

**PHARMACY & THERAPEUTICS COMMITTEE  
NEW DRUG EVALUATION**

**BROMFENAC (*XIBROM*<sup>®</sup>; *ISTA Pharmaceuticals, Inc.*)**

**DESCRIPTION:** <sup>1</sup>

Bromfenac ophthalmic solution 0.09% is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each ml contains 1.035mg of bromfenac sodium, which is equivalent to 0.9mg bromfenac free acid. It is available as 5ml in a 10ml squeeze bottle.

**INDICATION:** <sup>1-6</sup>

Bromfenac ophthalmic suspension is indicated for the treatment of postoperative inflammation and reduction of ocular pain following cataract surgery.

**CONTRAINDICATIONS/PRECAUTIONS:** <sup>1, 3, 6</sup>

Bromfenac ophthalmic solution is contraindicated in patients with known hypersensitivity to bromfenac or any of its ingredients.

The following precautions should be taken with bromfenac:

- Concurrent use of topical steroids or topical nonsteroidal anti-inflammatory drugs due to increased risk for delayed healing
- Bleeding tendencies or concurrent use of medications which could prolong bleeding times due to potential for increased bleeding time
- Patients with corneal epithelial defects, diabetes mellitus, ocular surface diseases, rheumatoid arthritis, repeat ocular surgeries, or repeat ocular surgeries due to increased risk for potentially sight-threatening adverse corneal effects
- Prolonged therapy (i.e., use which begins more than 1 day before surgery or continues beyond 14 days post surgery) due to increased risk for adverse corneal effects
- Use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or perforation. In the event of corneal epithelial breakdown, the drug should be discontinued immediately and patient should be closely monitored.
- Allergy to sulfite because bromfenac ophthalmic solution contains sodium sulfite
- Previous sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, or other NSAIDs due to potential for cross-sensitivity reaction

## **PHARMACOLOGY:** <sup>1, 4, 5, 7</sup>

Bromfenac is a nonsteroidal anti-inflammatory drug. It prevents prostaglandin H synthesis that causes papillary miosis. It decreases prostaglandin production by inhibiting cyclooxygenase 1 and 2, thereby inhibiting the inflammatory process. Due to the addition of the bromine group to its molecule, bromfenac has more affinity for lipids; therefore, it better penetrates the lipid layers of the eye.

## **PHARMACOKINETICS:** <sup>1</sup>

The plasma concentration of bromfenac following ocular administration of 0.09% bromfenac ophthalmic solution in humans is unknown. Based on the pharmacokinetic information from other routes of administration, after administering 1 drop of bromfenac ophthalmic solution to each eye (0.09mg), the systemic concentration of bromfenac is estimated to be below the limit of quantification (50ng/mL) at steady-state in humans. The better penetration of bromfenac allows it to be carried across the lipophilic cornea to enter ocular tissues that are susceptible to inflammation such as the aqueous humor, iris, ciliary body, choroids and retina. Due to its low IC assay, bromfenac is 6.5 times more potent than nepafenac ophthalmic solution 0.1% and 3.7 times more potent than diclofenac ophthalmic solution 0.5%.

## **CLINICAL STUDIES:** <sup>8, 9</sup>

The efficacy and safety of bromfenac ophthalmic solution 0.09% were evaluated in a multicenter, double-masked, randomized, parallel group, placebo-controlled study. Five hundred twenty-seven patients having cataract extraction and posterior chamber intraocular lens (IOL) implantation with a summed ocular inflammation score (SOIS) of  $\geq 3$  received bromfenac ophthalmic solution 0.09% (356 patients) or vehicle (171 patients), 1 drop twice daily continuing for up to 14 days. Patients were evaluated on days 3, 8, 15, 22 and 29 following the day of surgery. The primary efficacy was percentage of patients with cleared ocular inflammation (SOIS=0) on day 15 post surgery. The secondary efficacy was the percentage of patients with SOIS of 1 or better on day 15 post surgery. In addition, inclusion criteria required patients to have liver function tests (LFTs) less than grade 1 using the Common Toxicity Criteria (CTC) of the World Health Organization. Masked results from study subjects were evaluated by a board certified gastroenterologist specializing in liver disease. The key hepatic safety endpoint for the study was a post-treatment LFT of CTC grade 1 or higher. Bromfenac showed significantly better efficacy by day 15 (64% of bromfenac-treated patients had cleared inflammation compared to 43% of placebo-treated patients;  $p < 0.0001$ ). In addition, significantly more bromfenac treated patients had an SOIS decreased to 1 or better on day 15 than placebo-treated patients

