

# A Q.D. NSAID Option

Now with once daily dosing, bromfenac offers clinical efficacy with simplicity and comfort.

BY FARRELL "TOBY" TYSON, MD



The perioperative use of topical non-steroidal anti-inflammatory drugs (NSAIDs) in cataract surgery has become routine due to their ability to control pain and inflammation post-operatively. One of the barriers to patient compliance with NSAIDs,

however, is the dosing schedule—typically, these agents are labeled for dosing b.i.d., t.i.d., or q.i.d. following cataract surgery. Fortunately, the leading topical ophthalmic NSAID, bromfenac [XIBROM (bromfenac ophthalmic solution) 0.09%; ISTA Pharmaceuticals, Inc., Irvine, CA], recently gained FDA approval for once-a-day dosing to treat inflammation and pain associated with cataract surgery. BROMDAY (bromfenac ophthalmic solution) 0.09% (ISTA Pharmaceuticals, Inc.) delivers the efficacy ophthalmologists have come to expect from twice daily bromfenac with half the number of drops of XIBROM and a lower medication load than other NSAIDs. I participated as an investigator in the BROMDAY clinical studies; this article summarizes the data from those trials and discusses the potential impact of the first and only q.d. ophthalmic NSAID for cataract surgery on clinical practice.

## BROMFENAC EFFICACY

The unique chemical structure of the bromfenac molecule makes it effective as a once daily treatment. Bromfenac is halogenated with bromine, making it very potent against the cyclo-oxygenase (COX) enzymes that are responsible for inflammation and pain.



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"BROMDAY delivers the efficacy ophthalmologists have come to expect from twice daily bromfenac with half the number of drops and a lower medication load than other NSAIDs."

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This halogenation also makes the bromfenac molecule highly lipophilic, enabling it to penetrate the cornea efficiently and maintain high levels of active drug in the anterior chamber. Due to its excellent pharmacokinetics and bioavailability, bromfenac successfully controls postoperative inflammation and pain following cataract surgery at a relatively low concentration and with less frequent dosing. The efficacy of bromfenac was underscored in both XIBROM and BROMDAY clinical trials, because it eliminated inflammation without the aid of a topical corticosteroid. In fact, I used XIBROM as a stand-alone anti-inflammatory therapy in cataract surgery for patients not at high risk, and they rarely required rescue with a corticosteroid. I like the idea of eliminating the cost of the steroid for my patients and not having to worry about potential steroid-associated adverse events. Of course, I also expect

patient compliance and satisfaction with fewer medications and less frequent dosing.

### CLINICAL TRIAL RESULTS

The BROMDAY clinical trials, which involved more than 800 patients, provide robust proof of the efficacy of the drug's q.d. dosing. Once daily dosing was first investigated in a study comparing two concentrations of bromfenac (data on file, ISTA Pharmaceuticals, Inc.). In three subsequent studies, subjects were pre-treated with either BROMDAY or placebo 1 day prior to undergoing cataract surgery, and they were given only BROMDAY or placebo (they did not receive any topical corticosteroids) on the day of surgery and for 14 days post-operatively. Thus, the reduction of inflammation and pain as well as the discontinuation rates in the treatment groups were predicated on 16 drops of BROMDAY alone. The FDA based its approval of BROMDAY on two of the placebo-controlled studies it considered pivotal trials. An integrated analysis of all four studies has also been performed (data on file, ISTA Pharmaceuticals, Inc.).

It is worth noting that all of these studies used complete clearing of inflammation—a summed ocular inflammation score (SOIS) of zero (zero cells and zero flare)—as the primary endpoint. When both the pivotal and integrated results were re-graded to include *trace* inflammation (0 to 5 cells and zero flare) in the endpoint, mirroring the design of earlier NSAID clinical programs, nearly 8 out of 10 patients treated with BROMDAY achieved success by postoperative day 15. Specifically, 74% to 79% of patients treated with BROMDAY reached zero-to-trace inflammation compared to 40% to 42% of the patients treated with placebo across both the pivotal (two studies) and integrated (four studies) analyses.

Returning to the prospectively-defined primary endpoint, based on the summary of the two pivotal

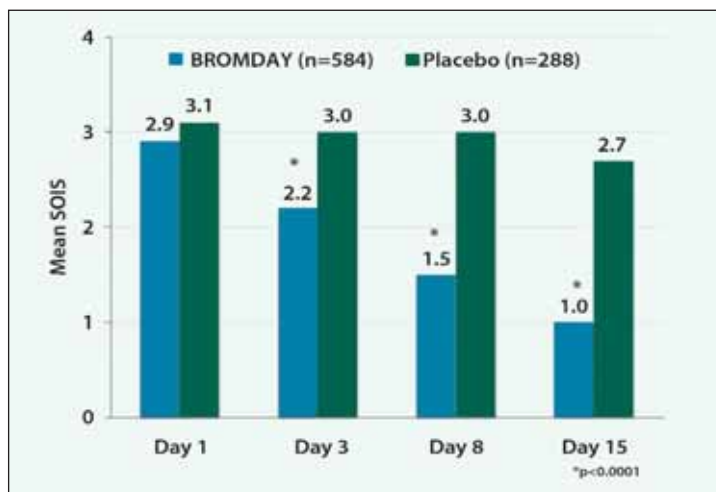


Figure 1. Integrated clinical trial results: mean SOIS at each study visit.

