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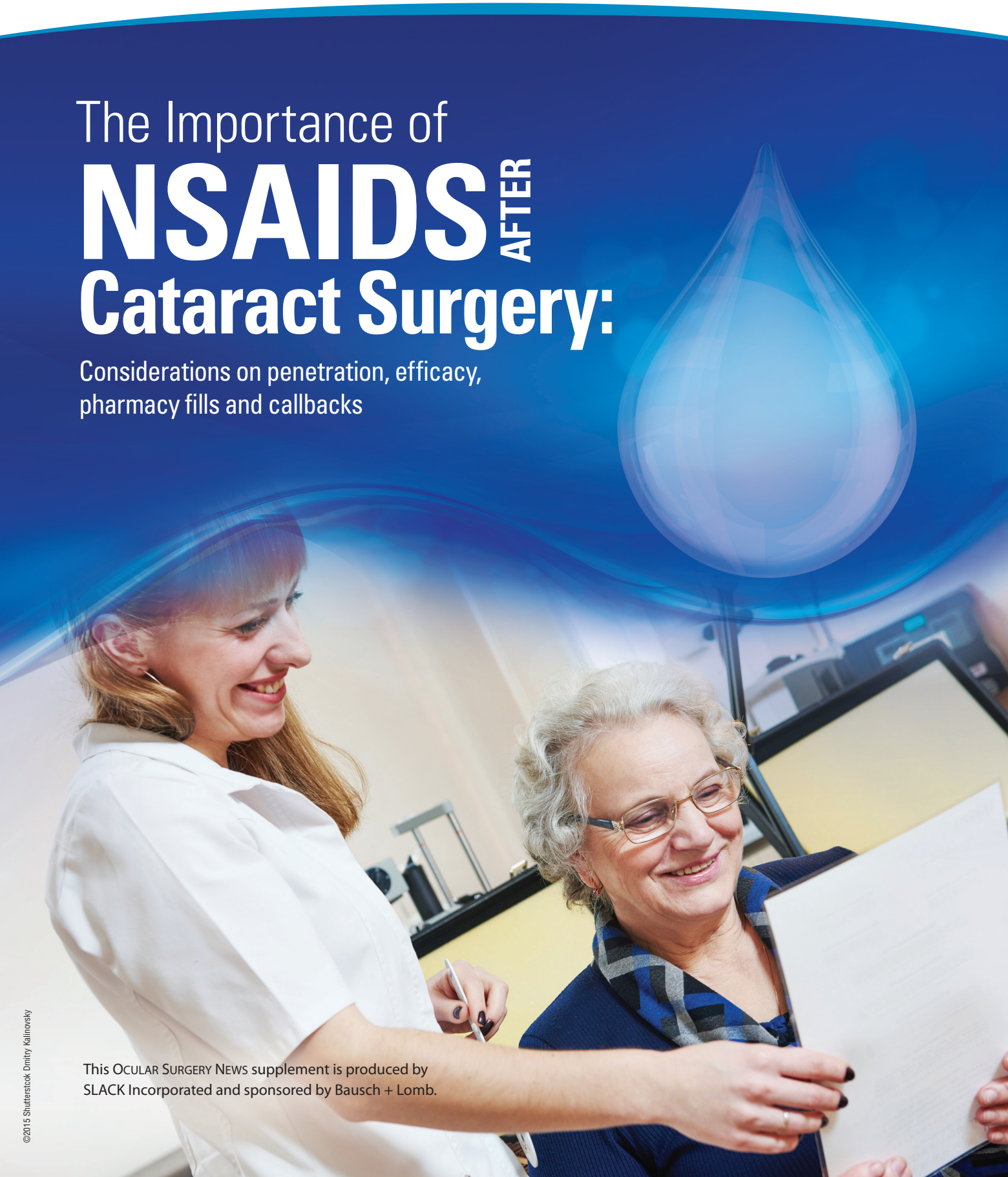
The Importance of NSAIDS AFTER Cataract Surgery:

Considerations on penetration, efficacy, pharmacy fills and callbacks



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Introduction

The goal of cataract surgery is to improve vision for patients, so ophthalmologists need more than just a quality IOL and the latest surgical tools on hand. For patients who have inflammation and/or pain after cataract surgery, surgeons should prescribe an NSAID that inhibits cyclooxygenase enzymes and also penetrates the cornea.

