

# Ocular NSAIDs

In light of recent concerns about the use of anti-inflammatory medications and the coincidence of grave side effects, a review of recently approved ocular NSAIDs is warranted.

BY SARA E. SMITH, MANAGING EDITOR

**D**espite their blemished history, nonsteroidal anti-inflammatory drugs (NSAIDs) offer several benefits after intraocular and refractive surgery. In the former, some NSAIDs can reduce patients' intra- and postoperative pain, help maintain pupillary dilation, control inflammation after surgery, and inhibit the development of cystoid macular edema (CME). In refractive surgery, some NSAIDs provide an analgesic effect and again diminish postoperative discomfort. However, a number of past generations of NSAIDs have been associated with problems that varied from corneal stinging to corneal melt, and their use has subsequently declined.

What follows is a brief review of indications and uses of ocular NSAIDs recently FDA approved.

## NEVANAC

### Ophthalmic NSAID Prodrug

Alcon Laboratories, Inc. (Fort Worth, TX) recently received FDA approval for Nevanac (nepafenac ophthalmic suspension) 0.1%, the first and only ophthalmic NSAID to be prepared as a formulation. Nevanac suspension first touches the cornea as nepafenac, which safely delivers analgesic effect to the corneal surface. Quickly, as it penetrates the intraocular tissues, intraocular hydrolysis converts the nepafenac molecule into a highly effective cyclooxygenase inhibitor (COX) called *amfenac*. This mechanism of action gives Nevanac target-specific activity that maximizes its efficacy at the targeted ocular sites where pain and inflammation reside.<sup>1</sup> Its enzymatic activity is similar to that of an arachidonic acid pathway. The agent uniformly inhibits prostaglandins in the iris/ciliary body as well as retina PGE<sub>2</sub> synthesis and demonstrates excellent properties in inhibiting the breakdown of the blood-aqueous and blood-retinal barriers.

The prodrug structure of Nevanac allows for ready bioavailability in the back of the eye, demonstrating excellent potential for treating conditions in the posterior segment. Data show that nepafenac 0.1% significantly inhibits vitreous humor prostaglandin formation that can lead to CME.<sup>2</sup>

"Unlike conventional NSAIDs, the active forms of which

decrease in activity as they penetrate the eye, Nevanac is specifically designed to maximize intraocular efficacy," Stephen S. Lane, MD, said. "Its unique prodrug structure allows Nevanac to achieve optimal distribution through the cornea into the iris/ciliary body and retina/choroid, providing superior inflammation suppression. At the same time, this rapid and targeted distribution may minimize surface tolerability issues," he said.

From a safety standpoint, nepafenac has been tested in various concentrations (up to 1.5%) and in both short- and long-term settings. It was found to be safe and well tolerated.<sup>3-5</sup> The clinical trials revealed neither evidence of epithelial, stromal, or intraocular toxicity with the drug, nor any burning or stinging.

### FDA Data

Alcon Laboratories, Inc., filed Nevanac suspension with the FDA earlier this year for the treatment of pain and inflammation following cataract surgery. In clinical trials, the agent has shown excellent results with regard to safety, efficacy, and pain management.<sup>6</sup>

Clinical trial patients received t.i.d. dosing with Nevanac versus a vehicle on the day before cataract surgery and continued dosing for 14 days postoperatively. Investigators used no concomitant corticosteroid therapy during the trials. By day 14, 82% of the Nevanac patients were considered clinical cures, compared with 25% of the placebo group. Furthermore, 62% of the patients in the Nevanac group had zero cells or flares by day 14. Treatment failures with Nevanac never exceeded 10% at any of the times tested, whereas more than 50% of the patients treated with a vehicle were considered treatment failures by day 14. Nevanac demonstrated significant anti-inflammatory efficacy at every time point measured in the study, with significant clinical cure rates achieved as early as postoperative day 1.

The difference in patients' rate of postoperative pain in the clinical trial was also statistically significant. Almost 90% of those taking Nevanac were pain-free by the third postoperative day, compared with less than 50% of the patients on placebo. As early as the first postoperative day, more than 80% of the Nevanac

patients reported feeling no pain whatsoever, compared with 40% of the placebo patients.

