HOPES AND HURDLES FOR STEM CELL THERAPY P. 74 • USING CORNEAL ANALYSIS TO PLACE AN IOL P. 16
CAN THE OUTER RETINAL LAYERS PREDICT VISION LOSS? P. 78 • WILLS EYE RESIDENT CASE SERIES P. 103
GLAUCOMA: THE PROS AND CONS OF PRESERVED DROPS P. 90 • GET THE EYE READY FOR LASIK P. 86

REVIEW® of Ophthalmology

April 2015

reviewofophthalmology.com

Bilateral Same-Day Surgery YES or NO?

P. 42

Antibiotics and Cataract Surgery: New Frontiers P. 28

Clinical Advances in Ocular Allergy P. 50

How to Assess the Ophthalmic Start-up P. 62

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REVIEW NEWS Volume XXII • No. 4 • April 2015

DME: Greater Improvement With Eyelea When VA Is Worse

In an NIH-supported clinical trial comparing three drugs for diabetic macular edema, Eylea (aflibercept) provided greater visual improvement, on average, than did Avastin (bevacizumab) or Lucentis (ranibizumab) when vision was 20/50 or worse at the start of the trial. However, the three drugs resulted in similar average improvement when starting vision was 20/40 to 20/32. Investigators found no major differences in the safety of the three drugs. The trial was funded by the National Eye Institute, part of the National Institutes of Health.

"This comparative effectiveness study will help doctors and patients make informed decisions when choosing treatments for diabetic macular edema," said NEI Director Paul A. Sieving, MD, PhD. The trial was conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net), which is funded by NEI. The results were published online in the *New England Journal of Medicine*.

DME can occur in people with diabetic retinopathy, a type of diabetic eye disease that can cause the growth of abnormal blood vessels in the retina. The macula is the area of the retina used when looking straight ahead, for tasks such as reading, driving and watching television. Macular edema occurs when fluid leaks from retinal blood vessels and accumulates in the macula, distorting vision. Macular edema can arise during any stage of diabetic retinopathy and is the most common cause of diabetes-related vision loss. About 7.7 million Americans have diabetic retinopathy. Of these, about 750,000 have DME.

DRCR.net investigators enrolled 660 people with macular edema at 88 clinical trial sites across the United States. When the study began, participants were 61 years old on average, and had had type 1 or type 2 diabetes 17 years on average. Only people with a visual acuity of 20/32 or worse were eligible to participate. At enrollment, about half the participants had 20/32 or 20/40 vision, and the other half had 20/50 or worse vision. In many states, a corrected visual acuity of 20/40 or better in at least one eye is required for a driver's license that allows both day- and nighttime driving.

Each participant was randomly assigned to receive Eylea (2.0 milligrams/0.05 milliliter), Avastin (1.25 mg/0.05 mL) or Lucentis (0.3 mg/0.05 mL). Participants were evaluated monthly and received the assigned study drug by injection directly into the eye until the DME resolved or stabilized. Additionally, laser treatment was given if DME persisted without continual improvement after six months of injections. Laser treatment alone was the standard treatment for DME until widespread adoption of these drugs a few years ago.

All three drugs target vascular endothelial growth factor, which can cause leakage from blood vessels and the growth of new, abnormal blood vessels. Anti-VEGF drugs work for DME by reducing vascular leakage. Based on Medicare allowable charges, the per-injection costs of each drug at the doses used in this study were about $1,960 for Eylea, about $70 for Avastin and about $1,200 for Lucentis. During the year-long study, participants on Avastin and Lucentis received, on average, 10 injections, versus nine for those on Eylea.

One year after starting treatment, vision had improved substantially for the majority of trial participants. When visual acuity was 20/32 or 20/40 at the start of the trial, vision improved on average almost two lines on an eye chart in all three treatment groups. In contrast, for participants whose visual acuity was 20/50 or worse at the start of the trial, Eylea improved vision on average almost four lines, Avastin improved vision on average almost 2.5 lines, and Lucentis improved vision on average almost three lines.

"Eylea, Avastin and Lucentis yield substantial gains in visual acuity for most people with diabetic macular edema; however, on average, Eylea appears to provide additional benefit for patients who start treatment with moderate or worse vision loss," said John A. Wells, MD, the lead author of the study and a retinal specialist at the Palmetto Retina Center, Columbia, S.C.

All three drugs reduced macular edema, but Eylea and Lucentis reduced the swelling more than Avastin. Also, during the study, a smaller percentage of participants on Eylea (36 percent) underwent laser treatment for persistent edema that did

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not resolve with anti-VEGF treatment alone, compared with those on Avastin (56 percent) or Lucentis (46 percent).

The DRCR.net is dedicated to facilitating multicenter clinical research of diabetic eye disease. The network formed in 2002 and comprises more than 350 physicians practicing at more than 140 clinical sites across the country. For more information, visit the DRCR.net website at drcrnet.jaeb.org. The study is registered as NCT01627249 at clinicaltrials.gov.

Steroid-Loaded Nanoparticles May Cut Rejection

There are about 48,000 corneal transplants done each year in the United States. Of these, 10 percent end up in rejection, largely due to poor medication compliance. This costs the healthcare system and puts undue strain on clinicians, patients and their families.

Johns Hopkins Medicine researchers may have discovered a way to prevent rejection by using biodegradable nanoparticles that release needed medication into the eye after surgery. This discovery could solve the decades-old issue of medicine compliance and help patients achieve corneal transplant success.

"Medicine compliance is a major challenge in patient care," says Walter Stark, MD, chief of the Division of Cornea, Cataract and External Eye Diseases at Johns Hopkins. "About 60 to 80 percent of patients don't take medicine the way they are supposed to."

In an animal study published in the March 10 issue of the *Journal of Controlled Release*, researchers looked into ways to alleviate the strain of adhering to a post-surgery treatment regimen that is sometimes hard to manage.

Rats that underwent a corneal graft surgery were randomly divided into four groups and were given various treatments. One group was injected weekly for nine weeks with a safe, biodegradable nanoparticle loaded with corticosteroids for timed release of medicine. The other three groups received weekly injections of saline, placebo nanoparticles and free dexamethasone sodium phosphate aqueous solution after surgery, respectively.

Treatments were given until the graft was clinically deemed as failed or until the nine-week test period concluded. Researchers looked at corneal transparency, swelling and growth of new blood vessels to decide if a graft had failed. For rats that received the nanoparticle loaded with corticosteroids, 65 percent of the treatment remained in the eye and did not leak within one week of the surgery. The concentration of the treatment also remained stronger than in the other three treatment groups. Additionally, there were no signs of swelling, and the cornea was clear throughout the test period. There were also far fewer instances of unwanted growth of new blood vessels in this group.

Two weeks after surgery, rats that received the placebo nanoparticle and saline injections had severe swelling, opaque corneas and unwanted growth of new blood vessels, all indicating graft failure. After four weeks, rats that received free dexamethasone sodium phosphate aqueous solution all had graft failure as well. The only group that showed successful corneal transplant was the group of rats that received the corticosteroid-loaded nanoparticle injections. The grafts were still viable in 100 percent of these rats.

"Corneal grafts are not easy to come by, and a lot of testing and time goes into ensuring the safe use of a graft for cornea transplant," says Qingguo Xu, PhD, a research associ-

ate at the Center for Nanomedicine at the Wilmer Eye Institute at Johns Hopkins Medicine. "This is why we want to do a better job at making sure corneal transplants don't end up in rejection, and our study illustrates a potentially better way."

The steroid-loaded nanoparticle treatment group showed no signs of corneal transplant rejection. "That's 100 percent efficacy, a very promising finding," says Justin Hanes, PhD, director of the Center for Nanomedicine. "This type of treatment may also help prevent corneal transplant rejection in humans while making medicine adherence much easier on patients and their families."

The nanoparticle loaded with medication could eliminate the need for a patient to remember to take his medicine—often multiple doses per hour—after a surgery, alleviating compliance risk. These types of drug delivery systems could be paired with other drugs and used in other conditions, such as glaucoma, macular degeneration and corneal ulcers, among others. The research team intends to continue the collaboration between engineering and medicine to look further into better ways to treat eye diseases.

Jetrea Data at 24 Months Shows Positive Results

ThromboGenics announced positive top-line results from its OASIS study with Jetrea (ocriplasmin). The OASIS study is a randomized, sham-controlled, double-masked study that followed up patients for 24 months post-injection. The study was designed to provide long-term controlled efficacy and safety data for Jetrea in patients being treated for symptomatic

(continued on page 8)

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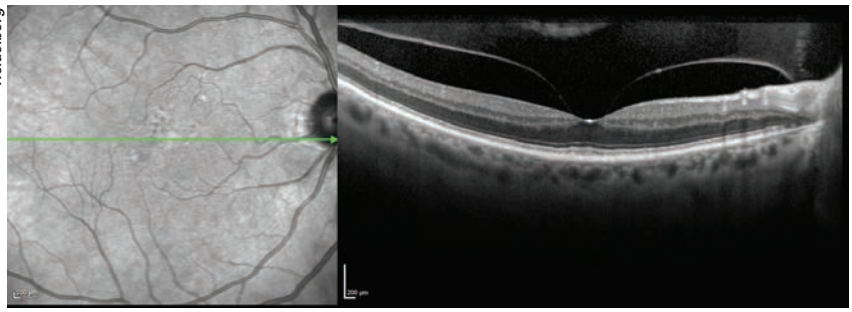

Vitreomacular adhesion, pre-treatment.

vitreomacular adhesion. The OASIS study is the first controlled study with Jetrea of its kind since the results of the pivotal Phase III program were announced in 2011. The study includes 24 month follow-up data, the longest period patients have been studied post-treatment with this novel medicine.

The key findings of the study were as follows:

• 41.7 percent of patients treated with Jetrea achieved VMA resolution at day 28 post-injection compared with only 6.2 percent of patients who received a sham injection ($p<0.001$); and

• The Jetrea safety profile in this 24 month follow-up study was consistent with the drug's overall safety profile as known from the approved label. No new safety events were identified.

The OASIS data compare favorably with the results from the pivotal Phase III program with Jetrea where VMA resolution was seen in 26.5 percent of patients at day 28 post-injection. In the Phase III program 10.1 percent of patients treated with a placebo injection achieved VMA resolution ($p<0.001$).