OCULAR SURGERY NEWS, with the support of Bausch + Lomb, gathered leading ophthalmologists during the 2015 American Society of Cataract and Refractive Surgery annual meeting to discuss the use of PROLENSA® (Bausch + Lomb) (bromfenac ophthalmic solution) 0.07% in terms of corneal penetration, potency, anti-inflammatory efficacy and pain reduction. Topics include the performance of Prolensa in clinical trials, the benefits of using the product in relationship to its cost and tactics for increasing pharmacy fills and decreasing callbacks.

I thank the faculty members for their participation, as well as Bausch + Lomb for sponsoring this OCULAR SURGERY NEWS supplement. For more educational materials on this topic, visit Healio.com/Ophthalmology/Education-Lab.

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The Importance of NSAIDs after Cataract Surgery:

Considerations on penetration, efficacy, pharmacy fills and callbacks

Douglas A. Katsev, MD: With cataract surgery being so prevalent in the U.S., surgeons need access to the ophthalmic medications that can treat inflammation and pain. What is your perspective on treating inflammation after cataract surgery?

P. Dee Stephenson, MD, FACS: As the founder of a boutique practice, I always think about how patients perceive their total experience with cataract surgery. In my opinion, helping to control breakthrough inflammation is necessary, especially for patients who receive premium IOLs.

Inder Paul Singh, MD: In my practice, my colleagues and I survey patients, asking them, "At what stage postoperatively did you discuss your surgery with friends and family?" Interestingly, the answer is not at day 1 or after 1 month, but the vast majority say it is after 1 week. The first postoperative week is critical; if patients do not use the drops physicians prescribe to them, they may be at a greater risk for ocular surface issues and unresolved inflammation.[1]

John R. Wittpenn, MD: Recurring or breakthrough inflammation is a risk if not properly addressed postoperatively. Once inflammation starts, the prostaglandin cascade is triggered and becomes more difficult to control, hence why it is necessary to eliminate inflammation as quickly as possible.

Kenneth J. Rosenthal, MD, FACS: Postoperative inflammation can likely to lead to tissue damage if persistent. Inflammation causes pain, which may leave patients concerned about their surgical outcomes. Therefore, control of postoperative inflammation is important, and the use of an NSAID is well-documented to be an invaluable tool toward that end.

Mitchell A. Jackson, MD: Rebound inflammation is a particularly unwelcome scenario in the comanagement setting because ophthalmologists have less control over what other physicians may prescribe when this occurs, and less control over the frequency of follow-up visits. It is during this time that inflammation can progress significantly, leaving the patient at risk for sight-threatening conditions such as cystoid macular edema, especially if the referring optometrist does not have a macular ocular coherence tomography device in the office.

Katsev: Many patients undergoing cataract surgery with modern tools and techniques expect to experience little to no pain. They may also complain about the pain they experience if surgeons do not administer an NSAID in the first few postoperative hours.

How does pain factor into outcomes and treatment regimens?

Cynthia Matossian, MD, FACS: The patient's perspective of his or her surgical course can vary from that of the surgeon. Surgeons focus on visual acuity or IOL centration, whereas patients may focus on pain during the immediate postoperative period. In fact, nearly 35% of patients complain of some degree of pain in the immediate postoperative period,[2] which may taint their perception of the surgical experience. Using an NSAID in the postoperative regimen will help control both inflammation and pain.[3]

Wittpenn: My patients' experience with postoperative pain under my current NSAID treatment regimen is similar to study results from Walters and colleagues, which showed that 78.8% of patients treated with once-daily doses of Prolensa (bromfenac ophthalmic solution) 0.07% were pain-free at day 1, according to ocular pain scores (Figure 1, page 4).[3]

Rajesh K. Rajpal, MD: Conversely, far fewer patients in that study's placebo group were pain-free at postoperative visits.[3] The primary endpoint was complete clearance of inflammation, with success considered to be zero cells in