(85% vs 53%, respectively;  $p < 0.0001$ ). Only 1.4% of bromfenac-treated patients reported eye irritation, including burning and stinging, compared to 4.7% of the placebo-treated patients. Liver function tests showed no toxic effects of ophthalmic administration of bromfenac.

In a single-center, randomized trial, the efficacy of bromfenac ophthalmic solution and diclofenac ophthalmic solution on postoperative anterior chamber inflammation and corneal barrier function was evaluated prospectively. Thirty-eight patients were enrolled in this study. Twenty-seven eyes of 19 patients received bromfenac ophthalmic solution and 22 eyes of 19 patients received diclofenac ophthalmic solution. Patients whose cataract nucleus hardness was rated as grade 2 or lower according to Emery-Little classification were enrolled in the study. Patients with history of uveitis, glaucoma or diabetes mellitus were excluded from the study. Preoperatively, levofloxacin ophthalmic solution 0.5%, and cefmenoxime ophthalmic solution 0.5% were applied 4 times a day, beginning 1 week prior to surgery. Mydriatics, such as 0.5% tropicamide and 0.5% phenylephrine hydrochloride and 5% phenylephrine hydrochloride, were applied before the surgery. In addition, bromfenac was applied 3 and 2 hours before surgery in the bromfenac-treated patients and diclofenac ophthalmic solution was applied 3, 2, 1, and 0.5 hours before surgery in the diclofenac-treated patients. The barrier function of the corneal epithelium was measured before and 1, 2, 4, and 12 weeks after surgery. Bromfenac had a significantly lower aqueous flare values on day 14 after surgery compared to diclofenac, ( $p < 0.05$ ). There were no significant differences between the drugs in anterior fluorophotometer values.

The anti-inflammatory effect of bromfenac ophthalmic solution on postoperative inflammation after phacoemulsification and intraocular implantation was evaluated in a multicenter, open-label and comparative trial. One hundred-eleven patients with aging-related cataracts were enrolled in this study. A mydriatic was administered 4 times at intervals of 30 minutes, beginning 2 hours before surgery. Bromfenac ophthalmic solution and diclofenac ophthalmic solution were applied twice (60 and 30 minutes before surgery). Bromfenac was administered twice a day and diclofenac was administered 3 times a day for 4 weeks, beginning 1 day after surgery. Certain mydriatics, betamethasone 0.1% and antimicrobial agents were administered concomitantly post surgery. The anterior chamber protein level was significantly lower in the bromfenac-treated patients than in the diclofenac group on day 3 post surgery; however, no significant difference was noted between the 2 groups on day 7. Anterior chamber cells also differed significantly between the 2 groups on day 3 but showed no significant difference on day 7. The flare level showed no difference between the 2 groups on days 1, 3, 7, or 14 post surgeries. Corneal epithelial disorder was reported more in diclofenac group than in the bromfenac group, but the difference was not significant.

**ADVERSE DRUG EVENTS:** <sup>1-4</sup>

The most common (2-7%) reported adverse events with bromfenac ophthalmic solution were: abnormal sensation in the eye, conjunctival hyperemia, eye irritation (including burning/stinging), eye pain, eye pruritus, eye redness, headache, and iritis. Corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown were reported during postmarketing use of bromfenac ophthalmic solution 0.09%. Because the events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

**DOSAGE AND ADMINISTRATION:** <sup>1,3,4,6</sup>

The recommended dose for the treatment of postoperative pain and inflammation following cataract surgery is 1 drop of bromfenac ophthalmic solution in the affected eye(s) 2 times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