The OASIS data shows the importance of improved patient selection in generating higher rates of VMA resolution with Jetrea. Recent real-world data has confirmed that access to more advanced diagnostic technology such as spectral-domain optical coherence tomography has enabled retina physicians to improve patient selection. As a result they have been able to select patients with focal VMA and an absence of epiretinal membrane, two criteria that have been shown to lead to better treatment outcomes with Jetrea.

Further analysis of all of the OASIS data, which will be interpreted with the help of retina physicians, is ongoing. The results from these analyses are planned to be released later this year. REVIEW

REVIEW Review Letters

To the Editor:

I have become justifiably saddened after looking through your November '14 editorial "Compliance Faces New Economic Challenges." Seeing the proof of your points every day in the clinic, I can't resist trying to wrap my arms around the big picture.

The big clue is that you didn't write about how the insurers will repay our patients for their errors. Will they compensate them financially? Will they take back the pain, suffering and loss of vision to those who were denied access to their medicines? Or, more realistically, will their stockholders enjoy a juicier dividend? I think the latter.

As one who is always trying to connect the dots, I do not see this as an isolated event. It is an insidious process. The next chunk of "errors" mounting from 40 to 50 percent will come in the name of ICD-10. After all of the scare tactics imposed upon physicians, the implementation of ICD-10, on the clinical side, isn't that tough. Diseases have codes and will use the new ones. My projection is that companies like UHC, who boast that they insure 75 million of us, will experience "technical issues" with the conversion that will translate to billions per month in profit. The Times will write an article about it as the dividend checks are being cashed. Insurance executives are already spending quality time with their architects, who are designing their new, larger, summer homes in the Hamptons.

Conversion is not that difficult, and one would imagine that companies with revenues larger than many countries should possess the wherewithal to knock this down with excellent precision and, given their scale, for a nominal cost. In the first quarter of ICD-10, they will pay 75 percent of our claims; they will sincerely apologize and then boast that, in the second quarter, that has improved to 82 percent. The profits will be immense and their penalty will be a scathing Times article.

Dear Anthem, Cigna, Aetna, Humana, United HealthCare and MetLife, please prove me wrong!

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April 2015 • Volume XXII No. 4 | reviewofophthalmology.com

Cover Story

42 | **Bilateral, Same-Day Cataract: Is This the Future?**
By Walter Bethke, Managing Editor
Despite its allure, surgeons need some questions answered before they'll embrace the procedure.

Feature Articles

28 | **Antibiotics and Cataract Surgery: New Frontiers**
By Christopher Kent, Senior Editor
Alternatives to topical drops appear to be effective—and they're becoming more popular.

50 | **Clinical Advances in Ocular Allergy**
By Mark Abelson, MD, and Lisa Smith
Researchers are exploring disease-modifying treatment options, not just symptomatic relief.

62 | **How to Assess the Ophthalmic Start-up**
By William C. Stewart, MD, Jeanette A. Stewart, RN, and Lindsay A. Nelson
Your initial due diligence when considering a medical startup should include these steps.

70 | **Trade-offs in New Tech Decision-Making**
By Jan Beiting
Balancing demands for cost-cutting while maintaining high quality requires keeping patients' interests front and center.

Departments

3 | Review News

16 | Technology Update
Using Corneal Analysis to Choose an IOL

20 | Medicare Q&A
Need-to-Know PQRS Changes in 2015

74 | Therapeutic Topics
Hopes and Hurdles for Stem Cell Therapy
Stem cell therapy is at the cutting edge of medical research. Here's where ophthalmology fits in.

78 | Retinal Insider
Outer Retinal Layers as Predictors of Vision Loss
Imaging advances reveal new correlations between retinal anatomy and vision loss.

84 | Cornea & Anterior Segment
IOP Control: Know Your Surgical Options
MIGS may change the equation about the best initial therapy for open-angle glaucoma.

86 | Refractive Surgery
Getting the Eye Ready for LASIK
The air/tear interface is key to refraction and warrants special preoperative attention.

90 | Glaucoma Management
The Pros and Cons of Preservatives
Preservatives can be hard on your patients' corneas; the alternatives are not ideal.

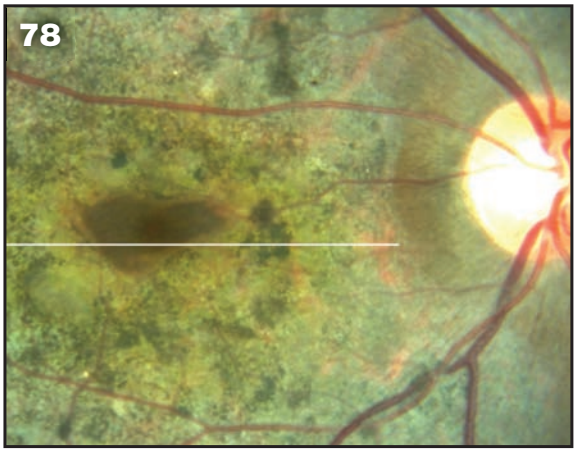
94 | Research Review
IOP Changes After Refractive Surgery

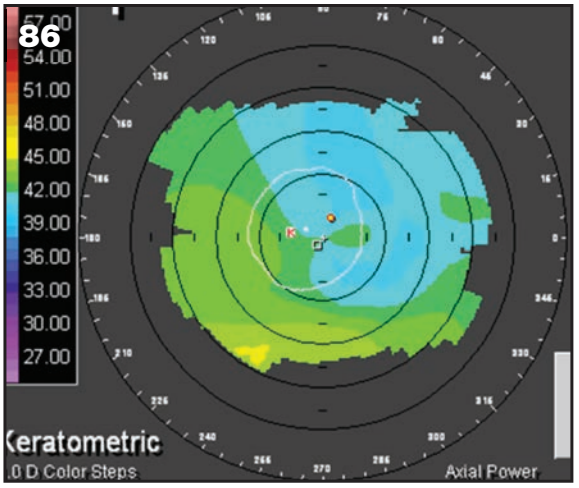
96 | Products

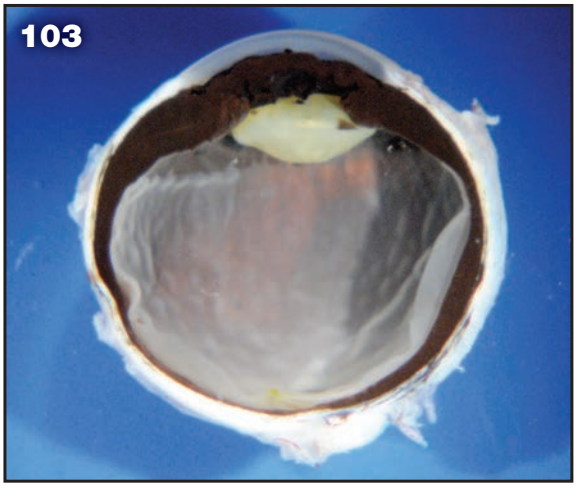
99 | Classified Ads

103 | Wills Eye Resident Case Series

106 | Advertising Index







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Bacitracin Ophthalmic Ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic.

This product should not be used in patients with a history of hypersensitivity to Bacitracin.

www.perrigobacitracin.com

Please see adjacent page for full prescribing information.

References: 1. Kempe CH. The use of antibacterial agents: summary of round table discussion. *Pediatrics*. 1955;15(2):221-230. **2.** Kowalski RP. Is antibiotic resistance a problem in the treatment of ophthalmic infections? *Expert Rev Ophthalmol*. 2013;8(2):119-126. **3.** Recchia FM, Busbee BG, Pearlman RB, Carvalho-Recchia CA, Ho AC. Changing trends in the microbiologic aspects of postcataract endophthalmitis. *Arch Ophthalmol*. 2005;123(3):341-346. **4.** Freidlin J, Acharya N, Lietman TM, Cevallos V, Whitcher JP, Margolis TP. Spectrum of eye disease caused by methicillin-resistant *Staphylococcus aureus*. *Am J Ophthalmol*. 2007;144(2):313-315. **5.** Hecht G. Ophthalmic preparations. In: Gennaro AR, ed. *Remington: the Science and Practice of Pharmacy*. 20th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000. **6.** Bacitracin Ophthalmic Ointment [package insert]. Minneapolis, MN: Perrigo Company; August 2013. **7.** Data on file. Perrigo Company.

Perrigo® Specialty Pharmaceuticals

Bacitracin Ophthalmic Ointment USP

STERILE **Rx Only**

DESCRIPTION: Each gram of ointment contains 500 units of Bacitracin in a low melting special base containing White Petrolatum and Mineral Oil.

CLINICAL PHARMACOLOGY: The antibiotic, Bacitracin, exerts a profound action against many gram-positive pathogens, including the common Streptococci and Staphylococci. It is also destructive for certain gram- negative organisms. It is ineffective against fungi.

INDICATIONS AND USAGE: For the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

CONTRAINDICATIONS: This product should not be used in patients with a history of hypersensitivity to Bacitracin.

PRECAUTIONS: Bacitracin ophthalmic ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic. The prolonged use of antibiotic containing preparations may result in overgrowth of nonsusceptible organisms particularly fungi. If new infections develop during treatment appropriate antibiotic or chemotherapy should be instituted.

ADVERSE REACTIONS: Bacitracin has such a low incidence of allergenicity that for all practical purposes side reactions are practically non-existent. However, if such reaction should occur, therapy should be discontinued.

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION: The ointment should be applied directly into the conjunctival sac 1 to 3 times daily. In blepharitis all scales and crusts should be carefully removed and the ointment then spread uniformly over the lid margins. Patients should be instructed to take appropriate measures to avoid gross contamination of the ointment when applying the ointment directly to the infected eye.

HOW SUPPLIED:

NDC 0574-**4022**-13 3 - 1 g sterile tamper evident tubes with ophthalmic tip.

NDC 0574-**4022**-35 3.5 g (1/8 oz.) sterile tamper evident tubes with ophthalmic tip.

Store at 20°-25°C (68°-77°F)
[see USP Controlled Room Temperature].

