerance.

The followings are the Overall Summary and Evaluation of toxicology for bromfenac from NDA 20-535.

In the acute toxicity study, the LD<sub>50</sub> for female rats was 39.6 mg/kg po and 15.0 mg/kg iv, and for male rats was 46.0 mg/kg iv. The predominant toxicity observed in these studies was GI related. Hemorrhagic spots in the GI tract, thickened intestinal walls, and adhesions of intestine to peritoneal walls were major characteristics of GI lesions. Kidney toxicity was also observed, which included hematuria and pale kidneys at necropsy. The maximum nontoxic doses were ≤10 mg/kg po for the rat, rabbit and dog, and ≤1.0 mg/kg iv for the rat. It appeared that female rats were more susceptible to Bromfenac-caused toxicity than male rats.

Long-term toxicity/carcinogenicity studies were conducted in mice and rats. In a two-year study in mice, drug-induced toxicities were observed in the liver and the stomach at doses of 5.0/7.5 mg/kg/day. These lesions were identified as ulcers and/or subacute inflammation in the glandular mucosa of the stomach, and cytological alterations in the hepatocytes. There was no treatment-

related increases in tumor incidences in all animals. The report showed that an eight-week dose range finding study was conducted in mice prior to the two-year study. However, the study result was not submitted in the NDA. In a 13-week toxicity study in rats, no treatment-related toxicities were found in animals at ≤0.5 mg/kg/day. At 2.5 mg/kg/day, intestinal ulcers/necrosis was observed. In a 24-month study in rats, dose-dependent hepatic (vacuolar alterations, cytoplasmic changes, inflammation, and necrosis) and gastrointestinal (inflammation, and necrosis) toxicities were identified at 12- and 24-month postmortem macro- and/or micro-scopic examinations. Nephrotoxicity (papillary necrosis) was also revealed at terminal necropsy. However, there were no treatment-associated increases in the tumor incidences in animals. No drug-related macro- and microscopic changes were observed during the six-month interim sacrifices in all doses (0.05, 0.3, and 0.6 mg/kg/day). It appeared that female rats were more sensitive to intestinal toxicity than male rats in this study. In a 13-week study in rhesus monkeys, no toxicity was found at 15 mg/kg/day. Emesis was found at 45 and 135 mg/kg/day and GI lesions were found at 135 mg/kg/day. A 12-month study was conducted in cynomolgus monkeys. Treatment-related death and enteric toxicity (ulcers) occurred in animals receiving 10 and 30 mg/kg/day in this study.

Bromfenac at doses up to 0.9 mg/kg/day in male and female rats did not cause any adverse effects in the fertility. However, increased postimplantation embryonic loss, increased stillborn pups, decreased live pups at birth, prolonged gestation period, and dystocia were observed in the rat reproduction studies. No fetal malformations were found in rats at doses up to 0.9 mg/kg/day and in rabbits at doses up to 7.5 mg/kg/day. The postnatal growth of pups from lactating dams receiving 0.9 mg/kg/day of Bromfenac was decreased.

Bromfenac was evaluated for mutagenicity potential in the Ames test, the Chinese hamster ovary cell chromosomal aberration test, the mouse lymphoma forward mutation assay, *in vivo* mouse micronucleus assay, and *in vivo/vitro* rat unscheduled DNA synthesis assay. Bromfenac was not mutagenic in these tests.

For review of toxicity information for orally administered bromfenac (sections 2.6.6.2 to 2.6.6.6), see review of NDA 21-535 dated December 18, 1995. The summary of toxicity

findings is described in section 2.6.6.1, Overall Toxicology Summary. The toxicology studies for bromfenac ophthalmic solution are reviewed under 2.6.6.7 Local Tolerance.

**2.6.6.2 Single-dose toxicity:** Refer to NDA 21-535.

**2.6.6.3 Repeat-dose toxicity:** Refer to NDA 21-535.

**6.6.6.4 Genetic toxicology:** Refer to NDA 21-535.

**2.6.6.5 Carcinogenicity:** Refer to NDA 21-535.

**2.6.6.6 Reproductive and developmental toxicology:** refer to NDA 21-535

**2.6.6.7 Local tolerance:**

**4-Week Ocular Toxicity Study in Rabbits (GLP study, Study D-18)**

The ocular toxicity of 0.5% AHR-10282B ophthalmic solution was investigated in rabbits by four-week repeated topical instillation. Using two groups of rabbits, the 0.5% AHR-10282B ophthalmic solution and isotonic saline were instilled into the right eye at single dose of two drops nine times daily.

