
**Global Experience With Xibrom
(Bromfenac Ophthalmic Solution)
0.09%: The First Twice-daily
Ophthalmic Nonsteroidal
Anti-inflammatory Drug**

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Ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) are becoming a cornerstone for the management of ocular pain and inflammation. Their well-characterized anti-inflammatory activity, analgesic property, and established safety record have also made NSAIDs an important tool to optimize surgical outcomes. Ophthalmic NSAIDs currently play four principal roles in ophthalmic surgery, including the prevention of intraoperative miosis during cataract surgery, management of postoperative inflammation, the reduction of pain and discomfort after cataract and refractive surgery, and the prevention and treatment of cystoid macular edema (CME) after cataract surgery.¹⁻³

In clinical practice, an optimal ophthalmic NSAID therapy will have highly effective anti-inflammatory activity, a rapid onset of action that produces sustained relief of inflammation and pain, an excellent safety profile, a formulation that is comfortable and well-tolerated, and a convenient dosing regimen. Based upon its features, bromfenac ophthalmic solution 0.09% seems to satisfy each ideal NSAID parameter. This chapter will review the clinical and postapproval experience with bromfenac ophthalmic solution 0.09% (Xibrom, ISTA Pharmaceuticals, Inc., Irvine, CA).

Bromfenac sodium ophthalmic solution 0.1% was first approved in May 2000 as Bronuck (Senju Pharmaceutical Company, Ltd., Osaka, Japan) and is presently approved by the Ministry of Health in Japan for the clinical indications of the treatment of postoperative inflammation, blepharitis, conjunctivitis, and scleritis.⁴ The same formulation was approved in the United States by the Food and Drug Administration (FDA) in March 2005 as Xibrom (bromfenac ophthalmic solution 0.09%)

for the treatment of postoperative inflammation in patients who have undergone cataract extraction.⁵ Despite the stated difference in concentrations, the strength of Bronuck 0.1% is equivalent to Xibrom 0.09%. In January 2006, the FDA-approved indication for Xibrom was expanded to include the reduction of ocular pain after cataract extraction.⁶ Xibrom is the first and only ophthalmic NSAID with an approved twice-daily dosage.

■ NSAID Mechanism of Action

All NSAIDs produce anti-inflammatory and analgesic effects by inhibiting the activity of cyclooxygenases (COXs), enzymes that convert arachidonic acid to cyclic endoperoxides, thereby blocking synthesis of prostaglandins. Prostaglandins mediate many forms of systemic and localized inflammation including inflammation in ocular tissues. In animal models, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, and leukocytosis.^{7,8}

There are 2 important isoforms of COX. COX-1 is an enzyme that is expressed constitutively in almost all tissues, particularly in the gastrointestinal tract, platelets, endothelial cells, and kidneys.⁹ COX-1 is responsible for the production of prostaglandin-2, which is important for homeostatic functions, such as maintaining the integrity of the gastrointestinal mucosa, mediating platelet function, and regulating renal blood flow.

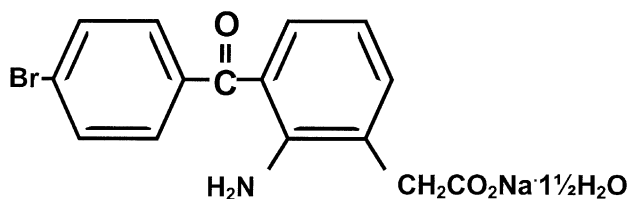
The expression of COX-2 occurs in response to the exposure to a noxious stimulus. The induction of this enzyme leads to the production of prostaglandins that cause inflammation and pain. It has been demonstrated in rats that COX-2 is the primary mediator for ocular inflammation.⁷ Therefore, inhibition of COX-2 is thought to be the most important therapeutic mechanism of ophthalmic NSAIDs.

■ The Chemical Structure of Bromfenac

The chemical structure of bromfenac is similar to amfenac, the active form of the prodrug nepafenac, except for the key addition of a bromine atom in the 4-position of the benzoyl ring (Fig. 1).¹⁰ Importantly, compounds that contain a halogen have greater potency ($I^- \sim Br^- > Cl^- > F^- > H$).¹⁰ The addition of bromine to the bromfenac molecule imparts more pronounced effects on its in vitro and in vivo potency, absorption across the cornea, and penetration into ocular tissues.^{11,12}

■ Preclinical Studies of Bromfenac Ophthalmic Solution

Preclinical data confirm that the unique bromine moiety in bromfenac enhances both the in vitro potency of the molecule and the tissue penetration of the ophthalmic formulation.



Amfenac

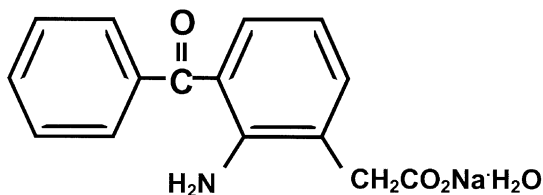


Figure 1. Chemical structures of bromfenac and amfenac.