## ACULAR LS

### New Product Line Extension

Allergan, Inc. (Irvine, CA), added to their Acular product line with a new formulation, Acular LS (ketorolac tromethamine ophthalmic solution) 0.4%. Acular LS was developed to reduce the incidence of ocular pain and burning/stinging following corneal refractive surgery. The optimized formulation of ketorolac tromethamine is used for a range of other conditions including postsurgical inflammation. The most frequently reported adverse reactions for Acular LS, occurring in approximately 1% to 5% of the overall study population, were ocular redness, swelling and pain, and corneal infiltrates and headache.<sup>7</sup> However, studies demonstrate that Acular LS reduces pain in cataract surgery patients immediately and 24 hours after surgery,<sup>8</sup> and the drug is effective in reducing ocular pain when used q.i.d. for up to 4 days after PRK.<sup>9</sup>

### Acular LS' Effect on Inflammation

Managing pain and inflammation are essential to cataract and refractive outcomes. Surgeons should aim for ensuring a quick return of vision and patient comfort while rapidly eradicating inflammation and lessening the risk of complications such as CME.

According to medical literature,<sup>10-12</sup> in order to achieve the aforementioned goals, clinicians should employ a pre- and postoperative regimen of NSAIDs and appropriate usage of steroids at the time of cataract surgery. However, it is important to note that not all ocular NSAIDs are interchangeable in treating or preventing various pathologies.

Topical steroids alone do not suppress the synthesis of inflammatory mediators, such as the prostaglandins.<sup>10</sup> Topical NSAIDs, by suppressing the COX pathway responsible for prostaglandin production, have been shown to reduce aqueous flare and the development of cystoid macular degeneration when used after cataract surgery.<sup>11</sup> Starting a topical NSAID such as Acular LS q.i.d. for 3 days before cataract surgery and maintaining the patient on the NSAID for a minimum of 1 month postoperatively may be the best routine prophylaxis against CME.<sup>11</sup> Acular LS has been proven to prevent CME in multiple studies.<sup>12-14</sup>

A study evaluating the dose response curve and improvement in surgical efficacy and outcomes with Acular LS showed that the drug is a beneficial surgical tool for cataract surgery.<sup>12</sup> In this study, 100 patients were randomized into four groups to receive preoperative Acular LS for 3 days, 1 day, 1 hour, or placebo in a double-masked fashion prior to phacoemulsification. The study evaluated the efficacy of Acular LS on maintaining preoperative mydriasis, phaco-

emulsification time and energy, operative time, corneal clarity, pachymetry, endothelial cell counts, postoperative inflammation, intra- and postoperative discomfort, intraoperative complications, and CME. The group that received Acular for 3 days prior to phacoemulsification had a better maintained pupil size, phacoemulsification time and energy, operative time, corneal clarity, as well as postoperative inflammation, and intraoperative and postoperative discomfort than those in the 1-day, 1-hour, and placebo groups. The investigators also reported a trend toward improved pachymetry on postoperative day 1 and endothelial cell counts at 3 months in the 3-day pretreatment group relative to placebo. They also used OCT to evaluate CME and found that Acular LS, when dosed 1 or 3 days preoperatively, reduced CME to 0%, whereas control groups reached 12% CME.<sup>12</sup>

### Acular LS in Cataract Surgery

John R. Wittpenn, Jr, MD, uses Acular LS for all of his cataract surgery patients. "I employ Acular LS 2.5 days preoperatively, and I continue with this regimen up until the point of pupillary dilation for the cataract surgery procedure," Dr. Wittpenn said. "This use of Acular LS reduces ocular pain, improves pupillary dilation, and minimizes postoperative inflammation." Dr. Wittpenn continues to use the agent in these patients q.i.d. for up to 4 to 5 weeks postoperatively without tapering to prevent late-onset CME.