The ocular lesions were grossly evaluated according to the Draize scoring criteria and corneal injuries by the fluorescein staining. No ocular abnormalities were observed in either group on any observation days. The corneal epithelial and endothelial layers were examined by scanning electron microscope, and their ultrastructural morphology was intact. AHR-10282B ophthalmic solution had no effect either on the pupil size or intraocular pressure.

**13-Week Ocular Toxicity Study in Rabbits (GLP study, Study D-19)**

One drop of 0.1, 0.2 and 0.4% bromfenac sodium ophthalmic solutions or physiological saline were topically instilled into both eyes of rabbits four times daily at 3-hour intervals for 13 weeks. There were 6 animals in each group.

No abnormal changes attributable to drugs were observed in the clinical observations, body weight, food consumption, ophthalmologic, hematological, blood biochemical, urinalysis, and histopathological examinations. No bromfenac-related changes were observed when the corneas were examined by transmission and scanning electron microscopy.

The bromfenac sodium ophthalmic solution had no local ocular irritating potential or any systemic toxicity in rabbits at concentrations of 0.1, 0.2 and 0.4% under the test condition.

**Corneal Epithelial Repair Test in Rabbits (QA report, yes, Study D-20)**

To investigate the possible effect of 0.2% AHR-10282B ophthalmic solution on the healing of injured ocular tissues, the de-epithelialized corneas of rabbit eyes were examined for the rate of wound healing and for the histopathology of the regenerated corneal tissues.

The corneal epithelium of the rabbit eyes was scraped off, and one drop of 0.2% AHR-10282B ophthalmic solution or physiological saline was topically instilled into each eye eight times daily at 1 hour intervals for 5 days. There were three rabbits in each group. The epithelial wound healing rate was not different between the drug product and the control. In the histopathological evaluation of the corneal epithelium after complete wound healing, the morphology of the regenerated corneal epithelium was not different between the treated and control groups.

Based on these results, the 0.2% bromfenac sodium ophthalmic solution is thought to have no adverse effect on the epithelial repair of the rabbit eye with denuded corneal epithelium.

**Anterior Eye Irritation Test of the Artificially Aged Samples in Rabbits (QA report, yes, Study D-21)**

The artificially aged (stored at 100°C for 90 hours, remaining concentration 84.8%) 0.1% bromfenac sodium ophthalmic solution was topically instilled into the rabbit eyes 16 times daily at 30 minute intervals, and the irritating potential in the anterior eye segment was evaluated.

In the microscopic evaluation, no abnormal changes were observed in the anterior eye segment. In the fluorescein staining test, stained dots covered the entire corneal area in 3/5 eyes treated with the artificially aged sample after the 16<sup>th</sup> instillation. However, these stained dots disappeared one day after the instillation and were thought to be mild injuries.

**Anterior Eye Irritation Test of the Fresh and Artificially Aged Samples in Rabbits (QA report, yes, Study D-22)**

The 0.1% AHR-10282B ophthalmic solution and its artificially aged sample were instilled into the rabbit eyes at a dose of two drops (about 100 µL) four times at 30-hour intervals or 16 times at 30-minute intervals. There were 5 animals in each group.

In the gross observation of the anterior segment, both the fresh and aged samples caused conjunctival injection and ocular discharge in one eye after 16 instillations. No other treatment-related gross abnormal changes were observed.

In the observation of corneal fluorescein staining, the number of stained dots increased after 16 instillations in one eye treated with fresh sample and two eyes treated with aged sample. No abnormal staining was observed in the eyes treated four times.

It was thought that both the fresh and aged samples were mildly irritating to the anterior segment of the rabbit eye after 16 instillations but not after 4 instillations. There was no difference between two samples in their irritating potencies.

**2.6.6.8 Special toxicology studies (GLP study, Study D-24)**

The artificially aged and fresh samples of 0.1% AHR-10282B ophthalmic solution were administered once orally at volume of 0.5, 1 and 2 mL/100 g body weight (2.25, 4.5, and 9 mg equivalent of AHR-10282B/kg, deteriorated sample) and 5, 10 and 20 mg equivalent of AHR-10282B/kg (fresh sample) to rats, respectively. The purpose of the study was to examine if the degradation of bromfenac was associated with enhancement of GI toxicity and new toxicities. No such finding was detected.