Potency Against the COX-2 Enzyme

NSAIDs vary in their relative potency against COX-1 and COX-2. Relative potency is assessed by determining the concentration of drug required to inhibit the COX enzyme activity by 50%, a value called the inhibitory concentration 50% or IC_{50} . A smaller IC_{50} value signifies greater inhibition of the enzyme (ie, a lower concentration of drug is needed to inhibit the enzyme). Several in vitro assays are used to determine IC_{50} , making the values dependent upon the animal model (tissue and stimulus) used in the experiment and variable between laboratories. Thus, it is important that the assay type is defined when making comparisons between IC_{50} measurements.

As a result of its chemical structure, bromfenac has been shown to be the most potent ophthalmic NSAID in inhibiting the COX-2 enzyme. In vitro studies have shown that the inhibition of prostaglandin synthesis with bromfenac was approximately 12 times greater than that of indomethacin.⁸ The inhibitory effects of bromfenac on COX-2 have been shown to be 3.7 times greater than diclofenac,¹³ 6.5 times greater than amfenac,¹⁴ and 18 times more potent than ketorolac (Tables 1 and 2).¹⁵ The COX-2 purified from rabbit alveolar macrophage was used for the COX-2 enzyme inhibition assay of bromfenac, diclofenac, and amfenac.^{13,14} COX activity of ketorolac and bromfenac was determined by measuring prostaglandin-2 production after incubating with human recombinants COX-2 and arachidonic acid.¹⁵

TABLE 1. *Relative Potency of Bromfenac, Diclofenac, and Amfenac In Vitro: IC₅₀* Values of Cyclooxygenase-2 (COX-2)^{13,14}*

	IC ₅₀ COX-2 (nM)
Bromfenac	23
Diclofenac	85
Amfenac	150

*IC₅₀ is the drug concentration required to inhibit COX-2 enzyme activity by 50%. The smaller the number, the more potent the molecule (less concentration needed to inhibit the enzyme). The inhibitory effect of bromfenac is 3.7 times greater than diclofenac, and 6.5 times greater than amfenac.

Penetration Into Ocular Tissue

The ability to penetrate ocular tissues may be an important determinant of the efficacy of an ophthalmic NSAID. Studies with bromfenac ophthalmic solution in both animals and humans have demonstrated that the drug penetrates rapidly and extensively into all ocular tissues after ophthalmic application.

Two animal studies have demonstrated that bromfenac ophthalmic solution rapidly achieves measurable levels in all major ocular tissues and that detectable levels are sustained over 24 hours. First, Bakalyan and colleagues¹⁶ examined the distribution of a single application of radiolabeled bromfenac ophthalmic solution in New Zealand White Rabbit eyes. After the administration of 50 μ L of ¹⁴C-bromfenac sodium ophthalmic solution (20 to 25 μ Ci) to the right eyes of 14 randomly assigned animals, samples of the cornea, aqueous humor, iris/ciliary, choroid, and retina were collected at multiple time points for analysis. Peak concentrations of radiolabeled bromfenac were observed in the aqueous humor and most of the ocular tissues at 2 hours (Fig. 2A). Bromfenac concentrations were highest in the cornea and similar amounts of radiolabeled bromfenac were detected in the aqueous humor, iris/ciliary body, choroid, and to a slightly lesser degree, the retina. Bromfenac was detected in all samples over 24 hours (Fig. 2A).

TABLE 2. *Relative Potency of Bromfenac and Ketorolac In Vitro: IC₅₀* Values of Cyclooxygenase-2 (COX-2)¹⁵*

	IC ₅₀ COX-2 (nM)
Bromfenac	6.6
Ketorolac	120

*IC₅₀ is the drug concentration required to inhibit COX-2 enzyme activity by 50%. The smaller the number, the more potent the molecule (less concentration needed to inhibit the enzyme). Inhibitory effect of bromfenac is 18 times greater than ketorolac.