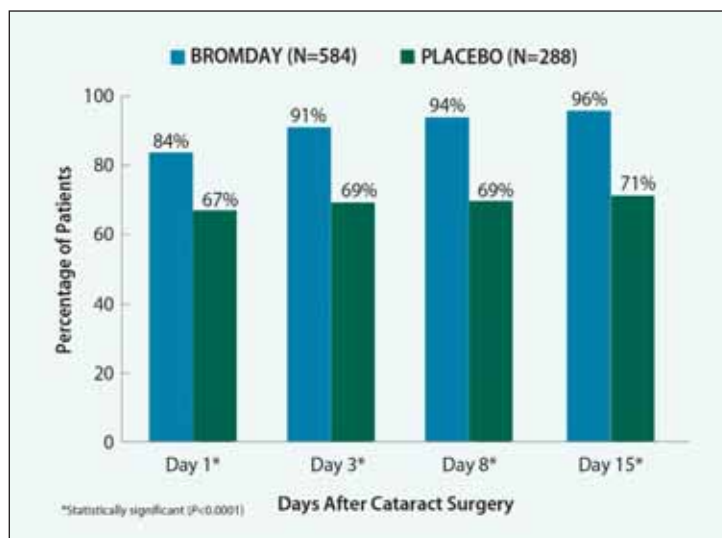


Figure 2. Integrated clinical trial results: proportion of patients reporting no pain at each study day.

trials provided in the BROMDAY prescribing information, 46% to 47% of BROMDAY-treated patients and 25% to 29% of placebo-treated patients achieved complete clearance of inflammation (SOIS of 0) by day 15. Against the secondary efficacy endpoint, 83% to 89% of patients on BROMDAY and 51% to 71% of patients on placebo reported being pain free at post-operative day 1 in the pivotal trials.

The analysis of the larger integrated data set is

**MY PERIOPERATIVE REGIMEN**

With routine cataract cases, I currently administer ZYMAXID (gatifloxacin ophthalmic solution) 0.5%; (Allergan, Inc., Irvine, CA) b.i.d. and XIBROM (ISTA Pharmaceuticals, Inc.) b.i.d. and no steroid. If I feel an eye needs additional control of inflammation, as may be the case in complicated and/or high-risk cataract surgery, I will add DUREZOL (difluprednate ophthalmic emulsion) 0.05%; (Alcon Laboratories, Inc., Fort Worth, TX). I am excited to have a q.d. option available for my patients, and I certainly plan to integrate once daily BROMDAY as the NSAID into my postoperative regimen.

consistent with the results of the pivotal trials. Subjects treated with BROMDAY showed a clinically significant reduction of inflammation as early as the eighth postoperative day (after 10 drops of BROMDAY) (Figure 1). At day 15, 51% of patients treated with BROMDAY and 27% of the patients treated with placebo achieved complete clearance of inflammation (SOIS of 0) at postoperative day 15. Additionally, 84% of subjects taking BROMDAY reported feeling no pain on the first postoperative day, compared with 67% of those in the placebo group (Figure 2).

Another revealing measure of a medication's success in clinical trials is its discontinuation rate. In the integrated analysis, more than 30% of the subjects in the placebo group had dropped out of the study due to lack of efficacy and had to be rescued with another anti-inflammatory agent (an ophthalmic NSAID and/or ophthalmic corticosteroid) at day 15, compared with less than 3% of the patients in the BROMDAY group.

**PATIENT ADHERENCE**

Patient adherence to postoperative medical therapy is also affected by the tolerability of the medication. In terms of ocular comfort, the integrated results showed a statistically significant improvement in four out of seven symptoms (pain, tearing, foreign body sensation, and photophobia) in BROMDAY patients compared with those taking the placebo. The incidence of the other three symptoms (itching, eye discharge, and haziness)

**BROMDAY LABEL SUMMARY****INDICATIONS AND USAGE**

BROMDAY 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.

**DOSAGE AND ADMINISTRATION**

Instill one drop into the affected eye(s) once daily beginning 1 day prior to surgery, continued on the day of surgery and through the first 14 days post-surgery.

