**National PBM Drug Monograph**

# Bromfenac 0.09% Ophthalmic Solution (Xibrom®)

**June 2006**

**VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel**

## Executive Summary:

### Indication

- Bromfenac 0.09% ophthalmic solution is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.

### Dosing

- The recommended dosage of bromfenac 0.09% ophthalmic solution for the treatment of postoperative inflammation in patients who have undergone cataract extraction is one drop into the affected eye(s) twice daily beginning 24 hours after cataract surgery and continuing through the first two weeks of the postoperative period.

### Efficacy

- FDA approval was based on the results of two unpublished, double-blind, placebo-controlled studies using bromfenac 0.1% ophthalmic solution. In one study enrolling 296 patients, ocular inflammation was absent in 62.6% of bromfenac-treated patients, compared with 39.8% of placebo-treated patients at 15 days ($P < 0.01$). In the other study enrolling 231 patients, ocular inflammation was absent in 65.8% of bromfenac-treated patients and 47.9% of placebo-treated patients at 15 days ($P < 0.01$).

### Safety

- The most common adverse events reported included abnormal sensation in eye, conjunctival hyperemia, eye irritation (including burning/stinging), eye pain, eye pruritus, eye redness, headache, and iritis. These events were reported in 2% to 7% of patients.
- Three case reports have been published describing corneal melting in patients using bromfenac ophthalmic solution.
- Concentrations of bromfenac sodium and its metabolites achieved following ophthalmic administration were not observed to induce cytotoxicity in a human liver microsome study.
- Bromfenac 0.09% ophthalmic solution is Pregnancy Category C.

## Introduction

A cataract is an opacity of the lens of the eye that causes partial or total blindness. Cataract formation typically is bilateral, although it is often asymmetrical. Most cases of cataract occur in patients over age 60 or in younger individuals who have risk factors such as diabetes mellitus, systemic steroid use, or a history of significant eye trauma. The only treatment for cataract is to surgically remove the opacified lens from the eye to restore transparency of the visual axis.[1]

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating bromfenac 0.09% ophthalmic

solution for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

## Pharmacology/Pharmacokinetics

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2.[2]

The plasma concentration following ophthalmic administration is unknown; however, based on the recommended dose of one drop to each eye (0.09 mg) and pharmacokinetic information from other routes of administration, the systemic concentration of bromfenac is estimated to be below the level of quantification (50 ng/mL) at steady state in humans.[2]

In a rabbit model of ocular inflammation, effects of bromfenac were observed in the contralateral eye, suggesting possible systemic effects.[3]

## FDA Approved Indication(s) and Off-label Uses

Bromfenac 0.09% ophthalmic solution is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.[2] Potential off-label uses include ocular allergy and reduction of post-cataract cystoid macular edema (CME).[4,5]

Approval rating: 3S

## Current VA National Formulary Status

| | Non-VA Formulary | VA Formulary | |
|---|---|---|---|
| | Bromfenac sodium 0.09% [2] | Ketorolac tromethamine 0.5% [6] | Diclofenac sodium 0.1% [7] |
| **FDA Approved Indications** | | | |
| Treatment of postoperative inflammation following cataract extraction | X | X | X |
| Reduction of ocular pain in patients who have undergone cataract extraction | X | | |
| Temporary relief of pain and photophobia following corneal refractive surgery | | | X |
| Temporary relief of ocular itching due to seasonal allergic | | X | |

| | | | |
|---|---|---|---|
| conjunctivitis | | | |

## Dosage and Administration

The recommended dosage of bromfenac 0.09% ophthalmic solution for the treatment of postoperative inflammation in patients who have undergone cataract extraction is one drop into the affected eye(s) twice daily beginning 24 hours after cataract surgery and continuing through the first two weeks of the postoperative period.[2]

## Adverse Events (Safety Data)

### Deaths and Other Serious Adverse Events

No deaths have been reported with bromfenac 0.09% ophthalmic solution. In postmarketing surveillance, less frequently reported events observed included corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown.[2]

Three case reports of corneal melting have been published in patients using topical bromfenac to treat ocular surface inflammation and postoperative inflammation. Severe corneal melting was characterized by mild hyperemia, very faint infiltration, and mild pain. None of the patients in the report had undergone cataract extraction surgery. One patient had been using bromfenac ophthalmic solution for 40 days. All cases were resolved with conservative treatment that included the use of a bandage soft contact lens and/or antibiotics and lubrication.[8]