**Table 2.6.6.1: Toxicity Studies for Bromfenac Sodium (AHR-10282B)**

	Study Items (Study Number)	Species	Route (Period of Administration)	Dose or Concentrations	Results
Single and Repeated Dose Toxicity	Single dose toxicity (D-01)	Rat	p.o.	12.5, 25, 50 mg/kg/day	Approximate lethal dose: M and F, 25 mg/kg/day
	Single dose toxicity (D-02)	Cynomolgus monkey	p.o.	250, 500, 1000 mg/kg/day	Approximate lethal dose: M, >1000 mg/kg/day
	Repeated dose toxicity (D-03) (D-04) (D-05) (D-06) (D-07) (D-23)	Rat	p.o. (13 weeks)	0.1, 0.5, 2.5	NOAEL: 0.1 mg/kg/day NOAEL: 45 mg/kg/day NOAEL: 0.3 mg/kg/day NOAEL: 0.05 mg/kg/day NOAEL: 3 mg/kg/day Induced gastrointestinal damage was reversible following withdrawal of drug.
		Rhesus monkey	p.o. (13 weeks)	15, 45, 135	
		Rat	p.o. (6 months)	0.05, 0.3, 0.6	
		Rat	p.o. (12 months)	0.05, 0.3, 0.6	
		Cynomolgus monkey	p.o. (12 months)	3, 10, 30	
Rat	p.o. (4 weeks)	1.5, 2.5 mg/kg/day			
Reproductive and Developmental	Reproductive and developmental effects Segment I (D-08)	Rat	p.o.	0.06, 0.3, 0.9	NOAEL for general toxicology: M, 0.9 mg/kg/day; F, 0.06 mg/kg/day NOAEL for reproductive toxicology: M, 0.9 mg/kg/day; F, 0.3 mg/kg/day
	Segment II (D-09) (D-10)	Rat	p.o.	0.06, 0.3, 0.9	NOAEL: pregnant animals, 0.9 mg/kg/day; fetuses, 0.9 mg/kg/day
		Rabbit	p.o.	1.0, 2.5, 7.5	NOAEL: pregnant animals, 2.5 mg/kg/day; fetuses, 2.5 mg/kg/day; teratogenicity, 7.5 mg/kg/day
	Segment III (D-11)	Rat	p.o.	0.06, 0.3, 0.9 mg/kg/day	NOAEL: dams, 0.06 mg/kg/day; offspring, 0.3 mg/kg/day
Antigenicity	Antigenicity (D-12)	Guinea pig	s.c., 5 injections (+FCA) at weekly intervals	0.1 mg/animal 1.0 mg/animal	PCA: 1/6 guinea pigs gave a false positive reaction PHA and ACA: negative ASA: positive in 1/6 animals (nose scratching)
		Mouse	i.p., once biweekly, total: 3 injections (+Alum)	0.005 mg/animal 0.05 mg/animal	PCA: negative in mice
Genotoxicity	Reverse mutation test in bacteria (D-13)	<i>Salmonella typhimurium</i> , <i>Escherichia coli</i>	Non-activation assay, Metabolic activation assay	156.3 ~ 5000 µg/plate	Negative
	Chromosome aberration test with mammalian cells in culture (D-14)	Chinese hamster ovary cells	Non-activation assay, Metabolic activation assay	200 ~ 500 µg/mL 250 ~ 1500 µg/mL	Negative Negative
	Micronucleus test with rodents (D-15)	Mouse	p.o., single dose	50, 167, 500 mg/kg/day	Negative
Carcinogenicity	Carcinogenicity (D-16)	Mouse	p.o., 2 years	0.2, 1.0, 5.0	Negative
	(D-17)	Rat	p.o., 2 years	0.05, 0.3, 0.6 mg/kg/day	Negative

NOAEL: No observed adverse effect level

Table 2.6.6.1: Toxicity Studies for Bromfenac Sodium (AHR-10282B) (continued)

