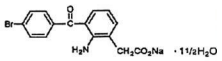
BROMFENAC - bromfenac sodium solution/ drops
Mylan Pharmaceuticals, Inc.

STERILE

DESCRIPTION
Bromfenac ophthalmic solution 0.09% is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each mL of bromfenac ophthalmic solution contains 1.035 mg bromfenac sodium (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 $C_{15}H_{11}BrNNaO_3 \cdot 1\ 1/2\ H_2O$. The structural formula of bromfenac sodium is:



Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. Bromfenac ophthalmic solution is supplied as a sterile aqueous 0.09% solution, with a pH of 8.3. The osmolality of bromfenac ophthalmic solution is approximately 300 mOsmol/kg. Each mL of bromfenac ophthalmic solution contains: **Active:** bromfenac sodium hydrate 0.1035%. **Inactives:** benzalkonium chloride (0.05 mg/mL), 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 the pH, and water for injection, USP.

CLINICAL PHARMACOLOGY

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.

Pharmacokinetics
The plasma concentration of bromfenac following ocular administration of bromfenac ophthalmic solution 0.09% in humans is unknown. Based on the maximum proposed dose of one drop to each eye (0.09 mg) 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.

CLINICAL TRIALS
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 bromfenac ophthalmic solution or vehicle in a 2:1 ratio following surgery. One drop of bromfenac ophthalmic solution 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 bromfenac ophthalmic solution on ocular inflammation after cataract surgery was demonstrated (62% to 66% vs. 40% to 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 bromfenac ophthalmic solution 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.

INDICATIONS AND USAGE
Bromfenac ophthalmic solution is indicated for the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract extraction.

CONTRAINDICATIONS
Bromfenac ophthalmic solution is contraindicated in patients with known hypersensitivity to any ingredient in the formulation.

WARNINGS
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 nonasthmatic people.
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.

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.

PRECAUTIONS

General

All topical non-steroidal 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.
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.
Postmarketing 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.
Postmarketing 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.
It is recommended that bromfenac ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for Patients

Bromfenac ophthalmic solution should not be administered while wearing contact lenses.

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 mcg/kg in 60 kg person on a mg/kg/basis, assuming 100% absorbed) and 5 mg/kg/day (3000 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 (4500 times RHOD) revealed no evidence of teratogenicity due to bromfenac. However, 0.9 mg/kg/day in rats caused embryo-fetal lethality, increased neonatal mortality, 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.

Non-Teratogenic Effects
Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of bromfenac ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers

Caution should be exercised when bromfenac ophthalmic solution is administered to a nursing woman.

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

The most commonly reported adverse experiences reported following use of bromfenac ophthalmic solution 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 events were reported in 2% to 7% of patients.

CLINICAL PRACTICE

The following events have been identified during postmarketing 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 events, 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 PRECAUTIONS, General)**.

DOSAGE AND ADMINISTRATION

For the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract extraction, one drop of bromfenac 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.

HOW SUPPLIED

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. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

NDC 0378-7109-35	5 mL in 10 mL container
NDC 0378-7110-35	2.5 mL in 6 mL container

Storage

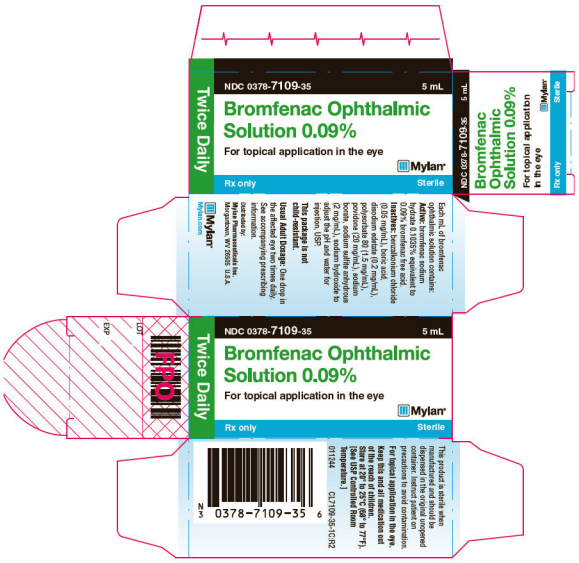
Store at 20º to 25°C (68º to 77°F). [See USP Controlled Room Temperature.]

Rx Only

Distributed by:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
NOVEMBER 2012
011246
CL:BROM:R2

PRINCIPAL DISPLAY PANEL - 5 ML BOTTLE CARTON

NDC 0378-**7109**-35
5 mL
Twice Daily
Bromfenac Ophthalmic
Solution 0.09%
For topical application in the eye
Mylan®
Rx only
Sterile



PRINCIPAL DISPLAY PANEL - 2.5 ML BOTTLE CARTON
NDC 0378-**7110**-35
2.5 mL
Twice Daily
Bromfenac Ophthalmic
Solution 0.09%
For topical application in the eye
Mylan®
Rx only
Sterile

PRINCIPAL DISPLAY PANEL - 2.5 ML SAMPLE BOTTLE CARTON
NDC 0378-**7111**-35
2.5 mL
Twice Daily
Bromfenac Ophthalmic
Solution 0.09%
For topical
application in the eye
PROFESSIONAL SAMPLE
NOT TO BE SOLD

Mylan®
Rx only
Sterile