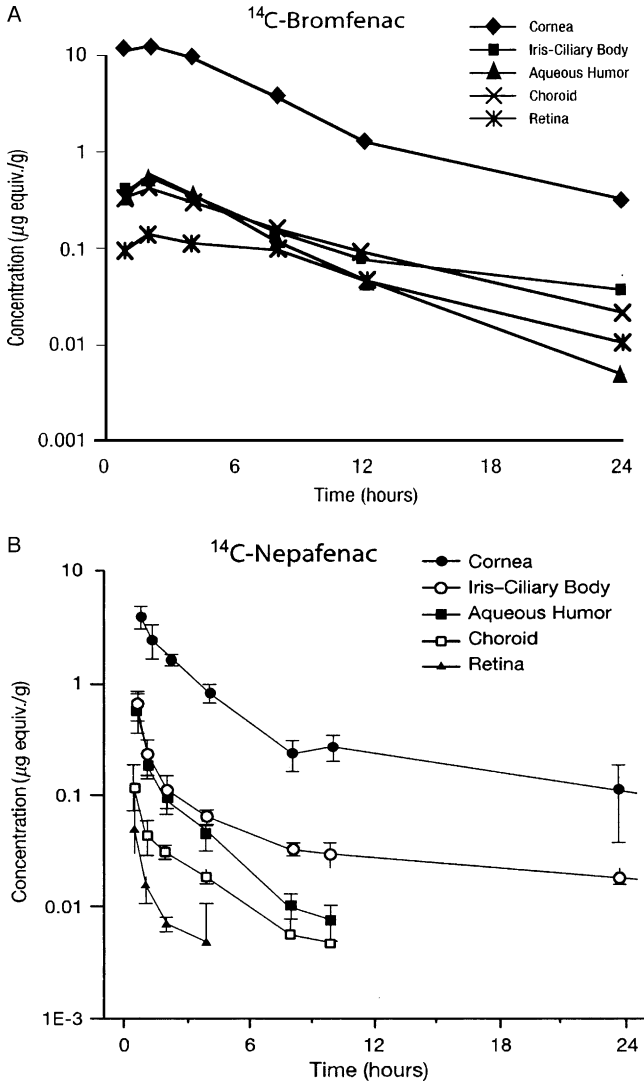


Figure 2. A, Concentrations of radioactivity in ocular tissues after a single topical ocular dose of ¹⁴C-bromfenac showing detectable levels in all ocular tissues over 24 hours.¹⁶ B, Concentrations of radioactivity in ocular tissues after a single topical ocular dose of ¹⁴C-nepafenac showing undetectable levels in the aqueous humor and choroid after 12 hours and undetectable levels in the retina beyond 6 hours.¹⁷

By comparison, in a separate but similar evaluation of ¹⁴C-nepafenac with 3 times the commercially available dose, initial penetration into ocular tissues produced detectable drug levels in the cornea and iris/ciliary body beyond 24 hours but not in the aqueous humor or choroid beyond 12 hours and in the retina beyond 6 hours (Fig. 2B).¹⁷

Second, McNamara and associates¹⁸ recently replicated the bromfenac ophthalmic solution 0.09% results with a single drop of Xibrom. In the same animal model, peak concentrations of ¹⁴C-bromfenac were observed at or before 2 hours with measurable levels in all ophthalmic tissues, including the retina, over 24 hours, after a single ophthalmic dose. Although the clinical significance of these animal studies is unknown, the data suggest that because bromfenac ophthalmic solution rapidly reaches sustained concentrations in all ocular tissues, it may find utility in treating disorders associated with inflammation in other ocular tissues.

Ogawa and colleagues¹⁹ evaluated the pharmacokinetic profile of bromfenac ophthalmic solution in human subjects undergoing cataract surgery, in part to validate the sufficiency of BID dosing. A single drop of bromfenac ophthalmic solution at the commercial concentration was administered to 54 subjects at a variety of specified time points before cataract surgery. At the start of each case, 100 μ L of aqueous humor was extracted for analysis. The results showed rapid absorption (within 15 min) with the peak aqueous humor concentration of bromfenac occurring at 150 to 180 minutes after instillation (Fig. 3). The mean concentration was 78.7 ng/mL (Table 3). Bromfenac remained at

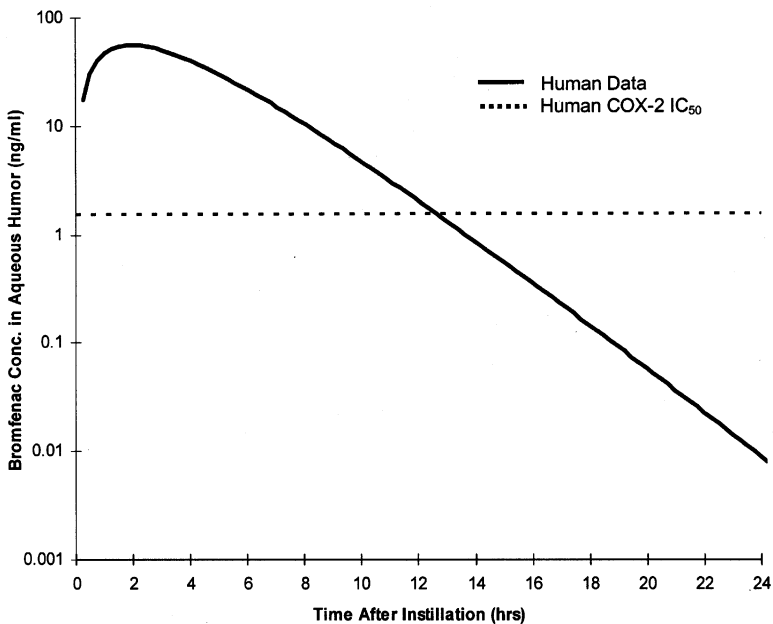


Figure 3. Projection showing that concentrations of bromfenac sodium ophthalmic solution 0.1% in the aqueous humor remain above the IC₅₀ (1.5 ng/mL) for COX-2 in humans for 12 hours after instillation of a single drop.¹⁹ Bromfenac sodium hydrate ophthalmic solution 0.1% is equivalent to bromfenac ophthalmic solution 0.09%.