"Only two of my last 500 cataract patients experienced significant surface irritation with burning and stinging that the medication had to be stopped," Dr. Wittpenn said. "But that is the beauty about Acular LS, that the incidence of ocular surface toxicity is virtually nonexistent."

Dr. Wittpenn said he does not use Acular LS in patients with a known epithelial healing disorder, such as neurotrophic patients, as the anesthetic effect of the drug can cause complications in this group.

## XIBROM

### Twice-Daily Dosing

The FDA recently approved Xibrom (bromfenac 0.09%; Ista Pharmaceuticals, Inc., Irvine, CA), a topical, twice-daily, NSAID solution for the treatment of ocular inflammation following cataract surgery. The company asserts that Xibrom is one of the most selective and potent COX-2 inhibitors known.

### Clinical Trial Results

Before Xibrom received FDA approval in March of this year, Ista Pharmaceuticals, Inc., announced positive results from its initial analysis of the company's US phase 3 clinical trials of the drug. In two double-masked, placebo-controlled US phase 3 studies,<sup>15</sup> a statistically significant pro-

**AT A GLANCE: OCULAR NSAIDs**

Name of NSAID	Manufacturer	Indication
Nevanac (nepafenac ophthalmic suspension) 0.1%	Alcon Laboratories, Inc.	For pain and inflammation associated with cataract surgery
Acular LS (ketorolac tromethamine ophthalmic solution) 0.4%	Allergan, Inc.	For the reduction of ocular pain and burning/stinging following corneal refractive surgery
Xibrom (bromfenac ophthalmic solution) 0.09%	Ista Pharmaceuticals, Inc.	For the treatment of postoperative inflammation in patients who have undergone cataract extraction

portion of patients treated with Xibrom achieved treatment success compared with placebo. Treatment success was defined as the complete absence of ocular inflammation. In one study involving 296 patients at 20 study sites, 62.2% of Xibrom-treated patients cleared their ocular inflammation at 15 days, compared with 39.8% of patients who received a placebo. In a second US study involving 231 patients at 19 study sites, the rates of ocular inflammation clearance at the primary endpoint of 15 days were 65.8% for Xibrom-treated patients and 47.9% for patients receiving placebo. Statistical significance in each trial reached a *P* value of  $>.01$ . The company's analysis showed that Xibrom's treatment efficacy was evident as early as day 3 in both trials. Furthermore, adverse events were mild and occurred less frequently than with placebo. Xibrom was also well tolerated, with an incidence of burning and stinging of less than 1.5%.

**Japanese Data**

As part of the Xibrom NDA, Ista submitted postmarketing information to the FDA from Senju Pharmaceuticals Co. Ltd. (Osaka, Japan [bromfenac was developed by Senju Pharmaceuticals Co. Ltd.]) on 2.7 million patients using it in Japan between 2000 and 2003 (data on file at Ista Pharmaceuticals, Inc.). At present, 6 million patients have received Xibrom since it was first marketed in Japan without a single reported case of serious systemic adverse events and only 13 reported cases of serious ocular adverse events (including four corneal erosions, three corneal perforations, and no corneal melts), a rate of 0.00000216% (data on file at Ista Pharmaceuticals, Inc.).

**Xibrom and CME**

Xibrom's effectiveness for the treatment of CME has not been studied. If effective, it may increase patients' compliance. CME in patients on prostaglandin analogues usually responds favorably to the cessation of the prostaglandin drug and the initiation of therapy with a topical NSAID.<sup>11</sup>

**Future Indications for Xibrom?**

In the medical literature, bromfenac ophthalmic solution has been studied for indications other than its approved uses.<sup>16-18</sup> In a study investigating the reduction of post-cataract surgery pain, bromfenac decreased the number of days for the resolution of ocular pain.<sup>16</sup> Other studies evaluated bromfenac as a possible treatment for allergic conjunctivitis and showed it to be safe and effective for the treatment of the pathologic condition.<sup>17,18</sup>

**Personal Experience**

Henry Perry, MD, from New York, whose facility was involved in the Bromfenac Study Group, has been using Xibrom in his practice for approximately 6 months. "At the present time, I use Xibrom for refractive surgery," Dr. Perry told *Cataract & Refractive Surgery Today*. "I instill just one drop of Xibrom in LASIK patients immediately after their surgery. It appears that the one drop, because of Xibrom's increased potency, is enough to decrease the patients' symptoms for at least 4 to 6 hours."