Manufactured For
Perrigo®
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0S400 RC J1 Rev 08-13 A

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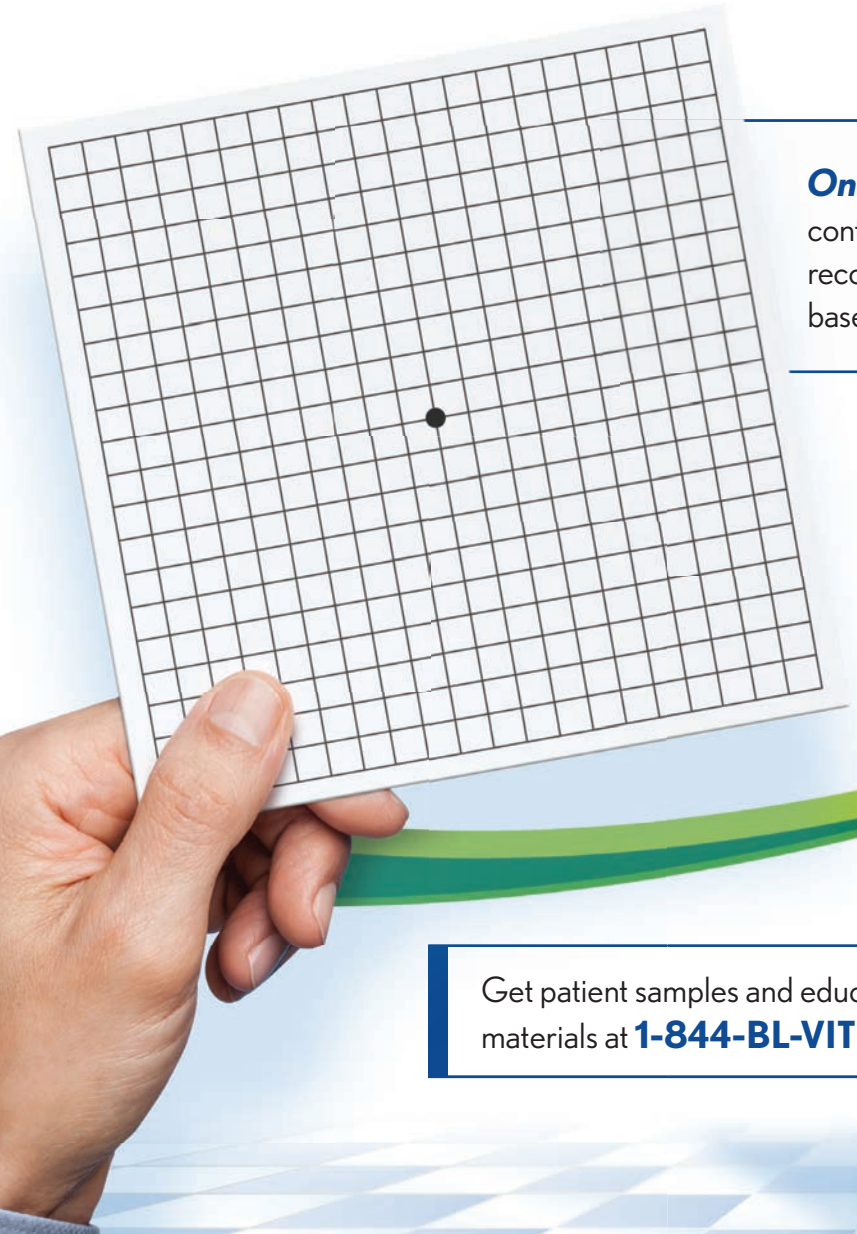
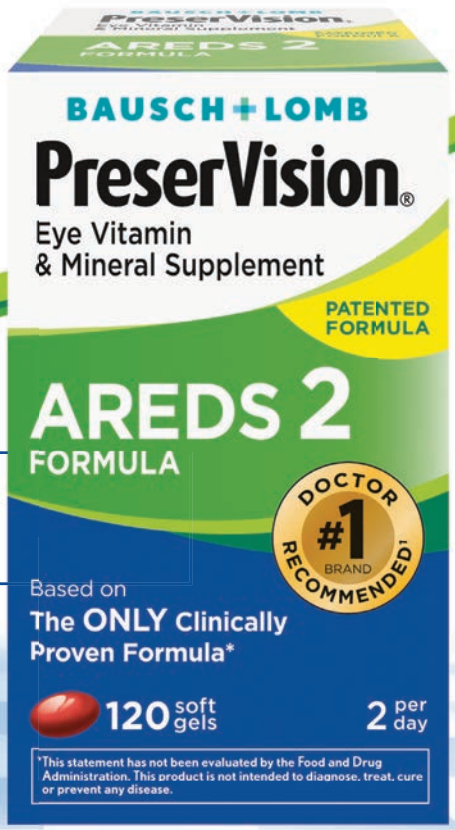


***Only* PreserVision® AREDS 2 Formula** contains the exact ingredient dosages recommended by the National Eye Institute† based on the evidence from the AREDS2 study.[1,2]*



Get patient samples and education materials at **1-844-BL-VITES.**

†For patients with moderate to advanced age-related macular degeneration.

***This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

References: 1. Yong JJ, Scott IU, and Greenberg PB. Ocular nutritional supplements. *Ophthalmology*. 2014:1-5. **2.** Chew EY, Clemens TE, SanGiovanni JP, et al. Lutein and zeaxanthin and omega-3 fatty acids for age-related macular degeneration. *JAMA*. 2013;309(19):1-11.

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Using Corneal Analysis To Help Choose an IOL

Imaging often reserved for laser refractive surgery patients can help evaluate premium intraocular lens candidates, as well.

Walter Bethke, Managing Editor

Since its arrival, corneal topography has almost always been associated with refractive surgery. Now however, as cataract surgery leans more toward refractive cataract surgery with the addition of premium lenses, surgeons say that corneal imaging can provide details that can help them predict whether a patient will be successful with a premium lens or if he might be better off with a monofocal. Here are the top tips from corneal experts on using your topographers and tomographers to help implant premium intraocular lenses.

Higher-order Aberrations

Surgeons say one of the top benefits topography and tomography systems offer them is the ability to catch irregular astigmatism, represented by higher-order aberration data, that would diminish the presbyopic IOL's ability to work well.

"It's important to remember that the corneas of your patients aren't always perfect," says Naoyuki Maeda, MD, Phd, of Japan's Osaka University Graduate School of Medicine. "Even if a cornea looks perfectly clear, it might have irregular corneal astigmatism due to undetected keratoconus, a very faint scar or mild pterygium. This faint scar or mild distortion can result in irregular astigmatism that's not appropriate for the use of a multifocal IOL." Devices useful for higher-order aberration, a.k.a., irregular astigmatism, measurement include the Oculus Pentacam, which measures corneal irregular astigmatism; and the Topcon KR-1W and Nidek OPD-Scan, which separate out lenticular and corneal higher-order aberrations. The Zeiss-Humphrey Atlas also provides data on corneal HOAs using ray tracing. "Higher-order aberrations are the enemy of the multifocal IOL," says Dr. Maeda. "The MF IOL divides light into far and near so, even with a perfect cornea, image contrast is reduced to some extent. The HOAs also cause image contrast to worsen in some situations."

To help determine if a patient has too much irregular astigmatism that might make a MF IOL unworkable, Dr. Maeda developed a numerical HOA cutoff based on the pupil diameter. "At a 4-mm diameter, 0.3 µm of HOA is similar to the blur produced by 0.5 D of defocus," he says. "And I think that a defocus, or spherical error, of 0.5 D following cataract surgery is clinically significant, so any HOAs more than 0.3 µm should make the surgeon worry. This number is just based on my experience, and hasn't been proven in a clinical study, and people may say it's kind of strict. However, I raised the bar just to be safe. I selected a pupil diameter of 4 mm because a patient's daytime pupil is around 3 to 4 mm, so I thought it was an appropriate size."

Stephen Klyce, PhD, adjunct professor of ophthalmology at New York's Mount Sinai School of Medicine, says the pupil size and corneal aberrations are key to understanding how a patient may see with a multifocal IOL; he has developed a way to simulate the patient's vision based on the aberrations at various pupil sizes. "When a patient's aberrations are represented visually, you'll often see point-spread functions, modulation transfer functions, Zernike polynomial terms and other optical transforms that most clinicians cannot understand," Dr. Klyce says. "You can't understand from such data how well the patient is seeing.

We take the corneal distortions from corneal topography and convolve them with a Snellen eye chart. Then, clinicians as well as their patients can understand how well a patient should see with glasses."

As an example, Dr. Klyce cites a patient who had undergone LASIK for high myopia. During daytime conditions, at a pupil size of 4 mm, topography shows his aberrations are fairly high. When convolved with the eye chart, however, there's a little loss of contrast that causes some blurring of lines, but the patient still can see 20/16 -1. "This isn't bad, but with a 4-mm pupil this is daytime vision," Dr. Klyce says. "If you look at the aberrations from a 5-mm pupil, which mimic nighttime vision, the pupil opens up over the laser procedure's transition zone, incorporating a lot more aberrations than in daylight. The vision on the simulated eye chart is blurry, and this patient would not be a candidate for a multifocal lens; the addition of multifocal lens aberrations would lead to reduced visual performance."

Scott MacRae, MD, professor of ophthalmology at the University of Rochester Medical Center in New York, says that, when using the Orbscan II topographer, certain maps are preferable to others. "I like instantaneous curvature and tangential maps better than axial," he avers. "Axial maps involve more averaging and you get less local information in terms of local irregularities. The instantaneous map gives you finer detail in terms of the local curvature changes—or local irregularities—that are occurring. The Orbscan also provides an irregularity index for certain pupil sizes. Anything less than 1.5 on the irregularity index is reassuring."

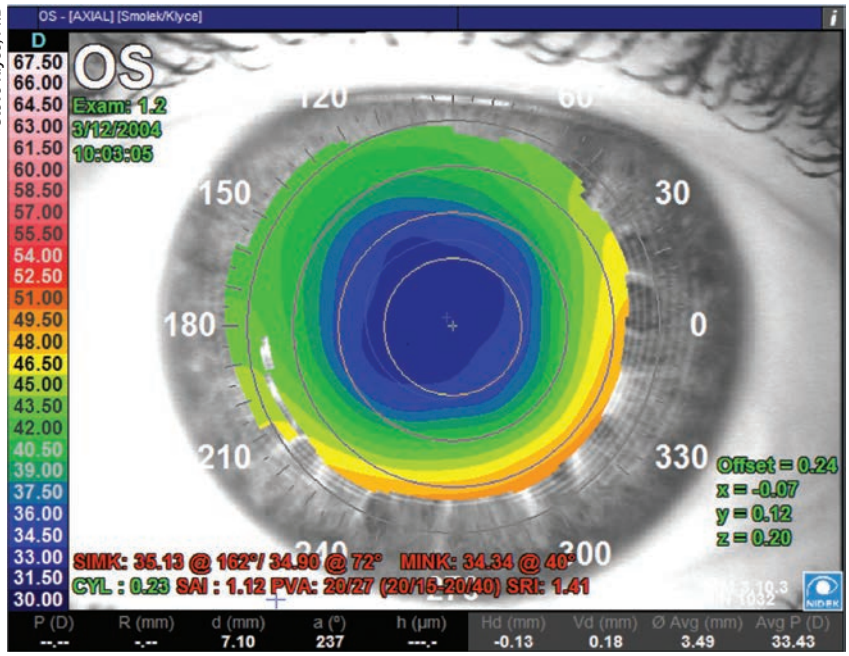


Figure 1. Topography of a patient who had previously undergone LASIK for high myopia. As the pupil diameter increases, so do his higher-order aberrations.