TABLE 3. Concentration of Bromfenac Sodium Ophthalmic Solution 0.1%* in Aqueous Humor at Multiple Time Points After a Single Dose¹⁹

Time of Instillation Before Surgery (min)	No. Cases	Bromfenac Concentration in Aqueous Humor (ng/mL) (mean + SD)
$t \leq 30$	1	9.8
$30 < t \leq 60$	5	11.5 + 6.6
$60 < t \leq 90$	11	36.4 ± 43.8
$90 < t \leq 120$	7	59.6 ± 45.2
$120 < t \leq 150$	7	65.5 ± 69.8
$150 < t \leq 180$	5	78.7 ± 68.1
$180 < t \leq 210$	3	63.1 ± 44.4
$210 < t \leq 240$	5	42.1 ± 14.3
$240 < t \leq 270$	4	40.0 ± 42.1
$270 < t \leq 300$	3	23.3 ± 15.3
$300 < t \leq 330$	2	22.3 ± 13.5
$t > 330$	1	52

*Bromfenac sodium hydrate ophthalmic solution 0.1% is equivalent to bromfenac ophthalmic solution 0.09%.

therapeutic concentrations above the IC_{50} (1.5 ng/mL) in the aqueous humor for the duration of the experiment. The measurements projected over 24 hours would remain above the IC_{50} for at least 12 hours, with measurable concentrations observable at or beyond 24 hours (Fig. 3). In conclusion, with effective concentrations in the aqueous humor persisting for 12 hours after a single application, BID dosing is sufficient to maintain anti-inflammatory efficacy.

■ Efficacy Evaluations of Bromfenac Ophthalmic Solution

Multiple clinical studies of bromfenac ophthalmic solution have been conducted in the United States and Japan to investigate a variety of clinical applications and indications. Clinical investigations have included the treatment of inflammation and pain after cataract surgery, the prevention of intraoperative miosis during cataract surgery, the treatment of allergic conjunctivitis, the treatment of anterior uveitis, and the treatment of CME after cataract surgery.

Efficacy in Treating Inflammation and Pain Following Cataract Surgery

Early clinical investigations of bromfenac ophthalmic solution determined the optimal concentration of the ophthalmic solution, as described by Masuda and colleagues.²⁰ In the multicenter, phase 2

clinical study, the safety and anti-inflammatory effects of twice daily 0.01%, 0.1%, and 0.2% bromfenac drops were compared in 228 cataract cases. The 0.1% and 0.2% groups showed superior anti-inflammatory activity and although adverse events did not seem concentration dependent, the 0.1% concentration was deemed optimal to minimize any potential for corneal toxicity.

Several subsequent clinical studies have compared the efficacy of bromfenac ophthalmic solution to diclofenac ophthalmic solution in reducing inflammation after cataract surgery.²¹⁻²³ For example, Kawaguchi and associates²¹ found that bromfenac has a more rapid onset of anti-inflammatory activity than diclofenac based upon a prospective, single-center, randomized trial in 38 subjects (49 eyes) who underwent cataract surgery. Measuring aqueous flare levels, the group noted that at each time point, flare was lower in the bromfenac group than in the diclofenac group, a difference that was statistically significant during the first 2 weeks after surgery ($P < 0.05$), even with preoperative dosing of both drugs. No difference was noted between the effects of the 2 solutions on corneal epithelial barrier function as measured by anterior fluorophotometry.²¹

Takamatsu et al²² found that bromfenac ophthalmic solution exerted anti-inflammatory effects that were comparable to or greater than diclofenac ophthalmic solution, including comparable suppression of CME and posterior capsule opacification. Of clinical importance, bromfenac was associated with less corneal epitheliopathy than diclofenac. Subjects at 2 facilities were divided into bromfenac and diclofenac treatment groups after uncomplicated cataract surgery. A retrospective analysis of data from the first facility included a total of 228 eyes from 157 subjects, whereas a prospective analysis from the second facility included a total of 58 eyes from 30 subjects. Early differences in the flare level seen between the 2 treatment arms disappeared by the 28th postoperative day. However, the incidence of corneal epitheliopathy was significantly higher in the diclofenac group in the first center, despite TID dosing in both arms.

Ohara and associates²³ also compared the effects bromfenac ophthalmic solution with diclofenac ophthalmic solution on postoperative inflammation after cataract phacoemulsification and intraocular lens implantation. Their multicenter, open-label, clinical study divided 111 subjects into 2 treatment groups, each of which received 2 drops of bromfenac or diclofenac preoperatively, and then bromfenac BID or diclofenac TID with concomitant ophthalmic steroid and anti-infective for 4 weeks, beginning the day after surgery. Anterior chamber cells and flare in the 2 groups showed no difference after day 7. Although corneal epithelial disorder tended to be seen more frequently in the diclofenac group, the difference was not statistically significant.

To support the USFDA approval, two phase 3 clinical trials using a common protocol were completed in the United States to evaluate the efficacy, safety, and tolerability of bromfenac ophthalmic solution 0.09% in treating postoperative inflammation and pain after cataract surgery.^{5,6,24-27} There are two very important aspects of the design of these clinical trials which distinguish them from previous ophthalmic studies. First, no pre dosing of the agent or concomitant steroid use was permitted before randomization into the clinical study. Second, the degree of ocular inflammation at entry into the clinical trial was moderate to severe.

These multicenter, randomized, double-masked, parallel-group, placebo-controlled studies, enrolled subjects who had undergone unilateral cataract extraction and posterior chamber intraocular lens implantation and had a Summed Ocular Inflammation Score (SOIS = anterior chamber cell score plus flare score, each on a scale of 0 to 4) of ≥ 3 . Subjects were excluded if they used any ocular, topical, or systemic medication that could interfere with normal lacrimation, wound healing, the test agent, or the interpretation of study results, within 1 week before Study Visit 1, including NSAIDs, steroids, or anticoagulants; had uncontrolled ocular or systemic disease; preexisting ocular inflammation or surgical complications; or had liver function test values of grade 1 or greater scored according to World Health Organization Common Toxicity Criteria. Subjects who met all study inclusion criterion were enrolled and were instructed to instill their assigned medication (either bromfenac or vehicle) twice a day for 14 days. These subjects were not pretreated and did not receive their first dose of bromfenac until postsurgery day 1 (16 to 32h after surgery). Furthermore, the mean SOIS score at entry for both the bromfenac and vehicle groups was 3.7. Subjects with minimal inflammation after cataract surgery were excluded from the study. In summary, this study had no pretreatment, no ophthalmic corticosteroid use, and only included subjects with moderate to severe ocular inflammation after cataract surgery.