Dr. Perry said that the 4 to 6 hours immediately following LASIK surgery is the most crucial time for Xibrom use, because patients tend to squeeze their eyes closed during that period, and this action, according to Dr. Perry, can sometimes generate problems with folds in the corneal flap. "I

Dosing	Adverse Reactions
One drop t.i.d.	The most frequently reported ocular adverse events following surgery were capsular opacity, decreased visual acuity, foreign-body sensation, increased IOP, and sticky sensation. These events occurred in approximately 5% to 10% of patients. Other ocular adverse events included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing, and vitreous detachment. These events occurred at an incidence of approximately 1% to 5% of patients. Some of these events may be the consequence of the cataract surgery procedure. Nonocular adverse events reported included headache, hypertension, nausea/vomiting, and sinusitis.
One drop q.i.d.	The most frequently reported adverse reactions were conjunctival hyperemia, corneal infiltrates, headache, ocular edema, and ocular pain. These events occurred in approximately 1% to 5% of patients. The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by 20% to 40% of patients in other clinical trials. Other adverse events included allergic reactions, corneal edema, iritis, ocular inflammation, ocular irritation, ocular pain, superficial keratitis, and superficial ocular infections. These adverse events occurred in approximately 1% to 10% of the time in patients.
One drop b.i.d.	The most frequently reported adverse experiences reported following use of Xibrom after cataract surgery include abnormal sensation in the eye, conjunctival hyperemia, eye irritation (including burning/stinging), eye pain, eye pruritus, eye redness, headache, and iritis. These events were reported in about 2% to 7% of patients.

think that the use of Xibrom, because of its longer duration of action, is probably a better fit for refractive surgery," he said. Dr. Perry also uses Xibrom in PRK patients for approximately 24 to 48 hours postoperatively, as PRK patients tend to have a longer duration of pain than LASIK patients.

Dr. Perry has not experienced any problems with the use of Xibrom, which he says seems to be better tolerated than other NSAIDs because of its lack of stinging upon instillation, and it appears to be safe and efficacious. ■

*Stephen S. Lane, MD, is Clinical Professor at the University of Minnesota in St. Paul and is the past President of the ASCRS. He is a member of the Refractive Medical Advisory Board of Alcon Laboratories, Inc., a clinical investigator for Nevanac suspension, and a paid consultant for Alcon Laboratories, Inc. Dr. Lane may be reached at (651) 275-3000; sslane@associatedeyecare.com.*

*John R. Wittpenn, Jr, MD, is Associate Professor of Ophthalmology at the State University of New York in Stony Brook and is a partner at Ophthalmic Consultants of Long Island in Rockville Centre, NY. He is a consultant to Allergan, Inc., and a member of the company's Speaker's Bureau, but states that he holds no financial interest in any company or product mentioned herein. Dr. Wittpenn may be reached at (631) 941-1400; jrwwittpenn@aol.com.*

*Henry D. Perry, MD, is Clinical Associate Professor of Ophthalmology Weill Cornell School of Medicine and Medical Director at the Lions Eye Bank for Long Island at North Shore University Medical Center in Manhasset, New York. He also is Senior Partner at Ophthalmic Consultants of Long Island in Rockville Centre, New York. He is a consultant to Allergan, Inc., and Ista Pharmaceuticals, Inc. Dr. Perry may be reached at (516) 766-2519; hankcornea@aol.com.*