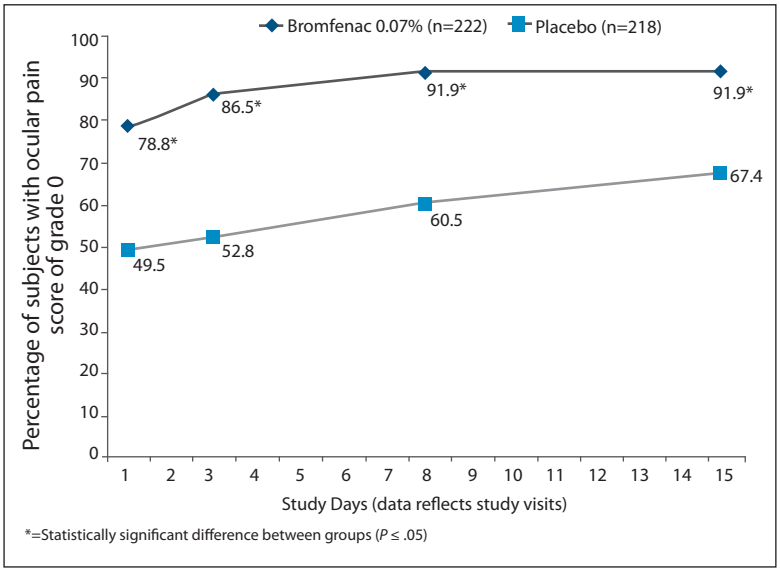

Figure 1. Percentage of subjects with ocular pain scores of grade 0 at study visits 1, 3, 8 and 15.

Reprinted from Ophthalmology, *121/1, Walters TR, Goldberg DF, Peace JH, Gow JA; Bromfenac Ophthalmic Solution 0.07% Once Daily Study Group, Once Daily Study Group. Bromfenac ophthalmic solution 0.07% dosed once daily for cataract surgery: results of 2 randomized controlled trials, 25-33, Copyright (2014), with permission from Elsevier.*

Table. Ocular inflammation grading scale for the calculation of the summed ocular inflammation score

Anterior Chamber Cells	
Grade	Cell Count
0	0
0.5	1–5 cells (trace)
1	6–15
2	16–25
3	26–50
4	>50

Anterior Chamber Flare	
Grade	Flare Count
0	Complete absence
1	Very slight (barely detectable)
2	Moderate (iris and lens clear)
3	Marked (iris and lens hazy)
4	Intense (fibrin clot)

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the anterior chamber as determined by the summed ocular inflammation score (Table). The secondary endpoint was pain control. Patients in the Prolensa arm dosed once a day achieved greater control of inflammation and pain, a nearly twofold difference vs. placebo (Figure 2).

Adding a corticosteroid is also an option. A survey conducted in 2014 showed that a significant percentage of physicians use both a corticosteroid and an NSAID to control pain and inflammation 1 day after cataract surgery.[4]

Jackson: Pain was the main criterion from the Ocular Comfort Grading Assessment (OCGA) integrated into the study by Walters and colleagues and, as discussed, more patients were pain-free at each follow-up visit using Prolensa vs. placebo.[3] The OCGA grades symptoms on a scale of 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe). Side effects included pain, tearing, itching, foreign-body sensation, photophobia, discharge and haziness. These effects were lower for patients given Prolensa vs. placebo.[3]

Prescribing Prolensa (bromfenac ophthalmic solution) 0.07%

Katsev: What challenges must ophthalmic NSAID formulations address for good penetration, and, in your opinion, why is Prolensa effective in reducing inflammation and pain vs. placebo?

Singh: To help with ocular absorption and penetration, some other NSAID manufacturers have increased concentrations and/or use vehicles that enhance residence time on the surface.

Wittpenn: Penetration through the lipid bilayer of the cornea is dependent on the entire formulation of a drop. Ionic molecules, found in brand-name and generic NSAIDs, have difficulty penetrating the cornea. Therefore, topical NSAID formulations should strive to maximize the amount of non-ionized molecules, as these are the most lipophilic.

Jackson: It has been difficult to lower pH to the point where non-ionic molecules penetrate the relatively hydrophobic cornea. In addition to lowering pH, there are various ways to achieve effective penetration, including bromine halogenation and increasing residence time on the cornea.[3]

Carlos Buznego, MD: Many systemic nonsteroidals work well at reducing general pain and inflammation, but topical ophthalmic NSAIDs have the added challenge of penetrating the lipid bilayer of the cornea.