Abnormal Shape

Surgeons say a cornea can have minimal irregular astigmatism but still have an abnormal shape that will hinder a multifocal lens, as occurs in post-refractive surgery patients.

"Everyone knows that it's very difficult to determine IOL power after refractive surgery with LASIK," says Dr. Maeda. "If a patient has an abnormal corneal shape, even if the cornea doesn't have irregular astigmatism, such as occurs after LASIK, it's very difficult to minimize post-cataract surgery refractive errors. However, in these premium lens patients, surgeons want to select patients in whom they can easily minimize the postoperative refractive error. To identify the shape characteristics, check for an abnormal corneal shape using the tomographer's axial power map qualitatively and the sagittal front-back ratio quantitatively. In our clinic, we've found that 3 percent of our patients have what would be considered an abnormal corneal shape." Dr. Maeda cautions that postop refractive errors in ultrasound measurements are usually larger than those produced by optical devices such as the IOLMaster and LenStar.

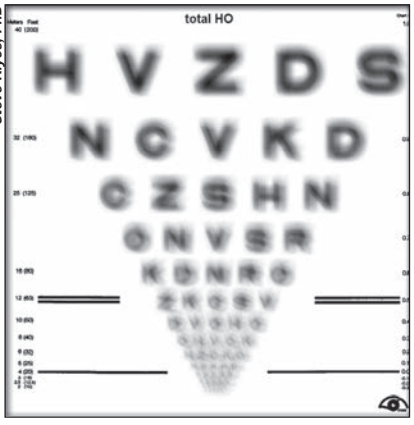
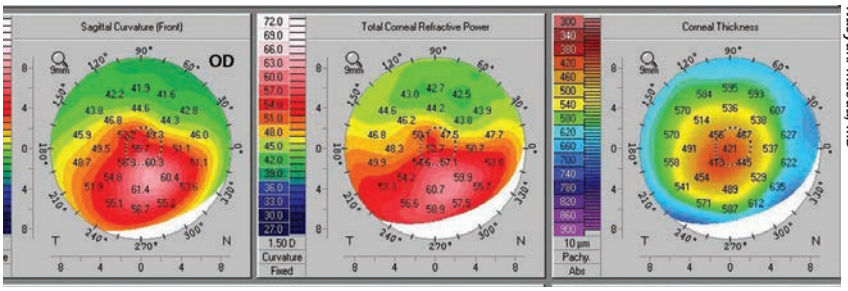


Figure 2. An eye chart convolved with the higher-order aberration data from the topography image in Figure 1 shows the blurriness the patient would experience with a 5-mm pupil.

Corneal Spherical Aberration

Since aspheric is the platform of choice for multifocal IOLs, surgeons say it pays to get a handle on the patient's spherical aberration. If the SA falls outside a certain number, the patient might be better with another sort of lens.



Naoyuki Maeda, MD

Pentacam from a patient with keratoconus. Total higher-order aberrations at the 4-mm zone are 1.463 µm, suggesting this patient won't see well without an RGP lens postop.

"The first generation of ReSTOR lens was a spherical IOL," Dr. Maeda explains. "However, this wasn't optimized, so Alcon changed it to an aspheric configuration. Major MF IOLs use an aspherical shape as their platform to reduce the spherical aberration. At the 6-mm zone, in general the spherical aberration of patients of European descent is +0.27 µm, so the aspheric IOL has -0.2 or -0.27 to compensate for it.

"When evaluating the IOL candidate," Dr. Maeda continues, "if he has a negative spherical aberration value, we shouldn't use an aspheric intraocular lens, but instead a spherical one. Therefore, I've set a cutoff of 0.1-µm RMS or higher for acceptability for use of an aspheric, multifocal lens. The acceptable range for a spherical lens is less than 0.1-µm RMS. I don't have any clinical study evidence that these cutoff values are correct, but theoretically I believe them to be useful values when making preoperative assessments. For instance, the ReSTOR IQ has a -0.2-µm RMS. So if the patient has SA of 0.1, this would create a SA of -0.1, so it makes sense as a cutoff value in this case. At our practice, we've found abnormalities in SA in 11 percent of our patients."

K Readings

Along the lines of dealing with the post-refractive surgery patient, surgeons say you may have to use corneal topography to get a true K reading.

"If a patient has any irregularity of the corneal surface or has had refractive surgery—and refractive surgery is old enough now that these cases are coming in in droves—traditional keratometry won't work well," advises Dr. Klyce. "We published a paper years ago regarding the disparity of keratometry readings and corneal power within the diameter of the pupil after refractive surgery. Keratometers measure at a 3- or 4-mm diameter on the corneal surface, and will miss any curvature changes within the central cornea. One needs to measure the corneal astigmatism and aberrations over the pupil rather than at the periphery. Typically, for intraocular lens calculations, one uses a topographic value called Average Corneal Power, rather than keratometry. ACP gives a much better estimate of the corneal power and cylinder of the part of the cornea actually used for vision. ACP is a value provided on Nidek topographers as well as on other topographers, tomographers and OCT-based instruments, where it may be called by other names.

"As an example of its usefulness," Dr. Klyce adds, "the ASCRS IOL calculator, created by Warren Hill, MD, Li Wang, MD, PhD, and Doug Koch, MD, for eyes that have undergone refractive surgery (iolcalc.org) has a numerical field requiring the input of one of these variables." Dr. Klyce says the online calculator is a major advance for optimizing refractive cataract surgery.

Dr. Maeda says a tomographer can help determine how much cylinder needs to be corrected for maximum effect from a toric or multifocal-toric intraocular lens. "It depends on the surgeon, but most surgeons agree that regular astigmatism should be kept below about 1 D postop," he says. "On the other hand, the toric intraocular lens is more expensive. We need to determine the value of the astigmatism, though I think most surgeons will agree that any cylinder value of 1.5 D or more should be corrected for a lens to have its optimum effect."

When the readings from the keratometer and those generated by the topographer disagree on the magnitude and/or axis of astigmatism in a post-refractive surgery patient, Dr. MacRae says that he will err on the side of his topography readings. "In such cases I would tend to use the results from the topographer," he says, "especially if the result is reproducible. This is because the keratometer is user-dependent, and so it's not as objective a reading as one gets from an automated system such as the corneal topographer. However, such a discrepancy could be another warning sign to the cataract surgeon that there's some irregularity of the surface as a result of dry eye, so you'd want to repeat the topography and look for consistency with that. Though it's true you can instill artificial tears, the fact is if you frequently have to put in artificial tears just to get a good image for a particular patient, that's an indication that you either have to work with the patient to try to get the surface irregularity eliminated on a more sustained basis before the surgery or that you have to shy away from implanting a multifocal lens in that patient. This is because if the patient's ocular surface is becoming irregular, the combination of an irregular surface and a multifocal IOL can reduce image quality, resulting in an unhappy patient." REVIEW

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Donna McCune, CCS-P, COE, CPMA

Need-to-Know Changes For the PQRS in 2015

Changes to the participation bonus, new ophthalmic measures and requirements that can affect future reimbursements.

Q Does the Physician Quality Reporting System continue in 2015 with the opportunity to receive a bonus for participating?

A The PQRS program does continue in 2015. However, 2014 was the final year for a bonus; there is no bonus for participation in 2015.

Q Will providers be penalized for non-participation?

A Yes. Providers who did not successfully participate in 2013 received letters from the Centers for Medicare & Medicaid Services in late 2014 indicating a 1.5-percent reduction to their Medicare reimbursement for 2015. Penalties in 2016 and 2017 will depend on the provider's level of participation and successful reporting in 2014 and 2015 respectively.

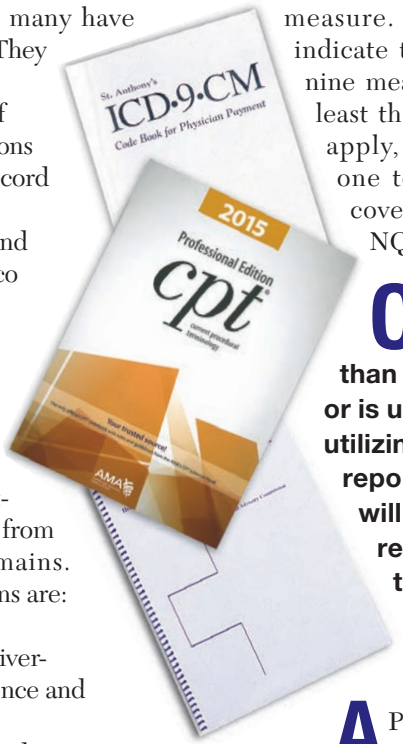
Q Are the requirements for successful participation in 2015 different than in prior years?

A Successful participation has always relied on providers performing services described as "quality measures" and submitting codes to support their performance of these measures. One change for 2015 is the need to report one measure categorized as a cross-cutting measure. Several measures meet this criterion, including ones that many have previously reported. They include:

- Documentation of Current Medications in the Medical Record (#130); and
- Preventive Care and Screening: Tobacco Use: Screening and Cessation Intervention (#226.)

Successful reporting also continues to rely on reporting quality measures from three separate domains. The six domain options are:

- Patient Safety;
- Person and Caregiver-Centered Experience and Outcomes;
- Communication and Care Coordination;
- Effective Clinical Care;
- Community/Population Health; and
- Efficiency and Cost Reduction.



To successfully report in 2015, providers must report at least nine measures covering at least three National Quality Strategy domains and include one cross-cutting measure. The instructions indicate that if fewer than nine measures covering at least three NQS domains apply, you may report one to eight measures covering one to three NQS domains.