### Common Adverse Events

The most common adverse events reported following the use of bromfenac 0.09% ophthalmic solution after cataract surgery included abnormal sensation in eye, conjunctival hyperemia, eye irritation (including burning/stinging), eye pain, eye pruritus, eye redness, headache, and iritis. These events were reported in 2% to 7% of patients.[2]

### Other Adverse Events

A previously available oral formulation of bromfenac sodium was withdrawn from the market because of the occurrence of hepatic toxicity. Concentrations of bromfenac sodium and its metabolites achieved following ophthalmic administration were not observed to induce cytotoxicity in a human liver microsome study.[9]

### Tolerability

| **Adverse Effect** | Bromfenac sodium 0.09% [4] | Ketorolac tromethamine 0.5% [6] | Diclofenac sodium 0.1% [7] |
|---|---|---|---|
| Transient burning and stinging | 1.4% | 40% | 15% |

Bromfenac ophthalmic solution is in Pregnancy Category C. Teratogenicity has not been observed in animal studies; however, bromfenac was associated with embryo-fetal lethality, increased neonatal mortality, and reduced postnatal growth at high doses in rats, and increased post-implantation losses at high doses in rabbits. Use during pregnancy is recommended only if the potential benefit justifies the potential risk to the fetus. Use should be avoided during late pregnancy because of the known effects of prostaglandin-inhibiting agents on the fetal cardiovascular system (closure of the ductus arteriosus).[2]

Caution is advised if bromfenac ophthalmic solution is administered to a breast-feeding woman.[2]

## Precautions/Contraindications

**Precautions**

Bromfenac ophthalmic solution contains sodium sulfite, which is known to cause allergic-type reactions, including anaphylactic symptoms and asthma, in susceptible patients.[2]

Caution is advised in patients with a history of hypersensitivity to aspirin, phenylacetic acid, and other NSAIDs because of the potential for cross-sensitivity. [2]

NSAIDs can increase bleeding time by interfering with platelet aggregation. Ocularly applied NSAIDs may increase bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Bromfenac ophthalmic solution should be used with caution in patients with known bleeding tendencies or who are receiving other medications that may prolong bleeding time.[2]

All topical NSAIDs may slow or delay healing. Topical corticosteroids also are known to slow or delay healing. Concomitant use of topical NSAIDs and corticosteroids may increase the potential for delayed healing.[2]

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use may also result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. Use should be immediately discontinued in patients with evidence of corneal epithelial breakdown. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases, rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events that may be sight-threatening. Topical NSAIDs should be used with caution in these patients. Use of topical NSAIDs more than 24 hours before surgery or beyond 14 days after surgery may increase the risk for occurrence and severity of corneal adverse events.[2]

**Contraindications**

Bromfenac 0.09% ophthalmic solution is contraindicated in patients with known hypersensitivity to any of the product ingredients.[2]

Bromfenac ophthalmic solution should not be administered while the patient is wearing contact lenses.[2]

## Look-alike / Sound-alike Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

**LA/SA for generic name bromfenac:**

Potential name confusion: Bromfed-DM (2mg/5mL syrup)

Potential severity: Minor

Probability: Uncommon

Potential name confusion: Bromfenex PD (6mg capsule)

Potential severity: Minor

Probability: Uncommon

Potential name confusion: Nepafenac (0.1% ophthalmic suspension)
Potential severity: Minor
Probability: Uncommon

Potential name confusion: Diclofenac (0.1% ophthalmic solution)
Potential severity: Minor
Probability: Uncommon

Potential name confusion: Ketorolac (0.5% ophthalmic solution)
Potential severity: Minor
Probability: Uncommon

**LA/SA for trade name Xibrom:**

Potential name confusion: Xalatan (0.005% ophthalmic solution)
Potential severity: Minor
Probability: Uncommon

Potential name confusion: Xigris (2mg/mL injection)
Potential severity: Moderate
Probability: Remote

Potential name confusion: Xeloda (150mg tablet)
Potential severity: Severe
Probability: Uncommon