The bromfenac molecule present in Prolensa allows for good penetration into ocular tissues, as does its pH of 7.8, which is close to physiologic pH.[3,5,6]

Stephenson: I have observed that the near-physiologic pH of Prolensa makes the drop comfortable for my patients, who have reported less redness, foreign body sensation and photophobia, as shown by Walters and colleagues.[3]

Wittpenn: The bromine element of Prolensa also enhances efficacy by binding to cyclooxygenase (COX)-1 and COX-2 enzymes to prevent the prostaglandin cascade.[3] *(Note: clinical significance of in vitro data is unknown.)*

Jackson: Furthermore, bromfenac's low in vitro half maximal inhibitory concentration (IC_{50}) data demonstrates its potency, which is important when it comes to COX inhibition and mediators of inflammation in the ciliary body, such as prostaglandin E2.[7]

Stephenson: I have also found that the bromine element in Prolensa to be helpful before femtosecond laser-assisted cataract surgery because it controls the prostaglandin release after creating the capsulotomy.[8]

Matossian: Overall, I am impressed with how well the bromfenac molecule controls inflammation. In addition, Prolensa is a once-daily drop,[3] and the solution does not need to be shaken.[9] I am confident that when a patient removes the bottle from his or her pocket or purse and instills the drop into the eye, each drop delivers a predictable amount of medication.

Dosing

Katsev: How do you dose Prolensa?

Rajpal: I start my patients on it 1 day preoperatively, dose it again on the day of surgery and again once a day throughout the perioperative period.[10]

Matossian: I also introduce it once on the day before surgery and on a once-a-day protocol.[10] This way, patients gain practice in drop instillation before surgery.

Stephenson: I dose Prolensa 1 day before surgery, on the day of surgery before laser-assisted cataract surgery or manual cataract removal and once a day postoperatively for 14 days.[10] This once-daily regimen helps to eliminate breakthrough inflammation and pain.[3]

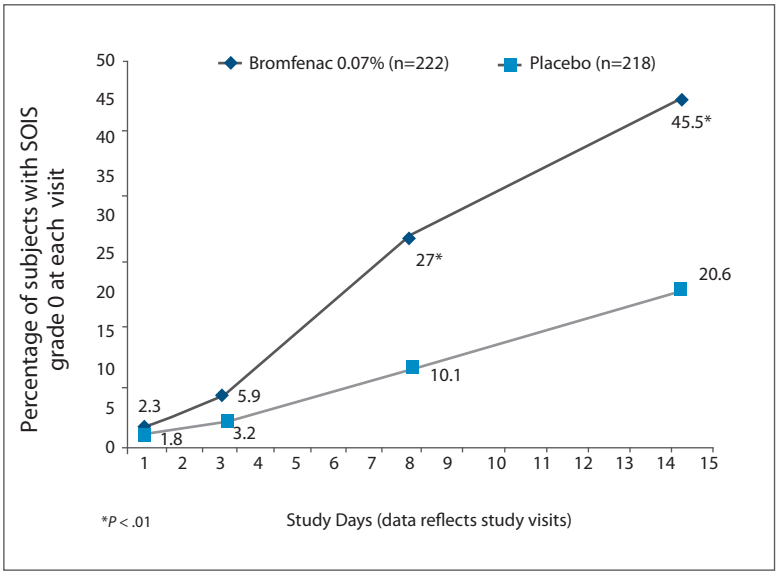

Figure 2. Percentage of summed ocular inflammation scores (SOIS) of grade 0 at study visits 1, 3, 8 and 15.

Reprinted from Ophthalmology, *121/1, Walters TR, Goldberg DF, Peace JH, Gow JA; Bromfenac Ophthalmic Solution 0.07% Once Daily Study Group, Once Daily Study Group. Bromfenac ophthalmic solution 0.07% dosed once daily for cataract surgery: results of 2 randomized controlled trials, 25-33, Copyright (2014), with permission from Elsevier.*

Jackson: The 3-mL bottle size is a good option for patients who have difficulty instilling drops into the eye. Its larger size helps ensure that patients have enough medication to last through the entire duration of treatment.

Warnings and precautions

Katsev: Should patients be aware of any warnings or precautions related to Prolensa?

Wittpenn: I recently spoke to a pharmacist about a patient who could not use Prolensa because of a sulfite allergy.[10] This is, of course, different from a sulfate or sulfa allergy; sulfite allergies are uncommon.

Jackson: Bleeding is a risk with NSAIDs as a class, including Prolensa.[10] NSAIDs block thromboxane A2, which is needed for platelet aggregation,[1] possibly leading to subconjunctival hemorrhages or sponta-

neous hyphema in rare cases.