	Study Items (Study Number)	Species	Route (Period of Administration)	Dose or Concentrations	Results
Topical instillation studies	Ocular toxicity (D-18)	Rabbit	Topical instillation, 4 weeks	0.5 %	No toxic change
	(D-19)		Topical instillation, 13 weeks	0.1, 0.2, 0.4%	No toxic change
	Effects on wound healing of the cornea (D-20)	Rabbit	Topical instillation, 5 days	0.2%	No effect
	Local irritancy of the artificially aged sample (D-21)	Rabbit	Artificially aged sample, 16 instillations	0.1%	Very slight corneal epithelial injuries
(D-22)	Fresh sample and artificially aged sample, 4, 16 instillations		0.1%	Non-irritating after 4 instillations. Very slight corneal injuries after 16 instillations.	
Others	Single dose toxicity of the artificially aged sample (D-24)	Rat	p.o. Fresh sample and artificially aged sample	0.1%, 0.5, 1.0, 2.0 mL/ 100 g	No enhancement of toxicities by decomposition
	Single dose toxicity of metabolites (D-25)	Rat	i.p.	4, 20, 100 mg/kg/day	No enhancement of toxicities by metabolites
	Single dose toxicity of metabolites	HepG2 cells	<i>In-vitro</i>	0.3, 1, 3, 10, 30, 100, 300, 1000 $\mu$ M	No enhancement of toxicities by metabolites

## OVERALL CONCLUSIONS AND RECOMMENDATIONS

### Conclusions:

Bromfenac sodium, AHR-10282B, is a cyclooxygenase inhibitor possessing analgesic, anti-inflammatory, and antipyretic activities in various animal experimental models. It belongs to a non-steroidal anti-inflammatory drug class (NSAID) without any narcotic-like activity. Bromfenac did not possess any significant effects on the central nervous system and cardiovascular function.

The oral formulation of bromfenac (Duract capsules) was developed by Wyeth-Ayerst and was approved for marketing under NDA 20-535 in 1997. However, because of the clinical findings of hepatotoxicity after marketing, Duract was withdrawn from the market in June 1998.

Bromfenac sodium was licensed to Senju Pharmaceutical Co., Ltd, Osaka, Japan for development as an ophthalmic solution. Senju conducted non-clinical and clinical studies for bromfenac ophthalmic solution and obtained approval for marketing in Japan in 2000. Senju recently sublicensed bromfenac for ophthalmic use in the United States to ISTA Pharmaceuticals, Inc. The non-clinical studies submitted in this NDA were conducted by Wyeth-Ayerst and Senju Pharmaceuticals.

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

The systemic toxicity studies for bromfenac sodium were previously reviewed under NDA 21-535. Bromfenac sodium caused predominantly the GI toxicity in animal studies through a systemic administration. Kidney and hepatic toxicity was also observed. Oral

formulation of bromfenac sodium was withdrawn from the market after the discovery of critical liver toxicity in the clinical use.

In an ocular toxicity study in rabbits, a 0.5% bromfenac sodium ophthalmic solution was instilled into the eye 9 times daily for 4 weeks. In another ocular toxicity study in rabbits, 0.1%, 0.2% and 0.4% bromfenac sodium ophthalmic solution were instilled into the eye 4 times daily for 13 weeks. No ocular abnormalities were observed at any concentration in either study. The proposed clinical dose of Xibrom (0.1% bromfenac sodium ophthalmic solution) is one drop twice daily for up to 2 weeks. At the similar dosing regimen, no adverse effects, systemic or ocular, were observed in the rabbit studies.

Following instillation of  $^{14}\text{C}$ -bromfenac in the eyes of male rabbits at a dose of 0.1 mg (two 0.05 mL drops of a 0.1% solution), plasma  $C_{\max}$  of 113 ng·eq/mL was observed at 30 minutes following administration. The calculated plasma half-life was 2.2 hours, and the  $\text{AUC}_{0-12}$  was 156 ng·eq·hr/mL. The plasma radioactivity was below detectable levels (0.4 ng·eq/mL) at 24 hours following a single administration.

Following repeated instillation of  $^{14}\text{C}$ -bromfenac in the eyes of male rabbits at a dose of 0.1 mg/day for 21 days, the plasma concentration of bromfenac at 24 hours following the last dose was measured as  $1.3 \pm 0.2$  ng·eq/mL. At 72 and 168 hours following the last dose, the plasma radioactivity levels were measured to be  $0.8 \pm 0.0$  ng·eq/mL and below detectable levels, respectively.

