

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Xibrom (bromfenac ophthalmic solution) 0.09% safely and effectively. See full prescribing information for Xibrom.

XIBROM (bromfenac ophthalmic solution) 0.09% Initial U.S. Approval: 1997

INDICATIONS AND USAGE

Xibrom is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction (1).

DOSAGE AND ADMINISTRATION

One drop should be applied to the affected eye two times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period (2.1).

DOSAGE FORMS AND STRENGTHS

Topical ophthalmic solution: bromfenac 0.09% (3)

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Sulfite Allergic Reactions (5.1)
- Slow or Delayed Healing (5.2)
- Potential for cross-sensitivity (5.3)
- Increase bleeding of ocular tissues (5.4)
- Corneal effects including keratitis (5.5)
- Contact Lens Wear (5.6)

ADVERSE REACTIONS

The most commonly reported adverse reactions in 2 to 7% of patients were abnormal sensation in eye, conjunctival hyperemia and eye irritation (including burning/stinging) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact ISTA Pharmaceuticals, Inc. at 1-877-788-2020, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION Revised: XX/2013

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Xibrom (bromfenac ophthalmic solution) 0.09% is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

One drop of Xibrom ophthalmic solution should be applied to the affected eye two times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

2.2 Use with Other Topical Ophthalmic Medications

Xibrom ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Topical ophthalmic solution: bromfenac 0.09%.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

5.2 Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

5.3 Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

5.4 Increased Bleeding Time

With some NSAIDs, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that Xibrom ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

5.5 Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for the occurrence and severity of corneal adverse events.

5.6 Contact Lens Wear

Xibrom should not be administered while wearing contact lenses. Remove contact lenses prior to instillation of Xibrom. The preservative in Xibrom, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of Xibrom.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most commonly reported adverse reactions reported following use of bromfenac after cataract surgery include: abnormal sensation in eye, conjunctival hyperemia, eye irritation (including burning/stinging), eye pain, eye pruritus, eye redness, headache, and iritis. These reactions were reported in 2 to 7% of patients.

6.2 Post-Marketing Experience

The following reactions have been identified during post-marketing use of bromfenac ophthalmic solution 0.09% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical bromfenac ophthalmic solution 0.09% or a combination of these factors, include corneal erosion, corneal

perforation, corneal thinning, and epithelial breakdown [see *Warnings and Precautions (5.5)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with Xibrom in pregnant women. No malformations were observed in reproduction studies in rats and rabbits with oral doses of bromfenac at exposures up to 150 times (rats) and 90 times (rabbits) the predicted human systemic exposure; however, both embryoletality and maternal toxicity were observed at the highest dose exposures. The systemic concentration of bromfenac is estimated to be below the limit of quantification (50 ng/mL) at steady-state in humans, following ocular administration [see *Clinical Pharmacology (12.3)*]. 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.

Clinical Considerations

Premature closure of the ductus arteriosus in the fetus has occurred with third trimester use of oral and injectable NSAIDs. Measurable maternal and fetal plasma drug levels are available with oral and injectable routes of NSAID administration. The maternal plasma level of Xibrom following ocular administration is unknown [see *Clinical Pharmacology (12.3)*].

Animal Data

Reproduction studies performed in rats at oral doses of bromfenac up to 0.9 mg/kg/day (systemic exposure 90 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and rabbits at oral doses up to 7.5 mg/kg/day (150 times the predicted human systemic exposure) produced no drug-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3 mg/kg/day (30 times the predicted human exposure), and caused dystocia, increased neonatal mortality and reduced postnatal growth at 0.9 mg/kg/day.

8.3 Nursing Mothers

It is not known if Xibrom is present in human milk. The systemic concentration of bromfenac is estimated to be below the limit of quantification (50 ng/mL) at steady-state in humans, following ocular administration [see *Clinical Pharmacology (12.3)*]. Based on the low level of systemic exposure, it is unlikely that Xibrom would be detected in human milk using available assays. Caution should be exercised when Xibrom ophthalmic solution is administered to a nursing woman.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 have not been established.