Buznego: Some patients may also be on a systemic anticoagulation regimen that could further inhibit platelet function.

Rajpal: However, with proper monitoring, I typically do not require that patients stop systemic anticoagulation while taking Prolensa.

Patient and staff counseling: Cost, pharmacy fills and callbacks

Patient counseling

Katsev: How do you counsel your patients about the importance of filling their Prolensa prescriptions? Also, in what ways do you convey the overall investment in postoperative care?

Buznego: Burning and stinging is not a chief complaint in bromfenac, as was shown in clinical trials where the rate was equivalent to that of placebo.[11] Therefore, I use this scenario as a teaching opportunity to explain the risks and benefits of Prolensa: patients are dosed once a day vs. three to four times, and the rate of burning and stinging is minimal.[10,11] I also instruct patients to contact me if side effects do occur.

Rosenthal: It is key that the conversation with patients begins with surgeons explaining the importance of postoperative medications and that, although the bottle is small, the medicine contained within is essential during perioperative care. Incidentally, I use the word "medication," not "drop," so that patients realize that I am giving them something equivalent in importance to systemic medications such as those for hypertension or diabetes.

If the patient understands its importance, I then segue to the significance of using the particular branded medication that I prescribe. I explain the high-quality, component parts of the surgical experience that I provide, from biometry to premium surgical equipment and IOLs, and that Prolensa is also a key component. Although it may seem expensive even with coupons, based on the average retail price in local pharmacies, I try to set expectations. In addition, I stress that treatment will last only a brief period of time and is not a lifetime or recurring expense.

Matossian: After my patients and I have discussed and selected the best IOL match for their eyes, I look my patients in the eyes and say, "I am going to do my best for you, but in turn, you have to promise me that you are going to do your best. That means using the recommended medications properly." Verbal responses of "Yes" or "I will try" means patients understand the responsibilities that I am asking of them.

From there, patients visit the surgical coordinator who discusses the importance of filling their Prolensa prescriptions, and provides any coupons available to help cover the cost. Overall, I have few patients who do not use the branded medicines that I prescribe.

Singh: So much of the experience is education and creating an interaction that leads to trust between the physician and the patient. Patients trust surgeons to provide specific surgical outcomes, but postoperatively, some of the responsibility must fall on patients. I am precise in my surgical abilities, so I need the same precision postoperatively. However, I find it difficult to spend a lot of time explaining the differences to my patients.

To help patients assume responsibility, surgeons must create avenues for education in the office to give them enough understanding of the importance of taking these medications. I created a form for them to read and take to the pharmacist. It shows them that there is no generic form of Prolensa. My surgical coordinator is also available to our patients to answer any questions.

Rosenthal: Clear communication is imperative for patients to achieve good surgical outcomes. Although physicians understand the pathophysiology behind inflammation and pain, patients tend to simplify these surgical side effects to mere redness and discomfort. If surgeons do not explain the consequences of untreated inflammation and pain, then patients will never understand the importance of choosing the proper medication.

Staff counseling

Katsev: Physicians may not want to discuss cost or coupon programs with patients, but they still want to provide the best patient experience; that is where staff can get involved. Physicians can demonstrate how important Prolensa is during postoperative care by sharing viewpoints with staff and educating them about Prolensa. I find that the staff likes working with the physicians in my practice because they are collectively involved in achieving good results.

In what other ways do you educate your staff about

branded medications?

Singh: It takes extra time and effort to deal with callbacks from pharmacies and patients about Prolensa, and I agree that the morale of the office improves when staff members understand the reasons why we prescribe it.

Matossian: I spend 1 hour per week educating my office staff with a formal training session that includes the front desk team and technicians. I create a weekly agenda and include topics such as why I recommend certain medications, the importance of customer service and the importance of following medication protocols. These meetings empower the staff because they learn the reasons behind my recommendations.

I also arrange time for technicians to meet with pharmaceutical representatives, either one-on-one or as a group, to learn about specific drugs and the coupons they offer to help patients save money. These sessions often occur over lunch.

Jackson: At the end of each day, my staff and I hold a meeting to discuss any issues that arose, good or bad, whether it was filling a prescription, patient wait time or concerns about insurance/copay cards. Each staff member has approximately 60 seconds to speak, and in 15 minutes, we learn what happened during the day and can immediately implement solutions for the next day, if necessary.