**COST COMPARISON:**

<b>DRUG</b>	<b>DOSAGE REGIMEN</b>	<b>COST / BOTTLE*</b>
Xibrom (bromfenac) 0.09% Ophthalmic Solution	Instill 1 drop into affected eye 2 times daily beginning 24 hours after surgery and continuing for 2 weeks	\$93.75-5 ml
Nevanac (nepafenac) 0.1% Ophthalmic Suspension	Instill 1 drop into affected eye 3 times daily beginning 1 day prior to surgery and continuing for 2 weeks	\$78.75- 3 ml
Acular LS (ketorolac tromethamine) 0.4% Ophthalmic Solution	Instill 1 drop into affected eye 4 times daily as needed for pain and burning/stinging for up to 4 days after surgery	\$77.96-5 ml
Voltaren (diclofenac) 0.1% Ophthalmic Solution	Instill 1 drop into affected eye 4 times a day beginning 24 hours after surgery and continuing for 2 weeks	\$72.95-5 ml

\*Average Wholesale Price

## **CONCLUSION:**

NSAIDs play an important role in preventing and treating postoperative inflammatory responses in ocular surgery; therefore, they are being used routinely in cataract and refractive surgeries. Bromfenac ophthalmic solution 0.09% (Xibrom) is a sterile, topical, non-steroidal anti-inflammatory compound for the treatment of ocular inflammation and pain following cataract surgery. Senju Pharmaceuticals Co. Ltd. has marketed this product in Japan since 2000. Bromfenac's molecular structure results in a more potent anti-inflammatory compound and enhanced penetration into inflamed ocular tissues. In vitro studies showed its inhibition of prostaglandin synthesis as approximately 12-fold greater than that of indomethacin and 1.8 and 3.7 times the inhibitory effect on COX-1 and COX-2 than diclofenac, respectively. However, efficacy measurements for inflammation post op appear comparable for bromfenac and diclofenac. Clinical studies also showed that only 1.4% of patients taking bromfenac reported burning or stinging. Corneal lens damage has been reported infrequently with all NSAIDs. Liver function tests revealed no toxic effects of ophthalmic administration of bromfenac. Bromfenac's twice daily dosing and lower daily cost may result in a greater compliance than more frequent dosing schedules.

## **RECOMMENDATION:**

May add to formulary.

## REFERENCES

1. Xibrom (bromfenac 0.09% ophthalmic solution) Package insert. ISTA Pharmaceuticals, Inc. July 2005.
2. Xibrom (bromfenac ophthalmic solution) 0.09% sterile.  
<http://www.rxlist.com/cgi/generic-4/xibrom.htm>
3. Micromedex. Bromfenac ophthalmic solution
4. Xibrom overview.  
[http://www.istavision.com/research/products\\_bromfenac.asp](http://www.istavision.com/research/products_bromfenac.asp)
5. Bromfenac 0.09% ophthalmic solution (Xibrom).  
[http://www.multum.com/bromfenac\\_ophth.htm](http://www.multum.com/bromfenac_ophth.htm)
6. Will new FDA approval spur NSAIDs interest?  
[http://www.revophth.com/index.asp?page=1\\_741.htm](http://www.revophth.com/index.asp?page=1_741.htm)
7. New drug approval notification.  
[http://www.rxsolutions.com/c/rxnews\\_view.asp?Article=569&type=18](http://www.rxsolutions.com/c/rxnews_view.asp?Article=569&type=18)
8. Bromfenac ophthalmic solution. Formulary.  
<http://www.formularyjournal.com/article/articleDetail.jsp?id=164914>
9. ISTA-BR-CS001. ISTA Pharmaceutical abstract.
10. Kawaguchi T, Kida T, et al. Effect of bromfenac ophthalmic solution on ocular inflammation and corneal epithelial barrier function following cataract surgery. *Folia Ophthalmol Jpn* 2003; 54: 276-9.
11. Ohara K, Ohkuba A, et al. Effect of bromfenac sodium on postoperative inflammation. ISTA Pharmaceutical abstract.