- Ke TL, Graff G, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal product with potential utility in the treatment of trauma-induced ocular inflammation: assessment of bioactivation and permeation of ocular barriers (animal study). *Inflammation*. 2000;24:4:371-384.
- Kapin MA, Yanni JM, Brady MT, et al. Inflammation-mediated retinal edema in the rabbit is inhibited by topical nepafenac. *Inflammation*. 2003;27:5:281-291.
- Heaton J, Hiddeman JW, Hackett RB, et al. Ocular effects of nepafenac ophthalmic suspension following six months of topical ocular administration to pigmented rabbits. Paper presented at: The ARVO Annual Meeting; May 3, 2005; Fort Lauderdale, FL.
- McGee DH, Heaton JD, Gruebel MM, et al. Ocular effects of nepafenac ophthalmic suspension following six months of topical ocular administration to cynomolgus monkeys. Paper presented at: The ARVO Annual Meeting; May 3, 2005; Fort Lauderdale, FL.
- Walker LM, Rice RL, Heaton JD, et al. Ocular effects of Nepafenac ophthalmic suspension following three months of topical ocular administration to cynomolgus monkeys. Paper presented at: The ARVO Annual Meeting; May 3, 2005; Fort Lauderdale, FL.
- Lane S. Nepafenac ophthalmic suspension 0.1% before and after surgery for postoperative anterior segment inflammation. Paper presented at: The ASCRS/ASOA Symposium on Cataract, IOL and Refractive Surgery; April 18, 2005; Washington, DC.
- Acular LS [package insert]. Irvine CA: Allergan, Inc.; May 2003.
- Price MO, Price FW. Efficacy of topical ketorolac tromethamine 0.4% for control of pain or discomfort associated with cataract surgery. *Curr Med Res Opin*. 2004;20:2015-2019.
- Solomon KD, Donnenfeld ED, Raizman M, et al. Safety and efficacy of ketorolac tromethamine 0.4% ophthalmic solution in post-photorefractive keratectomy patients. *J Cataract Refract Surg*. 2004;30:1653-1660.
- Arcieri ES, Santana A, Rocha FN, et al. Blood-aqueous barrier changes after the use of prostaglandin analogues in patients with pseudophakia and aphakia: a 6-month randomized trial. *Arch Ophthalmol*. 2005;123:186-192.
- Scheufele TA, Heier JS. Pseudophakic cystoid macular edema. *Cataract & Refractive Surgery Today*. 2005;5:8:55.
- Donnenfeld ED, Perry HD, Wittpenn J, et al. The dose response curve of a topical NSAID as a surgical tool prior to cataract surgery. Paper presented at: The ASCRS/ASOA Symposium on Cataract, IOL and Refractive Surgery; Washington, DC; April 2005.
- Flach AJ, Jampol LM, Weinberg D, et al. Improvement in visual acuity in chronic aphakic and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac tromethamine. *Am J Ophthalmol*. 1991;112:514-519.
- Heier JS, Topping TM, Baumann W, et al. Ketorolac versus prednisolone versus combination therapy in the treatment of acute pseudophakic cystoid macular edema. *Ophthalmology*. 2000;107:2034-2039.
- Schiffman MI, Donnenfeld ED, Holland EJ, et al. Investigation of liver toxicity following topical treatment with Xibrom 0.1%, an NSAID for post-cataract surgery inflammation. Paper presented at: The ASCRS/ASOA Symposium on Cataract, IOL and Refractive Surgery; April 18, 2005; Washington, DC.
- Donnenfeld E, Holland EJ, Stewart R, et al. Topical Xibrom 0.1%, an investigational NSAID, significantly and rapidly decreased post-cataract surgery inflammation and reduced ocular pain. *Invest Ophthalmol Vis Sci*. 2005;46:E-abstract 791.
- Igarashi A, Okada N, Takano Y, et al. Bromfenac sodium decreases eotaxin production from primary cultured corneal keratocytes stimulated by IL-4 and TNF-alpha. *Invest Ophthalmol Vis Sci*. 2004;45:E-abstract 4830.
- Miyake-Kashima M, Takano Y, Tanaka M, et al. Comparison of 0.1% bromfenac sodium and 0.1% pemirolast potassium for the treatment of allergic conjunctivitis. *Jpn J Ophthalmol*. 2004;48:587-590.