Treatment visits occurred on days 3, 8, 15, 22, and 29 after the day of surgery. In each of these visits, the amount of anterior chamber cells and flare was evaluated by slit-lamp examinations and graded. Additionally, subjects recorded their ocular discomfort twice daily in diaries. Important efficacy measures included clearing of ocular inflammation (defined as SOIS = 0) at 15 days postsurgery, mean SOISs at each study visit, and mean time to cessation of ocular pain as estimated from patient diary data.

The primary measure of efficacy was the percentage of subjects with cleared ocular inflammation (SOIS for anterior chamber cells and anterior chamber flare of zero, or SOIS = 0) on day 15 after surgery. For anterior chamber cells, 0 means a cell count of 0 to 5 (trace). Analysis of the pooled data from the 2 trials demonstrated that the percentage of

subjects treated with bromfenac 0.09% that had cleared inflammation by day 15 was 64% (228/356), significantly greater than the percentage in the vehicle-treated group (43.3%, 74/171; $P < 0.0001$).

Several secondary analyses were performed to fully evaluate the efficacy of bromfenac ophthalmic solution 0.09%. As shown in Figure 4, there was a statistically significant difference (bromfenac compared with vehicle) in the proportion of subjects achieving a mean reduction in anterior chamber cells grade at day 3 and at all subsequent visits ($P < 0.03$). Additionally, the percentage of subjects who achieved an SOIS of ≤ 1 at day 15 was statistically significant and clinically meaningful. Significantly more subjects in the bromfenac-treated group (303/356, 85%) had an SOIS reduced to ≤ 1 compared with subjects treated with vehicle (90/171, 53%; $P < 0.0001$).

At every postsurgical study visit from day 3 through day 29, the percentage of subjects treated with bromfenac who had cleared ocular inflammation significantly exceeded that seen in the vehicle group ($P \leq 0.01$). Findings of conjunctival erythema, conjunctival edema, and ciliary flush in biomicroscopy examinations were significantly better for subjects treated with bromfenac, supporting the efficacy of bromfenac ophthalmic solution 0.09% in reducing inflammation after cataract

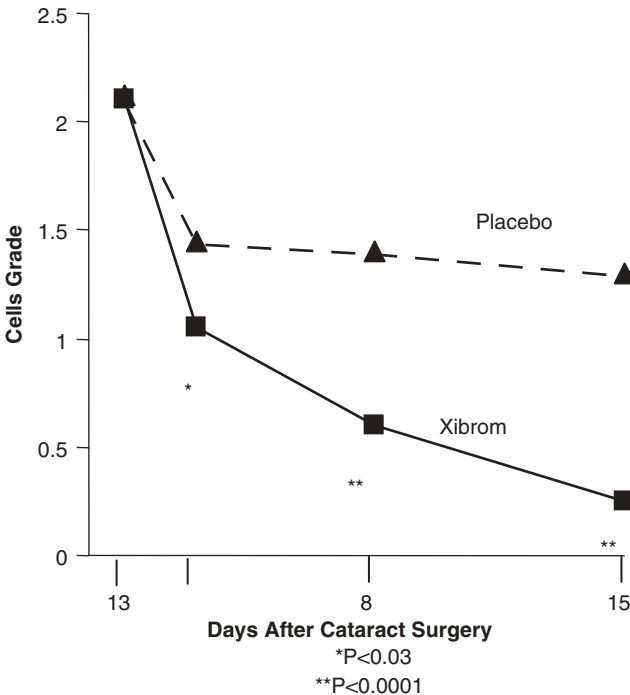


Figure 4. Xibrom US Phase III trial results for individual mean cell grade.²⁵

surgery. CME was reported as an adverse event for 1.4% of the subjects in the bromfenac group, compared with 4.7% ($P < 0.05$) in the vehicle group, suggesting that bromfenac treatment may have reduced the incidence of this important potential complication of cataract surgery.

Several reports have summarized the data on resolution of ocular pain from these 2 trials.^{26,27} Among subjects who experienced ocular pain after surgery, the median time for resolution of pain was 2 days for those treated with bromfenac compared with 5 days for those treated with vehicle ($P < 0.0001$). The proportion of subjects who were pain free was statistically significantly greater ($P \leq 0.0006$) for the bromfenac group than the vehicle group at all study visits (days 1, 3, 8, and 14 postsurgery). In January 2006, the FDA expanded the indication for bromfenac to include reduction of ocular pain after cataract surgery on the basis of these results.⁶

Other Clinical Applications of Ophthalmic NSAID Therapy

Further investigations suggest that bromfenac ophthalmic solution is clinically beneficial in a variety of other therapeutic and surgical settings in which ophthalmic NSAIDs have traditionally found a role, as well as in some novel applications. These clinical studies fall outside of the current US-approved indication for bromfenac in the treatment of ocular inflammation and reduction of ocular pain after cataract extraction. However, in addition to broadening the picture of the full clinical potential of this agent, these data underscore the unique pharmacokinetic properties that make bromfenac particularly useful in its approved indications.