Singh: I hold a monthly staff meeting with a new topic on the agenda each time we gather. In a recent meeting, we discussed specific medications so that the technicians and surgical coordinator could gain a better understanding of each one.

Wittpenn: Prolensa is my NSAID of choice, and I am a strong proponent of branded medications. However, since January 2015, I have noticed a marked increase of calls from patients and pharmacists wanting to substitute Prolensa with a generic even though a true generic doesn't exist. To decrease callbacks, I began educating my technicians about the new Medicare Part D program and the availability of coupons. Yet, they had several difficult questions about the process and did not have the appropriate time to dedicate to our patients, leading us to rethink our approach to financial discussions as a whole. Therefore, I made the decision to leave our technicians in charge of medical issues and appoint our surgical coordinators to help patients navigate the complexities of insurance matters, cost concerns and coupon programs, in addition to scheduling tasks. Any callbacks received from here on out will first be directed to them, and questions about medical issues are forwarded to me or my technicians.

Managing costs

Katsev: Although I am proactive in trying to provide an effective medication, I care about what our patients have to pay for it. I relate the cost of Prolensa to the out-of-pocket expense for the premium IOL packages that I offer. And with the availability of coupons, I can help my patients save money while also improving postoperative outcomes.

How do you explain the high out-of-pocket expense of Prolensa to your patients? How effective are copay cards and coupons at reducing costs?

Matossian: When my patients complain about the cost of their eye medication, I quickly remind them that these postoperative medications are for a short duration; they are not going to remain on them for life, like anti-hypertensive or diabetes medications.

Stephenson: The most difficult step is convincing patients to use branded medications. Fortunately, Bausch + Lomb offers several coupon programs to help patients manage costs. In addition, I have worked with some online pharmacies that accept coupons and provide better pricing than traditional pharmacies.

Buznego: Surgeons make every effort to provide the best quality care via surgical tools and techniques, so the key is to extend the positive patient experience with premium pharmaceuticals. One important step the pharmaceutical industry has taken is providing manufacturer's coupons, which my practice has used for a long time. In the past, the coupons were not useful for the majority of patients with

cataracts because Medicare does not accept them.

Now that Bausch + Lomb has added a new Medicare Part D coupon program for Prolensa to their armamentarium, my Medicare and Medicare Advantage patients can take advantage of the savings that other insured and cash-paying patients have enjoyed. With this coupon, patients will pay no more than $60 for a 3-mL bottle of Prolensa that will last them through the postoperative period.

Singh: People place value on everything purchased in life to justify the cost. It is no different for patients paying for medications. It is the physicians' responsibility as providers to educate patients and give them the value to help them justify the potential extra cost for brand name medications. I have found that more patients accept the potential increase in cost after my practice implemented an education program.

Callbacks

Katsev: How do you manage pharmacy and patient callbacks in your practice? What can physicians do to minimize them?

Stephenson: Callbacks from both patients and pharmacies have increased exponentially in my office. Since then, I have adopted and incorporated an information sheet on branded drugs into my practice, which illustrates why I feel branded drugs are so important. I have patients sign the information sheet, which makes them a part of the team: I do my part to provide good surgical outcomes, and they do their part by taking their medication as prescribed.

Rajpal: Once I explain my rationale behind using Prolensa, I find that patients pose little resistance. Furthermore, my surgical counselors have not reported problems guiding patients through the coupon programs that we offer. I prescribe Prolensa during the first appointment and have patients bring the drops with them when they return for preoperative testing so I can confirm before surgery that they have the correct drops. This process helps to keep the percentage of patient callbacks low.

Katsev: My patients frequently tell me that my staff is extremely helpful and caring, and this is because of the extra effort we take to help them understand the different medications and try to make them cost-effective for all of our patients with coupons.

Rosenthal: In most states, even if physicians require a brand name by indicating "dispense as written" (DAW) on the prescription, the pharmacist can still switch to a generic. I am fortunate enough to practice in a state where it is illegal for pharmacists to substitute with a generic without the physician's permission. Regardless, it was astonishing how often patients would present postoperatively with the wrong drops; by that time, it was too late to switch to a branded NSAID. Therefore, we write, "no substitutions, please do not call" on the prescription, which discourages pharmacies from contacting us unnecessarily.