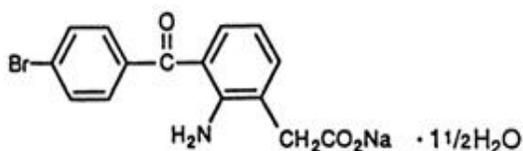
8.5 Geriatric Use

There is no evidence that the efficacy or safety profiles for Xibrom differ in patients 65 years of age and older compared to younger adult patients.

11 DESCRIPTION

Xibrom (bromfenac ophthalmic solution) 0.09% is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each mL of Xibrom contains

1.035 mg bromfenac sodium sesquihydrate (equivalent to 0.9 mg bromfenac free acid). Bromfenac sodium is designated chemically as sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate, with an empirical formula of $C_{15}H_{11}BrNNaO_3 \cdot 1\frac{1}{2}H_2O$. The structural structure for bromfenac sodium is:



Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. Xibrom ophthalmic solution is supplied as a sterile aqueous 0.09% solution, with a pH of 8.3. The osmolality of Xibrom ophthalmic solution is approximately 300 mOsmol/kg.

Each mL of Xibrom ophthalmic solution contains:

Active: bromfenac sodium sesquihydrate 0.1035% equivalent to 0.9 mg bromfenac free acid

Preservative: benzalkonium chloride (0.05 mg/mL)

Inactives: boric acid, disodium edetate (0.2 mg/mL), polysorbate 80 (1.5 mg/mL), povidone (20 mg/mL), sodium borate, sodium sulfite anhydrous (2 mg/mL), sodium hydroxide to adjust pH and water for injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

12.3 Pharmacokinetics

The plasma concentration of bromfenac following ocular administration of 0.09% Xibrom (bromfenac ophthalmic solution) in humans is unknown. Based on the maximum proposed dose of one drop to the eye (0.09 mg) twice a day and PK information from other routes of administration, the systemic concentration of bromfenac is estimated to be below the limit of quantification (50 ng/mL) at steady- state in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (systemic exposure 30 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and 5 mg/kg/day (340 times the predicted human systemic exposure), 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 (systemic exposure 90 and 30 times the predicted human exposure, respectively).

14 CLINICAL STUDIES

14.1 Ocular Inflammation and Pain

Clinical efficacy was evaluated in two randomized, double-masked, vehicle-controlled U.S. trials in which subjects with a summed ocular inflammation score ≥ 3 after cataract surgery were assigned to Xibrom or vehicle in a 2:1 ratio following surgery. One drop of Xibrom or vehicle was self-instilled in the study eye twice a day for 14 days, beginning the day after surgery. The primary endpoint was reduction of ocular inflammation (to trace inflammation or clearing) assessed 14 days post-surgery using a slit lamp binocular microscope. In the intent-to-treat analyses of both studies a significant effect of Xibrom on ocular inflammation after cataract surgery was demonstrated (62-66% vs. 40-48%).

An additional efficacy end point was the time required for resolution of ocular pain in subjects who reported pain. Overall, only 20% of the patients undergoing cataract surgery in these trials had pain on the first day after surgery. In these patients, the Xibrom group demonstrated a statistically significant difference in median time to resolution of ocular pain of 2 days compared to 4 days for patients receiving vehicle.

16 HOW SUPPLIED/STORAGE AND HANDLING

Xibrom (bromfenac ophthalmic solution) 0.09% is supplied in a white LDPE plastic squeeze bottle with a 15 mm LDPE white dropper-tip and 15 mm polypropylene gray cap as follows:

2.5mL in 7.5mL container (NDC 67425-004-12)

5mL in 10mL container (NDC 67425-004-50)

STORAGE

Store at 15° – 25°C (59° – 77°F).

17 PATIENT COUNSELING INFORMATION

17.1 Slowed or Delayed Healing

Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

17.2 Sterility of Dropper Tip

Advise patients to not touch dropper tip to any surface, as this may contaminate the contents.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

17.3 Concomitant Use of Contact Lenses

Advise patients that contact lenses should not be worn during the use of this product. The preservative in Xibrom, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of Xibrom.

17.4 Concomitant Topical Ocular Therapy

Advise patients that if more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart

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