The first use of NSAIDs in ophthalmology was for the prevention of miosis during cataract surgery.²⁸ Ohara and colleagues²⁹ compared bromfenac ophthalmic solution to diclofenac ophthalmic solution in an open label study of this application. After drop instillation at 60 and 30 minutes before surgery, pupil diameter and miosis rates were evaluated before surgery, at the end of irrigation and aspiration, and at the end of surgery. Neither parameter differed significantly between the 2 groups at any time point, although the miosis rate tended to be lower in the bromfenac group. The investigators concluded that bromfenac exerted a comparable antimiotic effect to diclofenac and would therefore be useful in suppressing miosis during cataract surgery.

NSAIDs have been found to be effective for the treatment of seasonal allergic conjunctivitis. Bromfenac ophthalmic solution was compared with the ophthalmic mast cell stabilizer pemirolast potassium for the treatment of seasonal allergic conjunctivitis in a clinical study by Miyake-Kashima et al.³⁰ After BID dosing of each type of drop in the opposite eye for 1 week, subjects were evaluated for improvement in 5 ocular signs and subjective symptoms. Both drugs significantly improved 4 of 5

objective signs but there was no significant difference between the drugs in objective efficacy. Neither drug significantly improved subjective symptoms after this brief treatment period nor was there any difference between them in the subjects' assessment.

Usui and Masuda³¹ reported on the evaluation of twice-daily bromfenac ophthalmic solution for the treatment of anterior uveitis over both 2-week and 12-week treatment courses. Effectiveness rates were calculated based on objective measurements of flare and unified cell/flare values obtained with a laser flare cell meter. Both evaluation methods revealed objective improvement. Using traditional anterior protein levels, efficacy rates were 62.7% (25/40) after 2 weeks and 76.9% (10/13) in the subjects who continued treatment for 12 weeks. Laser flare cell meter measurements produced efficacy rates of 51.9% (14/27) at 2 weeks and 80.0% (8/10) at 12 weeks. One case of superficial punctate keratitis was noted in the acute phase but this resolved with continued treatment and no additional adverse events were observed during longer-term treatment. The investigators concluded that bromfenac seemed to reduce inflammation associated with anterior uveitis with minimal side effects, potentially providing a safer alternative to long-term treatment with ophthalmic steroids.

Although none of the ophthalmic NSAIDs currently available in the United States are indicated for the prevention or treatment of CME after cataract surgery, published research and clinical experience suggest that the class may be useful in addressing this common complication.^{2,3,32} Rho et al³³ recently presented results of a study comparing bromfenac ophthalmic solution with diclofenac and ketorolac for the treatment of acute pseudophakic CME. Sixty-four eyes with documented CME after uncomplicated cataract surgery were randomized to receive bromfenac BID, diclofenac QID, or ketorolac QID for 3 months. After the treatment period, all 3 treatment groups achieved statistically significant visual improvement, evaluated by Early Treatment Diabetic Retinopathy Study letters gained over baseline, and, although the difference between the groups was not significant, there was a trend toward significance for bromfenac group. Rho concluded that twice daily bromfenac was statistically as effective as diclofenac or ketorolac dosed 4 times daily.

Solish³⁴ examined the potential use of NSAIDs in treating decreases in visual acuity experienced by some patients after glaucoma surgery, presumably as a result of CME. Twenty subjects with decreased vision after glaucoma procedures that had not improved with ophthalmic steroids were randomly assigned to receive either bromfenac BID (8 subjects) or ketorolac QID (12 subjects). Best corrected visual acuity was compared after 4 to 6 weeks of treatment. More subjects in the bromfenac group experienced improved visual acuity, with 2 subjects gaining 3 lines and 1 subject gaining 1 line, compared to the ketorolac group, in which 1 subject gained 1 line and 1 subject gained 2 lines. One

case of corneal thinning was noted in the bromfenac group and 1 case of punctate keratitis in the ketorolac group.

■ Safety Evaluations of Bromfenac Ophthalmic Solution

There has been periodic debate about the ocular and systemic safety of ophthalmic NSAIDs, related both to well-documented but relatively rare reports of corneal toxicity associated with ophthalmic use and clinical experience with their systemic formulations.^{35–37} However, the preponderance of clinical experience with the ophthalmic safety of the class has been positive and no reported systemic issues resulting from ophthalmic use have arisen. Bromfenac ophthalmic solution has an extensive global safety track record. The US FDA-evaluated local and systemic safety data from 9 phase 1-3 clinical trials conducted by Senju that include data on 893 subjects who received bromfenac for treatment periods ranging from 14 days up to 12 weeks and 2 identical phase 3 US clinical trials involving 356 subjects who received bromfenac for 14 days.^{19–23,38–41} In addition, data on thousands of patients collected in a mandatory postmarketing surveillance study and from spontaneous adverse event reports recorded since 2000, reflecting the experience of more than 10.3 million ophthalmic uses, confirm the excellent safety profile of the agent.⁴²