Q If a provider reports fewer than nine measures or is unsuccessful utilizing another reporting method, will there be a reduction to the providers Medicare reimbursement in 2017?

A Physicians who submit fewer than nine measures or three NQS domains are subject to the review process called "Measure Applicability Validation." This process, introduced in 2014, will be applied for the first time to those

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TRAVATAN Z® Solution has no FDA-approved therapeutic equivalent[3]

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INDICATIONS AND USAGE

TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dosage is 1 drop in the affected eye(s) once daily in the evening. TRAVATAN Z® Solution should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the IOP-lowering effect.

TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Pigmentation—Travoprost ophthalmic solution has been reported to increase the pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. The long-term effects of increased pigmentation are not known. While treatment with TRAVATAN Z® Solution can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes—TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Use With Contact Lenses—Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Adverse Reactions

The most common adverse reaction observed in controlled clinical studies with TRAVATAN Z® Solution was ocular hyperemia, which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus. In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

Use in Specific Populations

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

For additional information about TRAVATAN Z® Solution, please see the brief summary of Prescribing Information on the adjacent page.

***Study Design:** Double-masked, randomized, parallel-group, multicenter non-inferiority comparison of the efficacy and safety of travoprost 0.004% preserved with benzalkonium chloride (BAK) to TRAVATAN Z® Solution after 3 months of treatment in patients with open-angle glaucoma or ocular hypertension. Baseline IOPs were 27.0 mm Hg (n=322), 25.5 mm Hg (n=322), and 24.8 mm Hg (n=322) at 8 AM, 10 AM, and 4 PM for TRAVATAN Z® Solution. At the end of Month 3, the TRAVATAN Z® Solution group had mean IOPs (95% CI) of 18.7 mm Hg (-0.4, 0.5), 17.7 mm Hg (-0.4, 0.6), and 17.4 mm Hg (-0.2, 0.8) at 8 AM, 10 AM, and 4 PM, respectively. Statistical equivalent reductions in IOP (95% confidence interval about the treatment differences were entirely within ±1.5 mm Hg) were demonstrated between the treatments at all study visits during the 3 months of treatment.

References: 1. Data on file, 2013. **2.** Lewis RA, Katz GJ, Weiss MJ, et al. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. *J Glaucoma.* 2007;16(1): 98-103. **3.** Drugs@FDA. FDA Approved Drug Products: TRAVATAN Z. www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed July 31, 2014.

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

Alcon®
a Novartis company

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.
TRAVATAN Z® (travoprost ophthalmic solution) should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 2 hours after the first administration with maximum effect reached after 12 hours.

TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Pigmentation
Travoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with TRAVATAN Z® (travoprost ophthalmic solution) 0.004% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes
TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
TRAVATAN Z® Solution should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. TRAVATAN Z® Solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory or Neovascular Glaucoma
TRAVATAN Z® Solution has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS
Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The most common adverse reaction observed in controlled clinical studies with TRAVATAN® (travoprost ophthalmic solution) 0.004% and TRAVATAN Z® (travoprost ophthalmic solution) 0.004% was ocular hyperemia which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with TRAVATAN® or TRAVATAN Z® Solutions included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing.

Nonocular adverse reactions reported at an incidence of 1 to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence and urinary tract infections.

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
Teratogenic effects: Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day (250 times the maximal recommended human ocular dose (MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 mcg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 mcg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 mcg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of ≥ 0.12 mcg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

There are no adequate and well-controlled studies of TRAVATAN Z® (travoprost ophthalmic solution) 0.004% administration in pregnant women. Because animal reproductive studies are not always predictive of human response, TRAVATAN Z® Solution should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN Z® Solution is administered to a nursing woman.

Pediatric Use
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

Geriatric Use
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

Hepatic and Renal Impairment
Travoprost ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 mcg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day [250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mcg/kg basis (MRHOD)]. At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD).

PATIENT COUNSELING INFORMATION
Potential for Pigmentation
Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of TRAVATAN Z® (travoprost ophthalmic solution) 0.004%.

Potential for Eyelash Changes
Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with TRAVATAN Z® Solution. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice
Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of TRAVATAN Z® Solution.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Rx Only
U.S. Patent Nos. 5,631,287; 5,889,052, 6,011,062; 6,235,781; 6,503,497; and 6,849,253

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9/14 TRV14066JAD

providers who reported fewer than nine measures in 2014. This process allows CMS to determine whether the provider should have reported additional measures and/or measures covering additional NQS domains. If the MAV review done by CMS determines the provider accurately submitted and that no additional measures and/or NQS domains applied, the penalty is averted.

In order to avoid a 2-percent PQRS reduction in 2017, eligible professionals must be successful in some manner with PQRS.

Q Are there any changes to how eligible professionals report PQRS measures to CMS?

A No. Measures may be reported by individual providers or as a group practice. Some, not all, measures may be submitted on claims filed to Medicare. Some measures are eligible to be reported via electronic health records. Providers may choose to utilize a "registry" to report on their behalf. Reporting through a Qualified Clinical Data Registry continues to be an option. A QCDR is a CMS-approved entity that has self-nominated and successfully completed a qualification process. The American Academy of Ophthalmology's IRIS registry is a QCDR.

Those who want to report as a group practice must request this option from CMS and be approved to report in this manner. Reporting through an EHR also requires that the EHR vendor has been approved by CMS to report via this method.

Q Are providers required to report on every Medicare patient meeting the quality measure description?

A No. Each measure must be reported for at least 50 percent of the applicable Medicare Part B fee-for-service patients seen during the reporting period for eligible professionals submitting PQRS measures on their claims. For those utilizing a registry, the reporting threshold for the registry is also 50 percent.

Q What quality measures apply to eye-care providers?

A The 2015 measures for eye disease carried over from the 2014 program are:

- Primary Open-Angle Glaucoma (POAG): Optic Nerve Evaluation (#12);
- Age-related Macular Degeneration (AMD): Dilated Macular Examination (#14);
- Diabetic Retinopathy: Communication With the Physician Managing Ongoing Diabetes Care (#19);
- Diabetes: Eye Exam (#117);
- Age-Related Macular Degeneration (AMD): Counseling on Antioxidant Supplement (#140); and
- Primary Open-Angle Glaucoma (POAG): Reduction of Intraocular Pressure (IOP) by 15% OR Documentation of a Plan of Care (#141).

The diabetic retinopathy measure, Documentation of Presence or Absence of Macular Edema and Level of Severity Of Retinopathy (#18), was eliminated from reporting through claims or registry. It may only be reported through the EHR option.

Most eye-care practices will need to report measures that are not ophthalmology-specific. See Table 1 for a list of possible options. This list is not exhaustive, but will give you a starting point.

Table 1. Non-ophthalmology Measures to Report

Measure	Title
#110	Preventive Care and Screening: Influenza Immunization
#111	Pneumonia Vaccination Status for Older Adults
#130	Documentation of Current Medications in the Medical Record
#131	Pain Assessment and Follow-up
#137	Melanoma: Continuity of Care-Recall System (Registry only)
#138	Melanoma: Coordination of Care (Registry only)
#226	Preventive Care and Screening: Tobacco Use: Screening and Cessation Intervention
#265	Biopsy Follow-up (Registry only)

Q Were any new ophthalmic measures added in 2015?

A Yes; these new measures must be reported through a registry:

- Adult Primary Rhegmatogenous Retinal Detachment Repair Success Rate (#384);
- Adult Primary Rhegmatogenous Retinal Detachment Surgery Success Rate (#385);
- Cataract Surgery with Intra-Operative Complications (Unplanned Rupture of Posterior Capsule Requiring Unplanned Vitrectomy);
- Cataract Surgery: Difference Between Planned and Final Refraction.

Q Does the Cataract Measures Group still exist?

A Yes, but the Cataracts Measures Group may only be reported through a registry. In 2015, the Measures Group consists of the measures listed in Table 2.

Table 2. Cataract Measures Group

Measure	Title
#130	Documentation of Current Medications in the Medical Records
#191	Cataracts: 20/40 or Better Visual Acuity within 90 Days Following Cataract
#192	Cataracts: Complications within 30 Days Following Cataract Surgery Requiring Additional Surgical Procedures
#226	Preventive Care and Screening: Tobacco Use: Screening and Cessation Intervention
#303	Improvement in Patient's Visual Function within 90 Days Following Cataract Surgery
#304	Patient Satisfaction within 90 Days Following Cataract Surgery
#388	Cataract Surgery with Intra-Operative Complications (Unplanned Rupture of Posterior Capsule Requiring Unplanned Vitrectomy)

When reporting the measures group, all applicable measures must be completed for each patient being reported. Successful reporting of the measures group requires reporting for 20 or more patients with at least 11 being traditional Medicare Part B patients.

Q Does the PQRS link to any other CMS initiatives?

A Yes, it does. The Value Based Payment Modifier links directly to the PQRS program and rewards or penalizes providers for the quality and cost of care provided. In 2015, all providers are subject to the VBPM. Performance in 2015 will affect reimbursements in 2017, making success with PQRS in 2015 critical. Failure with PQRS in 2015 results in a 2 percent PQRS penalty plus a 2 to 4 percent VBPM penalty, depending on the size of the practice in 2017. REVIEW

Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.

Dry eye relief starts with restoring balance

Elevated tear film osmolarity (osmolarity imbalance or hyperosmolarity) is one of the primary causes of dry eye symptoms[1].

TheraTears® Dry Eye Therapy with Osmo-Correction™ corrects osmolarity imbalance to restore comfort with a unique hypotonic and electrolyte balanced formula that replicates a healthy tear.

WITH
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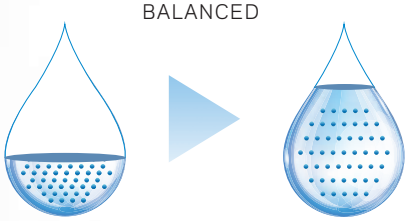
HYPOTONIC & ELECTROLYTE BALANCED



HYPEROSMOLARITY

Increased concentration of the tears leads to irritation and potential damage to the ocular surface.

HEALTHY TEAR

TheraTears® Dry Eye Therapy replicates the electrolyte balance of natural tears to restore comfort.

RESTORE + CLEANSE + NOURISH

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Reference: 1. Research in dry eye report of the Research Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf.* Apr 2007; 5(2): 179-193.