Patient education also comes into play to help prevent a substitution. I provide patients with a one-page handout on the importance of using Prolensa in the entire surgical experience, and my staff counsels patients as well. I also give Prolensa to my patients preoperatively and instruct them to take it 1 day before surgery; this provides my staff with more lead time to troubleshoot and take care of any insurance issues that may arise, while also eliminating undue stress from fielding last-minute callbacks.

Matossian: During my weekly training sessions, I emphasize the "Golden Rule": Treat others as you wish to be treated. I encourage our technicians to help patients benefit from the coupon system without viewing the callbacks as an annoyance because, if the tables were turned, the technicians would also want to save money from coupons, if applicable.

Jackson: A local pharmacist recently read me a list of drug formularies a particular insurance plan preferred over Prolensa; three were corticosteroids which are a different medication. This shows the challenges physicians face with generic substitutions, and it only seems to be worsening.

Some patients may request a generic medication despite a DAW notation, so I make sure to indicate a medical reason to specifically dispense Prolensa on the electronic health record. This way, the pharmacist is forced to call my office and speak to me or my staff before he or she can switch to a generic formulation.

Buznego: It has been difficult to come up with a standard recommendation on how to avoid substitutions because the majority of pharmacies are regulated on a state-by-

state basis. Even the verbiage "medically necessary" vs. "DAW" varies by state.

In my practice, I deal with a morass of substitutions because, when prescribed properly with A-rated therapeutic equivalents, such substitutions are mandatory by Florida law. Therefore, it is important to indicate the specific concentration that patients should be prescribed; other concentrations of bromfenac have generic versions. Fortunately, Prolensa bromfenac solution 0.07% has no generic equivalent.

Conclusion

Katsev: What feedback have you received from your patients about Prolensa? What best practices can you provide to colleagues about NSAID use for the treatment of pain and inflammation after cataract surgery, and about Prolensa in particular?

Rosenthal: In my opinion, the fact that I have had little feedback from patients about Prolensa is a testimony to its effectiveness. Typically, they comment on the once-a-day dosing regimen, and I reinforce the importance of using the drops as prescribed, especially because this drop is used for a longer period of time than other postoperative ophthalmic medications.

Stephenson: I receive few, if any, complaints from patients about pain and discomfort while on Prolensa.

Buznego: In addition to patient education and stressing the importance of branded medication, physicians have the ability to save patients money with cash and commercial coupon programs. The game changer is the Medicare Part D coupon plan that now allows the majority of patients to receive Prolensa for $60, by answering a couple of simple questions online.

Singh: I make sure to tell patients that I always try everything I can to provide the best chance of good surgical outcomes by offering femtosecond laser-assisted cataract surgery, using advanced tools intraoperatively and that I prefer to prescribe brand-name medications.

Rajpal: I believe it is critical that physicians manage inflammation prophylactically by treating patients starting 1 day preoperatively. Doing so with Prolensa has given me the ability to help minimize any significant inflammation after cataract surgery.

Katsev: Surgeons performing cataract surgery strive to provide patients with improved vision and quality of life. The use of a potent NSAID to effectively reduce pain and inflammation can help patients achieve optimal outcomes.

I thank the panel for their time and expertise, as well as Bausch + Lomb, for its support.

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BAUSCH + LOMB

PROLENSA™

(bromfenac ophthalmic solution) 0.07%

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROLENSA™ (bromfenac ophthalmic solution) 0.07% safely and effectively. See full prescribing information for PROLENSA™ ophthalmic solution.

PROLENSA™ (bromfenac ophthalmic solution) 0.07%
Initial U.S. Approval: 1997

----------INDICATIONS AND USAGE ----------

PROLENSA 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 surgery. (1)

---------- DOSAGE AND ADMINISTRATION ----------

Instill one drop into the affected eye 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 0.07% (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 3 to 8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and vision blurred. (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-323-0000, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PROLENSA™ (bromfenac ophthalmic solution) 0.07% 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 PROLENSA ophthalmic solution should be applied to the affected eye 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

PROLENSA 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 0.07%

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), including bromfenac, 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, including bromfenac. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

5.4 Increased Bleeding Time

With some NSAIDs, including bromfenac, 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 PROLENSA 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, including bromfenac, 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

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

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 following use of PROLENSA following cataract surgery include: anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and vision blurred. These reactions were reported in 3 to 8% of patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Treatment of rats at oral doses 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 treatment-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.