Ocular Safety

The most commonly reported adverse experiences in US phase 3 clinical trials of bromfenac ophthalmic solution included iritis, abnormal sensation in eye, eye pain, eye pruritus, headache, eye irritation (burning/stinging), and conjunctival hyperemia (Table 4). Safety assessments for subjects treated with bromfenac were generally equivalent to or better than those for subjects treated with vehicle. The percentages of subjects experiencing ocular adverse events were statistically significantly less in the bromfenac group than in the vehicle group ($P < 0.003$). Eye irritation was reported by 2.5% of the bromfenac group versus 4.7% vehicle. Burning and stinging was reported by 1.4% of the bromfenac group compared with 1.8% in the vehicle group. Twice the percentage of subjects in the vehicle group reported iritis and eye pain, the most common ocular adverse events, compared with the bromfenac group (Table 4). Results of postsurgical visual acuity examinations for the bromfenac group were either comparable to or better than those of vehicle group. Pupillary and funduscopic examinations found no significant differences, nor were increases in IOP significantly different between the 2 treatment groups.⁴³

Postmarket surveillance experience in Japan mirrors the safety results from US clinical trials. Unlike the majority of voluntary

TABLE 4. Common Ocular Adverse Events of Xibrom (Bromfenac Ophthalmic Solution) 0.09% Versus Vehicle⁴³

Ocular Adverse Events	Bromfenac 0.09%	Vehicle
Number	356 (100%)	171 (100%)
Iritis	7.0%	18.1%
Abnormal sensation in eye	6.5%	8.2%
Eye pain	4.2%	11.7%
Eye pruritus	3.9%	2.9%
Posterior capsule Opacification	3.9%	4.1%
Partial vision loss	3.1%	9.4%
Eye irritation (includes burning and stinging)*	2.5%	4.7%
Eye redness	2.2%	7.6%
Conjunctival hyperemia	2.2%	11.1%
Photophobia	2.0%	11.1%

*Burning and stinging for bromfenac ophthalmic solution 0.09% subjects = 1.4%.

postmarketing surveillance in the United States, the Japanese Pharmaceutical Affairs Law mandates a formal postmarketing surveillance process, requiring collection, study, and analysis of safety and efficacy data on pharmaceutical products after commercialization. A postmarket surveillance survey was begun on July 3, 2000 (the first day that bromfenac sodium ophthalmic solution 0.1% was available) and completed on January 14, 2004.⁴⁴ The resulting safety evaluation contains detailed demographic, medical history, complication/comorbidity, and treatment data on 3,425 patients. Most patients in the survey (89%) received bromfenac BID but 10.5% had greater dosing frequency. Treatment periods of more than 28 days accounted for 32.18% of the survey population. Roughly a third of all the patients received more than 50 drops of bromfenac (recommended dosing for the US indication is BID for 14 days or 28 drops) and nearly 150 received more than 200 drops.⁴⁴ There were 56 cases of adverse reactions out of a total of 3,425 patients (1.64%). Of these 56 cases, there were a total of 66 separate adverse events. All reported adverse drug events were local. The most frequently seen adverse drug event was corneal erosion (14 cases, 0.41%), followed by blepharitis (6 cases, 0.18%), superficial punctate keratitis, irritation, local pain, and pruritus (5 each, 0.15%). A total of 3 serious ocular adverse events were observed (a rate of 0.09%), involving 1 case each of endophthalmitis, ocular hypertension, and branch retinal vein occlusion. All of these were predictable from concurrent diseases and none were considered to be related to bromfenac.⁴⁴

In addition to the formal postmarket surveillance survey, data has also been collected from spontaneous adverse events reporting in Japan. Between January 15, 2000, and January 14, 2006, there were approximately 7.8 million patients treated with bromfenac ophthalmic

solution 0.1% in Japan, with over 10 million vials distributed. During this period, there were a total of 16 serious ocular adverse events spontaneously reported (0.0002%). These ocular adverse events included 4 corneal ulcers, 3 corneal erosions, 3 corneal perforations, 3 corneal infiltrates, 2 cases of corneal thinning, and 1 defect of the corneal epithelium.⁴²

Two of these previously reported cases of serious ocular adverse events were published by Mochizuki and colleagues in 2003.⁴⁵ These cases were included with a third (1 corneal erosion from 2001 and 2 corneal erosions from 2002) in a more recent paper by the same group.⁴⁶ Although the authors refer to these events as corneal melts (their earlier paper described the 2 cases as corneal ulcers), they report that all 3 resolved with conservative treatment and did not require penetrating keratoplasty. Because of predisposing clinical factors including preexisting corneal ulcer and prolonged duration of therapy, these 3 patients were not ideal candidates for NSAID treatment. Each patient also received other ophthalmic medications, one patient receiving bromfenac BID plus an ophthalmic fluoroquinolone and a corticosteroid (both QID) for 40 days.