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IS THE TIME TO PREVENT INTRAOPERATIVE MIOSIS AND REDUCE POSTOPERATIVE OCULAR PAIN

OMIDRIA™ (phenylephrine and ketorolac injection) 1% / 0.3% is *the first and only FDA-approved treatment* that both[1]:

- **Preemptively inhibits intraoperative miosis**
- **Decreases postoperative ocular pain for 10 to 12 hours**

Easy to integrate into routine operating procedures

Add preoperatively to irrigation solution

- One 4-mL single-patient-use vial to 500 mL[1]
- Can be added to irrigation solution in the surgical suite

No other preparation required

INDICATIONS AND USAGE

OMIDRIA is added to ophthalmic irrigation solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

OMIDRIA™ IS NOW AVAILABLE TO ORDER

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- Unit quantity: One (1) carton contains four (4) single-patient-use vials

OMIDRIA is reimbursed by CMS

For ordering information or for live reimbursement support for OMIDRIA, contact 1-844-OMEROS1 (1-844-663-7671), or visit www.omidria.com.

IMPORTANT SAFETY INFORMATION

OMIDRIA must be added to irrigation solution prior to intraocular use.

OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients.

Systemic exposure of phenylephrine may cause elevations in blood pressure.

Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other non-steroidal anti-inflammatories (NSAIDs), or have a past medical history of asthma.

The most commonly reported adverse reactions at 2-24% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Use of OMIDRIA in children has not been established.

Please see the Full Prescribing Information for OMIDRIA at www.omidria.com/prescribinginformation.

You are encouraged to report Suspected Adverse Reactions to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Reference: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2014.

OMIDRIA™
(phenylephrine and ketorolac injection) 1% / 0.3%

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Antibiotics & Cataract Surgery: New Frontiers

Christopher Kent, Senior Editor

Alternatives to topical drops appear to be effective—and they're becoming more popular.

Taking steps to minimize postoperative complications such as inflammation and infection has always been a part of cataract surgery. Endophthalmitis, in particular, is a complication every surgeon wants to avoid. So, it's no surprise that antiseptics and antibiotics are a standard part of surgery protocol.

Like everything else in medicine, however, that protocol has slowly been evolving—especially the ways in which antibiotics are used. Initially, many surgeons had their patients use antibiotic drops for a period of time before and after surgery. Now the use of antibiotics before surgery has come into question, and alternatives to the use of postoperative drops are proliferating. In particular, intracameral injection of antibiotics, with or without steroids, is becoming more widely accepted.

Here, four surgeons with experience using intracameral antibiotics share their thoughts on the pros and cons of different approaches.

Catching the Wave

"There's definitely a change in the dynamic of what we're doing to manage complications post-cataract surgery," says Francis Mah, MD, who specializes in cornea, external disease and refractive surgery at Scripps Health System in San Diego. "More and more prospective studies are showing the efficacy of intracameral antibiotics. Outside of the United States, I think the majority of surgeons believe that intracameral injections are superior to drops, based on the medical literature. In the meantime, there's plenty of interest in this kind of protocol here. The latest ASCRS survey of cataract surgeons showed that close to 80 percent were interested in it, or would definitely do it if there were an FDA-approved agent. However, only 20 to 30 percent of U.S. cataract surgeons are actually doing routine intracameral right now."

James P. Gills, founder and director of St. Luke's Cataract & Laser Institute in Tarpon Springs, Fla., who recently stopped performing cataract surgery, used intracameral antibiotics in conjunction with cataract surgery for many years. "When I was doing cataract surgery, my patients didn't have to buy or instill any preop or postop drops," he says. "Instead, I would use intracameral antibiotics, along with a very small dose of a steroid—vancomycin, ceftazidime and dexamethasone. The doses I used, as Robert Machamer, MD, and Gholam Peyman, MD, suggested, were one-tenth the therapeutic dose for endo-

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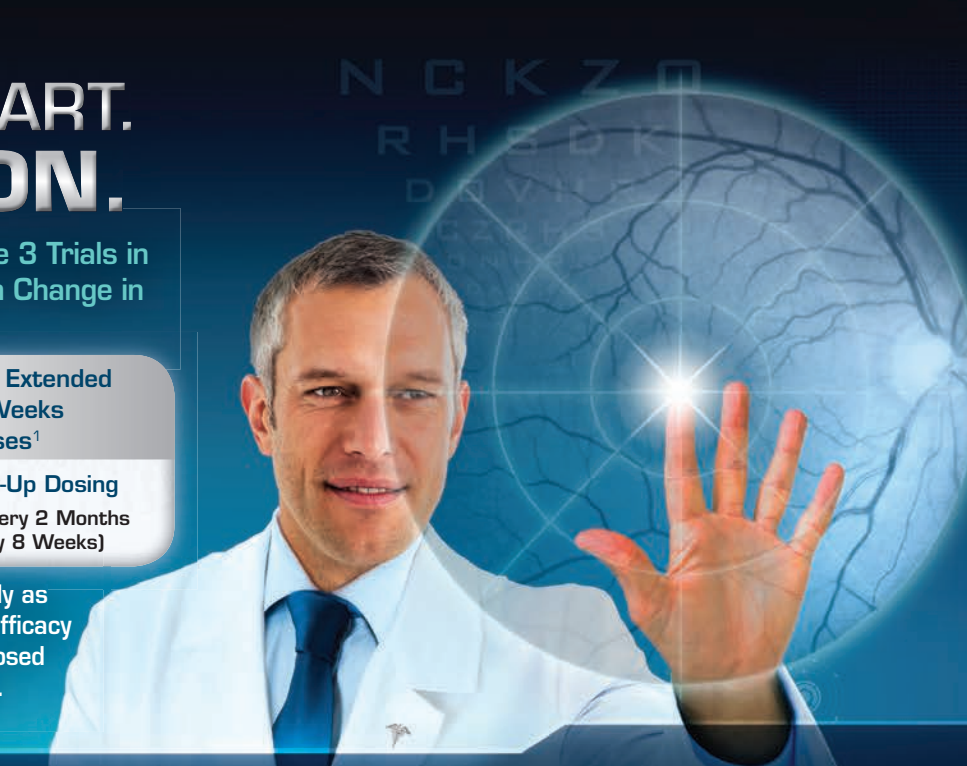
As Demonstrated in 2 Pivotal, Phase 3 Trials in Patients With DME Evaluating Mean Change in BCVA* at 52 Weeks vs Baseline[1]

EYLEA® (aflibercept) Injection Offers Extended Dosing in DME—2-mg Every 8 Weeks Following 5 Initial Monthly Doses[1]

Initial Dosing	Follow-Up Dosing
5 Initial 2-mg Injections Monthly (Every 4 Weeks)	2-mg Every 2 Months (Every 8 Weeks)

Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.



*BCVA = best-corrected visual acuity, as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

IMPORTANT SAFETY INFORMATION FOR EYLEA® (aflibercept) INJECTION

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.
- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies during the first year was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.
- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

IMPORTANT PRESCRIBING INFORMATION FOR EYLEA® (aflibercept) INJECTION

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

For more information, visit www.EYLEA.com.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. October 2014.

Please see brief summary of full Prescribing Information on the following page.

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), and Diabetic Macular Edema (DME).

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions. For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.3 Macular Edema Following Retinal Vein Occlusion (RVO). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly).

2.4 Diabetic Macular Edema (DME). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.5 Preparation for Administration. EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

2.6 Injection Procedure. The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay (*see Patient Counseling Information*).

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (*see Adverse Reactions*). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately (*see Dosage and Administration and Patient Counseling Information*).

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (*see Adverse Reactions*). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular edothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (*see Dosage and Administration*).

5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies during the first year was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

6.1 Clinical Trials 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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Conjunctival hyperemia	4%	8%
Corneal erosion	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) for 52 weeks.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%
Eye pain	9%	6%
Cataract	8%	9%
Vitreous floaters	6%	3%
Corneal erosion	5%	3%
Intraocular pressure increased	5%	3%
Conjunctival hyperemia	5%	6%
Vitreous detachment	3%	3%
Foreign body sensation in eyes	3%	3%
Lacrimation increased	3%	2%
Vision blurred	2%	2%
Intraocular inflammation	2%	<1%
Injection site pain	2%	<1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, eyelid edema, corneal edema, retinal detachment, injection site hemorrhage, and retinal tear.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-52 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy. Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers. It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist (*see Warnings and Precautions*). Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (*see Adverse Reactions*). Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

U.S. License Number 1760
EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

Issue Date: October 2014
Initial U.S. Approval: 2011

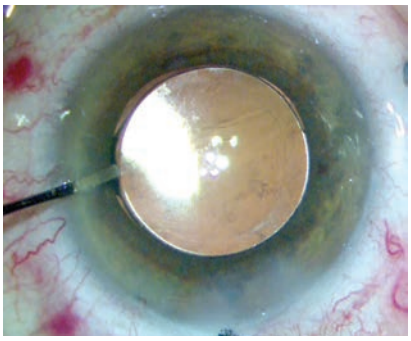
Regeneron U.S. Patents 7,306,799; 7,531,173; 7,608,261; 7,070,959; 7,374,757; 7,374,758, and other pending patents

LEA-0618

phthalmitis. This is a very low dose, but it's enough to stun any bacteria that might have been in the eye so they cannot reproduce. I used this technique for 35 or 40 years, and it worked extremely well. And we're not alone; Richard Mackool's practice has also reported outstanding results using intracameral vancomycin, along with Steven Arshinoff and Samuel Masket. The list goes on."

William F. Wiley, MD, director of the Cleveland Eye Clinic, agrees that this type of approach is gaining traction. "Almost all of my colleagues across the country are either considering using an injection at the end of cataract surgery or are already doing it," he says. "They realize that the cost of traditional medications has gotten out of hand and an alternative approach is reasonable. At a recent meeting I heard four or five lectures on the subject of minimizing postoperative drops, so awareness of the issue is spreading. There's definitely a need to try to decrease the expense and inconvenience of traditional medication."

Samuel Masket, MD, a clinical professor of ophthalmology at the Jules Stein Eye Institute, UCLA School of Medicine in Los Angeles, and a past president of the American Society of Cataract and Refractive Surgery, notes that the idea of intraocular antibiotics isn't really new. "It took the European Society of Cataract and Refractive Surgery study[1] to capsulize the significant positive difference made when intraocular antibiotics are used," he says. "But if we go back more than 20 years, two cataract surgeons known for their contributions to the field and significant patient volumes—Jim Gills, MD, and Howard Gimble, MD—were routinely either infusing or injecting antibiotics at the end of surgery. And they were not alone. When I surveyed the ASCRS membership in 1996 and 1997 there was already significant use of intracameral agents. Out of 1,270 surgeons who replied to the survey, 18 percent were using intraocular vancomycin.