**WARNINGS AND PRECAUTIONS**

- Sulfite allergic reactions
- Slow or delayed healing
- Potential for cross-sensitivity
- Increased bleeding of ocular tissues
- Corneal effects including keratitis
- Contact lens wear

**ADVERSE REACTIONS**

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

*Please see the full prescribing information for BROMDAY on the next page.*

were comparable to the placebo.

These clinical trial results give me confidence that BROMDAY is as effective as XIBROM with half the dosing. ♦

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BQD626-10/10

## Bromday™ (bromfenac ophthalmic solution) 0.09%

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Bromday (bromfenac ophthalmic solution) 0.09% safely and effectively. See full prescribing information for Bromday. Bromday (bromfenac ophthalmic solution) 0.09% Initial U.S. Approval: 1997

### INDICATIONS AND USAGE

Bromday 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

Instill one drop into the affected eye(s) once daily beginning 1 day prior to surgery, continued on the day of surgery and through the first 14 days post-surgery (2.1).

### DOSAGE FORMS AND STRENGTHS

Topical ophthalmic solution: bromfenac 0.09% (3)

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### FULL PRESCRIBING INFORMATION

#### 1. INDICATIONS AND USAGE

Bromday (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

For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of Bromday ophthalmic solution should be applied to the affected eye(s) once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

##### 2.2 Use with Other Topical Ophthalmic Medications

Bromday 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

### 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 2-7% 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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION  
Revised: 9/2010

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

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 orally applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that Bromday 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

Bromday should not be administered while wearing contact lenses

#### 6. ADVERSE REACTIONS

##### 6.1 Clinical Trial Experience

The most commonly reported adverse experiences 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 events were reported in 2-7% of patients.

##### 6.2 Post-Marketing Experience

The following events 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 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 Warnings and Precautions (5)]

#### 8. USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

##### Teratogenic Effects: Pregnancy Category C.

Reproduction studies performed in rats at oral doses up to 0.9 mg/kg/day (1300 times the recommended human ophthalmic dose [RHOD]) and in rabbits at oral doses up to 7.5 mg/kg/day (11,000 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.

##### Nonteratogenic Effects:

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

##### 8.3 Nursing Mothers

Caution should be exercised when Bromday is administered to a nursing woman.

##### 8.4 Pediatric Use

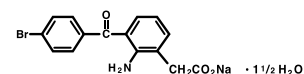
Safety and efficacy in pediatric patients below the age of 18 have not been established.

##### 8.5 Geriatric Use

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

#### 11. DESCRIPTION

Bromday (bromfenac ophthalmic solution) 0.09% is a sterile, topical, nonsteroidal anti inflammatory drug (NSAID) for ophthalmic use. Each mL of Bromday 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  $C_{18}H_{17}BrNaO_5 \cdot 1\frac{1}{2}H_2O$ . The structural formula for bromfenac sodium is:



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

##### Each mL of Bromday ophthalmic solution contains:

**Active:** bromfenac sodium hydrate 0.1035%

**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% Bromday (bromfenac ophthalmic solution) in humans is unknown. Based on the maximum proposed dose of one drop to the eye (0.045 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.

#### 13. NONCLINICAL TOXICOLOGY

##### 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (900 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 (7500 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 (1300 and 450 times RHOD, respectively).

#### 14. CLINICAL STUDIES

##### 14.1 Ocular inflammation and pain following cataract surgery

Clinical efficacy was evaluated in three randomized, double-masked, placebo-controlled trials in which subjects requiring cataract surgery were assigned to Bromday or placebo. Patients were dosed with one drop per eye starting the day before surgery and continuing for 14 days. The primary endpoint was clearing of ocular inflammation by day 15. An additional efficacy endpoint was the number of patients who were pain free on day 1 after cataract surgery.

In 2 of the 3 studies, Bromday ophthalmic solution had statistically significant higher incidence of completely clearing inflammation (46-47% vs. 25-29%) and also had a statistically significant higher incidence of subjects that were pain free at day 1 post cataract surgery (83-89% vs. 51-71%).

##### 16. HOW SUPPLIED/STORAGE AND HANDLING

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

1.7 mL in 7.5 mL container (NDC 67425-999-17)

**STORAGE** Store at 15° - 25°C (59° - 77°F).

#### 17. PATIENT COUNSELING INFORMATION

##### 17.1 Slowed or Delayed Healing

Patients should be advised of the possibility that slow or delayed healing may occur while using NSAIDs.

##### 17.2 Sterility of Dropper Tip

Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

##### 17.3 Concomitant Use of Contact Lenses

Contact lenses should not be worn during the use of this product.

##### 17.4 Concomitant Topical Ocular Therapy

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

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