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.

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

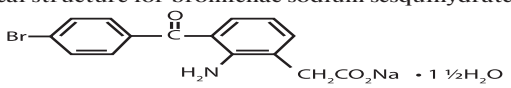
Safety and efficacy in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

There is no evidence that the efficacy or safety profiles for Prolensa differ in patients 70 years of age and older compared to younger adult patients.

11 DESCRIPTION

PROLENSA (bromfenac ophthalmic solution) 0.07% is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each mL of PROLENSA contains 0.805 mg bromfenac sodium sesquihydrate (equivalent to 0.7 mg bromfenac free acid). The USAN name for bromfenac sodium sesquihydrate is bromfenac sodium. Bromfenac sodium is designated chemically as sodium [2-amino-3-(4-bromobenzoyl) phenyl] acetate sesquihydrate, with an empirical formula of $C_{15}H_{11}BrNNaO_3 \cdot 1\frac{1}{2}H_2O$. The chemical structure for bromfenac sodium sesquihydrate is:



Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. PROLENSA ophthalmic solution is supplied as a sterile aqueous 0.07% solution, with a pH of 7.8. The osmolality of PROLENSA ophthalmic solution is approximately 300 mOsmol/kg.

Each mL of PROLENSA ophthalmic solution contains:
Active: Each mL contains bromfenac sodium sesquihydrate 0.0805%, which is equivalent to bromfenac free acid 0.07%
Preservative: benzalkonium chloride 0.005%
Inactives: boric acid, edetate disodium, povidone, sodium borate, sodium sulfite, tyloxapol, 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 (COX) 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 0.07% PROLENSA (bromfenac ophthalmic solution) in humans is unknown. Based on the maximum proposed dose of one drop to each eye (0.035 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, 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

Bromfenac 0.07% QD for the treatment of postoperative inflammation and reduction of ocular pain was evaluated in two multi-center, randomized, double-masked, parallel-group and placebo (vehicle)-controlled studies. Patients undergoing cataract surgery self-administered bromfenac 0.07% or vehicle once daily, beginning 1 day prior to surgery, continuing on the morning of surgery and for 14 days after surgery. Complete clearance of ocular inflammation (0 cell and no flare) was assessed on Days 1, 3, 8 and 15 post-surgery using slit lamp biomicroscopy. The pain score was self-reported. The primary efficacy endpoint was the proportion of subjects who had complete clearance of ocular inflammation by day 15. In the intent-to-treat analyses from both assessments, complete clearance at Day 8 and Day 15, bromfenac 0.07% was superior to vehicle as shown in the following table.

Proportion of Subjects with Cleared Ocular Inflammation (0 cells and no flare)				
Study	Visit	Bromfenac 0.07%	Vehicle	Difference (%) (Asympt-otic 95% CI)
Study 1	At Day 8	27/112 (24.1%)	7/108 (6.5%)	17.6 (8.4, 26.8)
	At Day 15	51/112 (45.5%)	14/108 (13.0%)	32.5 (21.4, 43.8)
Study 2	At Day 8	33/110 (30.0%)	14/110 (12.7%)	17.3 (6.7, 27.9)
	At Day 15	50/110 (45.5%)	30/110 (27.3%)	18.2 (5.7, 30.7)
Proportion of Subjects who Were Pain Free				
Study	Visit	Bromfenac 0.07%	Vehicle	Difference (%) (Asympt-otic 95% CI)
Study 1	At Day 1	91/112 (81.3%)	47/108 (43.5%)	37.7 (25.9, 49.6)
Study 2	At Day 1	84/110 (76.4%)	61/110 (55.5%)	20.9 (8.7, 33.1)

16 HOW SUPPLIED/STORAGE AND HANDLING

PROLENSA (bromfenac ophthalmic solution) 0.07% 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:

- 1.6 mL in a 7.5 mL container (NDC 24208-602-01)
- 3 mL in a 7.5 mL container (NDC 24208-602-03)

Storage: Store at 15º – 25ºC (59º – 77ºF).

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 replace bottle cap after using and to not touch dropper tip to any surface, as this may contaminate the contents.

Advise patients that a single bottle of PROLENSA be used to treat only one eye.

17.3 Concomitant Use of Contact Lenses

Advise patients to remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

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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