Samuel Masket, MD

Use of intracameral antibiotics at the end of cataract surgery (instead of topical drops) is not a new idea, but it finally appears to be gaining popularity in the United States.

"Despite this level of interest, it never really got the attention that it should have," he adds. "One of the problems was proving the efficacy of such a protocol; it wasn't until the ESCRS study that the idea really began to gain traction."

One Surgeon's Protocol

Dr. Masket describes the steps he takes when using intracameral antibiotics. "Since roughly 2007 I've used 50 µl of Vigamox, which is moxifloxacin, directly out of the bottle, injected into the anterior chamber as the last thing we do at surgery," he explains. "I want to stress that it's µl, not ml; it's half of one tenth of a liter, a very small amount. We only do this once we've checked that all incisions are hermetically sealed, whether with sutures or ReSure ocular sealant. We've tested the incisions with point pressure, we've done an operative Seidel test and we've set the intraocular pressure at physiological levels, as measured with a tonometer, so we know we have a sealed, non-leaking system. Once that's accomplished, the last thing I do is inject the Vigamox directly into the anterior chamber. I've done this for at least eight years and have not seen one case of infection. I've used it in each and every eye, irrespective of the procedure I'm doing, although of course the great majority of surgeries are cataract surgery." He acknowledges that some surgeons use a slightly different protocol. "Some people inject 0.1 µl rather than .05 µl," he says. "Also, some surgeons dilute it, which I don't believe is necessary."

Dr. Masket points out that the only agent that can be injected in this way happens to be Alcon's Vigamox. "It's not intended for intracameral use," he notes. "This is strictly an off-label use. But Vigamox happens to have a pH of 6.8, which is similar to aqueous; and its osmolality, or tonicity, is about the same as aqueous. Plus, it has no preservative. For those three reasons—tonicity, pH and absence of preservative—off-the-shelf Vigamox is compatible with the intraocular environment and is tolerated intracamerally without dilution."

But Is It Safe?

Given that many surgeons have achieved minimal endophthalmitis rates using this type of protocol, one might wonder why more surgeons aren't adopting this approach. Part of the reason is undoubtedly the absence of an injectable that's FDA-approved for this purpose, along with the respectable results associated with more traditional protocols. But there is also some concern about some poor outcomes that have been reported, often relating to factors such as compounding problems.

"I'd say that the one downside to injecting antibiotics that concerns surgeons is the toxicity issue, whether that's toxic anterior segment syndrome or an allergic reaction to the medication," says Dr. Mah. "Even after the positive results from the study conducted by the European Society of Cataract and Refractive Surgery, adoption has not been universal over in Europe—even in the countries that participated in the study. That's be-

cause of the safety concerns and fears about dilutional errors, TASS and allergic reactions.

"One way around these concerns is to avoid having to compound the injected drugs," he continues. "In Europe there is a French company, Thea, which manufactures an approved single-use injectable antibiotic for delivery inside the eye, sidestepping this problem. It comes premixed, requiring a single dilution. I believe the product is approved in 20 or 30 countries outside the United States, and I believe they have approached, or plan to approach, the FDA in this country. Other companies around the world are undoubtedly also working on drugs for this purpose that will not need to be compounded, and many surgeons in the United States are waiting for an FDA-approved, single-use intracameral antibiotic."

Studies that sidestep the compounding concern have generally been more positive. Dr. Masket notes that he was part of a three-site study that also included Stephen Lane, MD, and Robert Osher, MD. "We did a masked investigation that was published in 2008,[2] in which at the end of surgery we'd either inject Vigamox or BSS," he explains. "Then we looked at corneal thickness as a measure of corneal toxicity, OCT as a measure of macular toxicity and endothelial cell counts. We also looked at IOP and a few other parameters. We found no difference between BSS and out-of-the-bottle Vigamox with respect to toxicity or safety. Of course, this was not a study of efficacy. One would have to do thousands of cases to determine whether the protocol was efficacious."

Dr. Masket notes that the idea of using vancomycin has generated serious pushback. "The antibiotic that Drs. Gills and Gimble recommended was vancomycin," he says. "There was one study that compared two groups of patients, one with vancomycin infused, the other not, that found a higher incidence of cystoid macular edema in the vancomycin group. But it was a poorly done study that was refuted by numerous surgeons. Nevertheless, it's still occasionally quoted as a reason not to use vancomycin. In contrast, you have a study like the ESCRS study, which was well-designed and executed. Some people criticize it on the grounds that they stopped the study too soon for the numbers to be as significant as they should be, but they did that because the result was so obvious to them. They had a fivefold increase in infection when they did not use intracameral agents. They didn't feel they could continue the study for moral reasons.

"It's very unlikely that we make a meaningful contribution to antibiotic resistance."
—Samuel Masket, MD

"I believe it's inappropriate to discount the findings of the ESCRS study," he adds. "Besides, several other studies from well-known researchers, including the one I conducted with Drs. Lane and Osher, have shown that a protocol like this is safe and efficacious, especially when using moxifloxacin. But until the day comes when the studies have convinced the FDA that intracameral antibiotics are safe and efficacious, we're not going to have readily available single-dose units. Unfortunately, as far as the FDA is concerned, there is currently no irrefutable proof that intraocular antibiotics reduce the rate of infection."

Surgeons and others have also expressed concern about whether this type of protocol might increase antibiotic resistance. "The academic medical centers and the Centers for Disease Control, as well as the American Academy of Ophthalmology, have expressed concern about this," explains Dr. Masket. "This was considered especially important because vancomycin was the last treatment option for certain enterococcal infections outside the eye. But because vancomycin has low toxicity, and because there had never been a gram-positive infection in the eye that was found to be resistant to it, a lot of people have used it anyway, over a long period of time."

Dr. Masket doesn't believe that resistance is likely to be generated by using vancomycin inside the eye. "The problem is that if you're running it through bottles that eventually end up in the trash, a small amount of antibiotic could get washed out into the environment," he says. "However, the use of vancomycin and fluoroquinolones in industry and agriculture is massive—especially in agriculture. In contrast, it's been estimated that only 0.02 percent of the antibiotics being used are used in the eye, so it's very unlikely that we make a meaningful contribution to antibiotic resistance."

Alternative Delivery Methods

In addition to intracameral injection, other methods have been used (and are being developed) that can provide antibiotic coverage following cataract surgery.

- ***Infusion.*** Some surgeons have simply added the antibiotic to the fluid going into the eye, either in addition to an injection at the end of surgery or as a stand-alone approach to endophthalmitis prevention. "The problem with infusion is that it's hard to know exactly how much medicine is getting in and whether the concentration is adequate," says Dr. Masket. "Some antibiotics work best at certain concentrations. If the concentration is too low, the antibiotic will not have a meaningful effect on the bacteria.

LOTEMAX® GEL—UNIQUE FORMULATION DESIGNED TO CONTROL INFLAMMATION

MUCOADHESIVE TECHNOLOGY—
Engineered to adhere to the ocular surface[1-3]

DOSE UNIFORMITY—
No shaking required to resuspend drug[1,4,5]

LOW PRESERVATIVE AND TWO KNOWN MOISTURIZERS[1,2,4,6]

PROVEN EFFICACY AND ESTABLISHED SAFETY[1,2,7]

Indications and Usage

- LOTEMAX® GEL is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery

Important Risk Information about LOTEMAX® GEL

- LOTEMAX® GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures
- Intraocular pressure (IOP) increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored
- Cataracts—Use of corticosteroids may result in posterior subcapsular cataract formation
- Delayed healing—Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification
- Bacterial infections—Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infections
- Viral infections—Use of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex)
- Fungal infections—Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use
- Contact lens wear—Patients should not wear contact lenses when using LOTEMAX® GEL
- The most common ocular adverse drug reactions were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%)

Please see brief summary of full prescribing information on adjacent page.

References: 1. LOTEMAX GEL Prescribing Information, September 2012. **2.** Fong R, Leitritz M, Siou-Mermet R, Erb T. Loteprednol etabonate gel 0.5% for postoperative pain and inflammation after cataract surgery: results of a multicenter trial. *Clin Ophthalmol.* 2012;6:1113-1124. **3.** Shaikh R, Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. *J Pharm Bioallied Sci.* 2011;3(1):89-100. **4.** Data on file, Bausch & Lomb Incorporated. **5.** Coffey MJ, Davio SR. Viscoelastic and sedimentation characterization of loteprednol etabonate ophthalmic gel, 0.5%. Poster presented at: Association for Research in Vision and Ophthalmology (ARVO); May 6-10, 2012; Fort Lauderdale, FL. Poster #6283/D1143. **6.** Lotemax Prescribing Information, April 2006. **7.** Rajpal RK, Roel I, Siou-Mermet R, Erb T. Efficacy and safety of loteprednol etabonate 0.5% gel in the treatment of ocular inflammation and pain after cataract surgery. *J Cataract Refract Surg.* 2013;39:158-167.

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DISCOVER THE POWER OF GEL

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Brief Summary: Based on full prescribing information.

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

INDICATIONS AND USAGE

LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops.

Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

LOTEMAX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Viral Infections

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX.

ADVERSE REACTIONS

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (6 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

There are no adequate and well controlled studies in pregnant women. LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when LOTEMAX is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration

Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination

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

Contact Lens Wear

Patients should be advised not to wear contact lenses when using LOTEMAX.

Risk of Secondary Infection

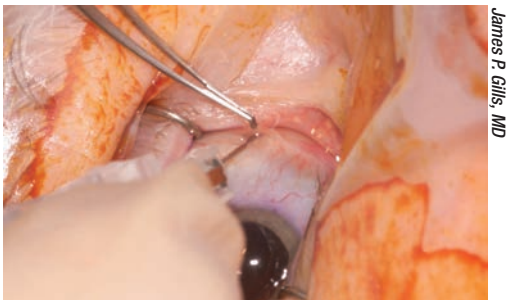
If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician.

FOR MORE DETAILED INFORMATION, PLEASE READ THE PRESCRIBING INFORMATION.