Systemic Safety

The systemic safety of bromfenac ophthalmic solution is also well established. Pharmacokinetic data after exaggerated dosing (2 drops QID for 28 days) in healthy individuals suggest that systemic absorption of bromfenac ophthalmic solution is negligible.⁴⁷ In these subjects, the plasma concentration of bromfenac was below the level of detection (50 ng/mL) at all measurement time points.⁴⁷ This conclusion is reinforced by the fact that there have been no (zero) systemic adverse drug events associated with the product across the entire body of clinical and surveillance data from the United States and Japan, representing more than 10 million patient uses.⁴²

To provide additional confirmation of systemic safety, Shiffman and associates⁴⁸ reported that after 14 days of BID dosing, liver function test values were within normal range limits for more than 90% of subjects and that there was no evidence of a risk of hepatic toxicity. These clinical findings are reinforced by the previously reported surveillance data.⁴⁴ In the 39 subjects with documented hepatic function disorders before initiation of treatment with bromfenac ophthalmic solution, none had worsening of hepatic functions or reported serious adverse events.⁴³

■ **The Importance of Convenience and Comfort to Compliance**

There are 2 key benefits of the formulation of bromfenac ophthalmic solution. First, the convenient and unique BID dosing schedule as a result of its relative potency and pharmacokinetics in ocular tissue.

Second, the comfortable and high tolerability of the ophthalmic solution as reflected in a burning and stinging rate of 1.4%. These distinguishing qualities may enhance patient compliance and adherence to the dosage schedule. Although the impact of dosing is probably more pronounced over chronic therapy, even acute therapy can be undermined by poor compliance related to frequency of dosing. Ikeda and colleagues⁴⁹ have shown that subjects who were prescribed ophthalmic drops once or twice a day are much more compliant than subjects with more frequent dosing regimens. Comfort, which is a key component of overall patient satisfaction, has become more important with the increase in elective ophthalmic procedures.

After approval in the United States, several studies and survey were undertaken to evaluate physician and patient satisfaction with bromfenac ophthalmic solution and its comfort profile in normal clinical practice. More than 580 US-based ophthalmologists were recently surveyed regarding their experience with bromfenac ophthalmic solution in more than 12,000 patients. Responses to the survey questions were based on the physician's determination of overall patient satisfaction, control of inflammation, ease of use and compliance, and safety and comfort upon instillation. Nearly all physicians (99% to 100%) reported that bromfenac either met or exceeded their expectations in each of the 6 categories surveyed (Table 5).⁵⁰

Two investigator-initiated studies have recently evaluated the relative comfort of bromfenac ophthalmic solution 0.09%. The tolerability and corneal anesthetic properties of bromfenac and ketorolac tromethamine ophthalmic solution 0.4% (Acular LS) in 20 healthy volunteers were recently compared.⁵¹ Subjects were administered a single drop of each medication in a random and masked fashion and then asked to rate the severity of burning and stinging on a scale of 0 to 4. Eighty-five percent of subjects (17/20) reported no burning and stinging with bromfenac, compared to 35% (7/20) with ketorolac. None of the subjects reported moderate or severe burning or stinging with bromfenac, compared to 30% (6/20) with ketorolac.

TABLE 5. Results of the Xibrom First Experience Program, a survey of US Ophthalmologists Evaluating Bromfenac Ophthalmic Solution 0.09%⁵⁰

Parameter	Expectations Exceeded (%)	Met All Expectations (%)
Overall patient satisfaction	58	42
Control of inflammation	46	53
Ease of use by patients	81	19
Patient compliance	70	29
Comfort upon instillation	62	38
Safety profile	61	39

Maris and colleagues⁵² recently reported results of another study comparing bromfenac and nepafenac ophthalmic suspension 0.1% (Nevanac) on these comfort parameters. Twenty healthy volunteers were administered 1 drop of each medication and asked to rate the subjective sensation of burning and stickiness. Anesthesia was evaluated with Cochet-Bonet esthesiometry of the central cornea at 1, 5, 10, and 15-min intervals from administration. Neither bromfenac nor nepafenac produced a significant decrease in corneal sensitivity in the 15-min evaluation period, a finding consistent with data on diclofenac and ketorolac.⁵³ Bromfenac and nepafenac produced comparable levels of subjective burning although nepafenac produced significantly more subjective stickiness compared to bromfenac. The ocular adverse event of sticky sensation was also seen in approximately 5 to 10% of the subjects during the controlled clinical studies of nepafenac.⁵⁴

■ Conclusions

Bromfenac ophthalmic solution 0.09% (Xibrom) is a significant addition to the ophthalmic armamentarium. Preclinical data demonstrate that the unique chemical structure of bromfenac makes it both a potent inhibitor of the COX-2 enzyme and a highly lipophilic molecule that rapidly penetrates to produce early and sustained drug levels in all ocular tissues. Clinically, these pharmacokinetic features are manifested in a rapid reduction of postsurgical inflammation and pain with BID dosing. Bromfenac ophthalmic solution has an extensive global safety record, with formal clinical evaluation supplemented by postmarketing experience in over 10 million ophthalmic uses. Finally, the convenient twice-daily dosing schedule and low incidence of burning and stinging on instillation (1.4%) may enhance patient compliance and adherence to ophthalmic therapy. Further clinical investigations will explore the expanding use of bromfenac in a variety of perisurgical and therapeutic applications.

Eric D. Donnenfeld, MD, is a paid consultant for ISTA Pharmaceuticals, Inc., and was a principal investigator in the US Phase III bromfenac clinical trials. Dr. Donnenfeld is also a paid consultant for Allergan, Inc., and Alcon Laboratories, Inc.

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