The recommended clinical dose of Duract (oral formulation of bromfenac sodium) is 25 to 50 mg every 6 to 8 hours, not to exceed 150 mg/day (2.5 mg/kg/day in a 60 kg body weight person). In an oral pharmacokinetic study in monkeys with single dose or repeat dose at 3 mg/kg/day, the  $C_{\max}$  were 2,440 and 5,860 ng/mL, respectively and the  $\text{AUC}_{0-24}$  were 2,970 and 4,490 ng·hr/mL, respectively. Based on these data, it appeared that the ratios between the AUC of 3 mg/kg/day oral dose in monkeys and 0.1 mg/day ocular dose in rabbits were 19 (2970/156) for single dose and 29 (4490/156) for repeat dose, respectively. Please note that two different animal species were compared here because no data from the same species were available for this calculation.

The daily administration of 2 drops/eye (or 100  $\mu\text{L}$ ) of 0.1% (1  $\mu\text{g}$ / 1  $\mu\text{L}$ ) Xibrom in a 60 kg body weight person equals to 100  $\mu\text{g}$ /person/day or 1.67  $\mu\text{g}$ /kg/day. The previously approved clinical dose of Duract (oral formulation of bromfenac sodium) is 25 to 50 mg every 6 to 8 hours, not to exceed 150 mg/day (2.5 mg/kg/day in a 60 kg body weight person). Therefore, the ratio of the recommended daily oral dose and daily ocular dose is 1500 (2.5 mg/kg/day or 2,500  $\mu\text{g}$ /kg/day  $\div$  1.67  $\mu\text{g}$ /kg/day = 1,500). The chance of adverse effects, which is found in the oral administration of Duract, is probably very small in the administration of Xibrom.

#### Recommendations:

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

#### Suggested labeling:

The non-clinical sections of labeling for Xibrom are similar to that for Duract (bromfenac sodium capsule). The information was based on the information submitted previously under NDA 21-535. Basically, there is no objection to the proposed labeling, except that the Pregnancy Category should be  C.

However, the sponsor did not identify what was the volume of one drop of 0.1% Xibrom and what was the average body weight of a person in sponsor's calculation of the dose. It is recommended that 50  $\mu$ L be used as the volume of one drop (unless a measured volume of a drop is available) in the calculation. It is also recommended that 60 kg be used as the human body weight.

Based on this reviewer's calculation, the daily administration of 2 drops/eye (or 100  $\mu$ L) of 0.1% (1  $\mu$ g/ 1  $\mu$ L) Xibrom in a 60 kg body weight person equals to 100  $\mu$ g/person/day or 1.67  $\mu$ g/kg/day. Therefore, dose of 0.6 mg/kg/day (or 600  $\mu$ g/kg/day) in rat carcinogenicity study equals to 360 folds of daily clinical ocular dose in men ( $600/1.67 = 360$ ). The ratio of animal dose and human ocular doses in the pregnancy section of labeling should also be modified using 1.67  $\mu$ g/kg/day as the human clinical dose.

However, the sponsor assumed 1 drop of 0.1% Xibrom as 35  $\mu$ L containing 43.75  $\mu$ g (of bromfenac sodium in the calculation). Therefore, the daily clinical dose (2 drops/day) is 87.5  $\mu$ g/person or 1.25  $\mu$ g/kg in a 70 kg body weight person. The ratio of animal dose to human clinical dose in the labeling was based on the calculation using 1.25  $\mu$ g/kg/day (0.6 mg/kg/day or 600  $\mu$ g/kg/day in animal equal to 480 folds of 1.25  $\mu$ g/kg/day;  $600/1.25 = 480$ ). It is recommended that 40-50  $\mu$ L be used as the volume of one drop (unless 35  $\mu$ L is a measured volume of a drop) in the calculation. It is also recommended that 60 kg be used as the human body weight.

Signatures (optional):

Reviewer Signature \_\_\_\_\_  
Conrad H. Chen, Ph.D., Pharmacologist

Supervisor Signature \_\_\_\_\_ Concurrency Yes \_\_\_ No \_\_\_  
Josie Yang, Ph.D., Pharmacology Team Leader

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/s/

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Conrad Chen  
2/4/05 09:51:02 AM  
PHARMACOLOGIST  
The approval of NDA 21-664 is recommended.

Josie Yang  
2/4/05 11:18:31 AM  
PHARMACOLOGIST