## Drug Interactions

### Drug-Drug Interactions

Bromfenac 0.09% ophthalmic solution should be used with caution in patients receiving other medications that may prolong bleeding time.[2]

Bromfenac 0.09% ophthalmic solution has been observed to attenuate the intraocular pressure–lowering effects of latanoprost ophthalmic solution in healthy volunteers.[10]

## Efficacy Measures

FDA approval was based on the results of two unpublished, double-blind, placebo-controlled studies using bromfenac 0.1% ophthalmic solution. These studies were performed in patients who had undergone cataract surgery and had baseline postoperative inflammation [Summed (cell plus flare) Ocular Inflammation Score (SOIS) of 3 or greater]. They were randomly assigned therapy with either bromfenac sodium 0.1% ophthalmic solution or placebo twice daily for 14 days starting the day after surgery. Therapy was initiated 16 to 32 hours after surgery. Mean baseline SOIS was 3.7. Efficacy assessments were completed on days 3, 8, 15, 22, and 29. The primary endpoint of both studies was the percent of patients achieving treatment success, defined as the complete absence of ocular inflammation. Secondary efficacy endpoints included mean change from baseline for SOIS prior to receipt of any rescue medication and time to resolution of ocular pain.[11]

In one study enrolling 296 patients, ocular inflammation was absent in 62.6% of bromfenac-treated patients compared with 39.8% of placebo-treated patients at 15 days ($P < 0.01$). Among patients who received no other medications, inflammation cleared in 57.6% treated with bromfenac compared with

23.5% treated with placebo. In the other study enrolling 231 patients, ocular inflammation was absent in 65.8% of bromfenac-treated patients and 47.9% of placebo-treated patients at 15 days ($P < 0.01$). Among patients in this study who received no other medications, inflammation cleared in 62% treated with bromfenac compared with 31.5% treated with placebo. For the combined study population, the mean change in SOIS from baseline was significant on days 3, 8, and 15 following initiation of therapy. The mean change was 1.4 with bromfenac compared with 0.9 with placebo on day 3 ($P < 0.0002$), 2.4 with bromfenac compared with 1.1 with placebo on day 8 ($P < 0.0001$), and 2.9 with bromfenac compared with 1.5 with placebo on day 15 ($P < 0.0001$). The mean number of days to resolution of ocular pain was 1.9 days with bromfenac compared with 5.9 days for placebo ($P < 0.0001$).[11]

## Clinical Trials

No published clinical trials are available for bromfenac 0.09% ophthalmic solution.

## Acquisition Costs

| Drug | Dose for the treatment of postoperative inflammation following cataract extraction | Bottle Sizes | Cost/Day/ Patient ($) * | Cost/Regimen/ Patient ($) *+ |
|---|---|---|---|---|
| Bromfenac sodium 0.09% | 1 drop 2 times daily to the affected eye beginning 24 hours after surgery and continuing 2 weeks | 5mL | 3.76 | 52.63 |
| Ketorolac tromethamine 0.5% | 1 drop 4 times daily to the affected eye beginning 24 hours after surgery and continuing 2 weeks | 3 mL<br>5mL<br>10mL | 1.72<br>2.85<br>5.72 | 24.07<br>40.02<br>80.06 |
| Diclofenac sodium 0.1% | 1 drop 4 times daily to the affected eye beginning 24 hours after surgery and continuing 2 weeks | 2.5mL<br>5mL | 1.48<br>3.06 | 20.65<br>42.82 |

* Based on Federal Supply Schedule
+ Assumes 1 unit/regimen

## Conclusions

Bromfenac 0.09% ophthalmic solution dosed twice daily likely has improved adherence over formulary agents which are dosed four times a day. Bromfenac 0.09% ophthalmic solution also has a lower incidence of burning and stinging following administration compared to ketorolac and diclofenac ophthalmic solutions. There are no comparative studies and limited efficacy data available for bromfenac 0.09% ophthalmic solution. Bromfenac 0.09% ophthalmic solution is more expensive than current VA formulary agents with a cost/day/patient of $3.76.

## Recommendations

Due to the lack of comparative data proving superiority over other formulary agents, a clear benefit of bromfenac 0.09% ophthalmic solution can not be supported. With the addition to this new topical NSAID to the marketplace, consideration may be given to submitting this class of drugs for contracting.

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