Bausch & Lomb Incorporated
Tampa, Florida 33637 USA
US Patent No. 5,800,807

Some antibiotics are time-dependent; they have to be in the eye for a particular amount of time, for reasons having to do with the bacterial replication cycle. If the antibiotic isn't around long enough, it won't be there through a complete replication cycle and as a result it won't have a meaningful effect. So surgeons who infuse antibiotic are not necessarily doing something wrong, but they're not necessarily doing something beneficial. If it's a very fast surgery with very little turnover of fluid, for example, very little antibiotic may get into the eye.

"Some doctors manage this by both infusing during the case and adding a bolus of antibiotic at the end of the case," he continues. "The concerns about the bolus at the end come down to errors in dilution. This is the result of what we call 'dealing with a kitchen pharmacy.' That's why the use of Vigamox has been so appealing to me. I know it's off-label, but I don't have to rely upon a circulating nurse or somebody else in the OR to make a decision about how to dilute the agent. In contrast, if we're going to inject something by bolus, then it does have to be diluted, and if a mistake is made, which unfortunately does occur from time to time, you may induce significant toxicity and end up with TASS. That can be sight-threatening. Those incidents are very rare, but they're enough to cause many centers and hospitals to believe it's not safe to dilute agents and place them inside the eye. That has certainly impacted the acceptance of this type of protocol. And unfortunately, even though I found the ESCRS study very convincing in terms of efficacy, that study used a second-generation cephalosporin called cefuroxime. There are questions regarding whether cefuroxime is the best or most appropriate agent. Perhaps more important, it requires preparation."



James P. Gills, MD

Subconjunctival injection of a drug such as a steroid can maintain the drug in the eye for as long as six weeks, eliminating another postop drop.

• ***Subconjunctival injection.*** Dr. Mah notes that subconjunctival injection of antibiotics has fallen out of favor. "Studies have suggested that the way the drug gets into the eye following a subconjunctival injection is similar to eye drops," he says. "It ends up getting in through the cornea. It simply sticks around for a longer period of time because there is a depot. How beneficial this approach is is debatable in the medical literature. I think an equal number of studies have found it to be beneficial vs. showing no clinical benefit. Anyway, in this age of topical anesthesia, patients don't want to have a subconjunctival hemorrhage, and they don't want the pain associated with the injection. So I think the subconjunctival approach is less and less popular nowadays."

Despite these concerns, Dr. Gills used a subconjunctival injection for the steroid part of his protocol so his patients wouldn't have to use steroid drops following surgery. "Within the past five years, we've used kenalog injections rather than topical steroids," he explains. "We inject 1.2 cc behind the limbus, subconjunctivally at 2 o'clock, sub-Tenon's. We don't put it into the anterior chamber because it blurs vision and the drug dissipates very quickly. With a sub-Tenon's injection, it lasts about six weeks. However, you have to make sure the injection is more than 8 mm away from the limbus because if you get any type of steroid deposit within 8 mm of the limbus, there appears to be a rise in pressure in a certain percentage of patients."

Dr. Gills admits that doing a subconjunctival injection of steroids carefully and accurately adds about 10 percent more time to the cataract surgery. "We do it because it's good for the patients, and our patients like it," he says. "A lot of our patients come in and say, 'I want that surgery where I don't have to go and buy all of those drops.' I think it's a practice-builder."

• ***Devices that slowly release antibiotic.*** Dr. Mah notes that several companies are working on developing unique direct-delivery systems or devices. "Ocular Therapeutix is already conducting a clinical trial of a punctal plug delivery system that elutes moxifloxacin," he notes. "PolyActiva in Melbourne, Australia, has developed a bioerodable implant that releases levofloxacin over a 30-day period. Other companies are also hoping to bring delivery systems to market. One big challenge, of course, is getting any such system approved by the U.S. Food and Drug Administration, especially when its use is related to cataract surgery. This could involve conducting studies with hundreds of thousands of patients. Plus, they face a second hurdle: Getting the drug paid for by Medicare and insurers."

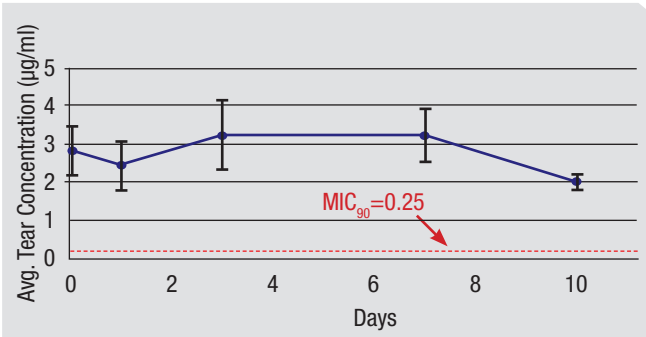
• ***Optimized topical drops.*** Dr. Wiley notes that Imprimis now also makes a combination drop that can be used after LASIK or cataract surgery. "It's the same theory, just not as dramatic a change from the more traditional protocol," he says. "For post-LASIK the traditional regimen is an individual steroid drop and an individual antibiotic drop. The most common medications for this purpose are a prednisolone steroid and a fourth-generation fluoroquinolone. We noted that there was no eye drop combination of a fourth-generation fluoroquinolone and prednisolone, so because we've had success using TriMoxi for cataract surgery, we asked Imprimis if they could make an eye

drop that would combine steroid and antibiotic.

"This made sense for three reasons," he continues. "First, it's much more convenient for the patient, reducing the number of drops by 50 percent. Instead of using two bottles, patients are just using one. Second, it lowers the expense to the patient dramatically. Right now our LASIK patients are spending $150 to $200 for the two individual drops. With the combination product, the cost would drop to $50 or so. Third, it's much more convenient for the surgery center. The drops can be delivered straight to the center, so we don't have to call in different drops for different patients at different pharmacies. When surgery day is coming up, we just say, OK, we have 20 patients, these are the names. We send the list to our pharmacy and they create the drops for those patients and send them to us. They're waiting for the patients after surgery. And of course, the same idea could be used following cataract surgery; those two medications are very common in cataract surgery."

Dr. Wiley points out that even when convenience is maximized, drops still have drawbacks. "There will always be concerns about compliance," he notes. "Some patients don't use the drops; they may not even buy them. If we inject the medication or implant a device, at least we know the patient is getting the drug. Along those lines, our clinic is also involved in studies with Ocular Therapeutix, implanting a punctal plug that has the steroid dexamethasone in it. The plug slowly releases the drug over a period of about a month. The advantage of this is that the patient won't require steroid drops or have floaters for the first 24 hours after an injection of triamcinolone. If I were using a device that provided the steroid, I'd just inject the antibiotic and not have the patient dealing with the side effect of cloudiness. Meanwhile, other companies are working on products such as a small pellet that's placed inside the eye at the time of surgery that can release either a steroid or an antibiotic."

Moxifloxacin Punctal Plug Drug Release



Ocular Therapeutix

Results of a Phase I study of Ocular Therapeutix punctal plug antibiotic delivery system involving 10 human eyes following cataract surgery. The plug was retained through day 10 in all eyes; average moxifloxacin levels in the tear film ranged from 2,465 to 3,236 ng/mL through day seven, maintaining levels well above the MIC_{90} for common pathogens. No adverse events or patient complaints were reported.

A Combination Injectable

Although no product is FDA-approved for this purpose, some companies are offering options that may simplify preparation by having multiple drugs combined in one injectable product. For example, when performing cataract surgery, Dr. Wiley uses Imprimis's TriMoxi, which combines triamcinolone and moxifloxacin.

"Unlike many other options intended to serve this purpose, TriMoxi is compounded, but it's not made in a commercial pharmacy," he notes. "You can have a local compounding pharmacy make something similar; however, you should make sure the local pharmacy is reputable and licensed, as there are well-recognized concerns regarding compounding. Also, Imprimis has some proprietary techniques for formulating the triamcinolone so it can go through a smaller needle; the drug is dissolved to a smaller molecular size than traditional triamcinolone. We place the TriMoxi in the vitreous at the time of cataract surgery with the goal of decreasing or eliminating the need for eye drops. Using TriMoxi in this way is off-label—but currently there are no compounded or commercially available antibiotics that are considered on-label for addressing endophthalmitis after cataract surgery.

"Before we switched to this approach we had our patients use three different medications for one month after surgery," he continues. "Right now, we still have our patients use one drop postoperatively, once a day for a week, so we haven't eliminated drops altogether. The drop we're using now is called Maxitrol; it's a combination antibiotic and steroid. Mostly, it's there just to cover the patients in case they need something postoperatively. They won't have to rush to the pharmacy to get a drop if they have an issue in the perioperative period. It also makes patients feel good to have a drop, and I'm more comfortable knowing they have that resource. It's never been clinically proven that using antibiotic drops after cataract surgery prevents endophthalmitis, but it makes me a little uncomfortable to go from traditional drop protocols to no drops at all. After we get a comfort level and refine the current regimen, we'll probably stop even using that drop. In fact, many practices nationwide are going completely dropless using the same kind of technique."

Dr. Wiley says they've done about 500 cases using this protocol and have seen no endophthalmitis. "Nationwide and internationally, I know of

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a number of colleagues who are using the same or a similar technique, and they've been happy with their endophthalmitis prophylaxis," he says. "So it seems to be working very well. Meanwhile, our patients like the simplicity and the cost-savings. Some of our patients were paying upwards of $600 to $800 for branded medications around the time of cataract surgery. We found that some patients were holding off on having cataract surgery because they couldn't afford the medications. In contrast, Maxitrol is available on a generic basis, easy to obtain, very inexpensive (under $20) and simple to use—once a day for a week. Now patients feel more comfortable proceeding with the surgery."

Dr. Wiley points out that many surgeons currently inject an antibiotic at the end of cataract surgery, but not a steroid. "Over the past decade or so many surgeons have been injecting Vigamox, a commercially available antibiotic," he says. "They dilute it themselves at their surgery center or hospital and inject it at the time of surgery. And it's fairly common for doctors to use vancomycin. In fact, the use of antibiotics inside the eye around the time of surgery is not new; the newer thing is combining it with a steroid and placing it in the vitreous."

Dr. Masket says he's not ready to try the combination-drug injectables from Imprimis. "The current delivery concept is to put the agent into the vitreous through the zonules," he says. "You put a cannula into the anterior chamber, poke it through the zonules so that it goes into the vitreous; then you've got the mixture sitting in the vitreous. I am not enamored of the concept of a transzonular delivery system; I think it needs further investigation. There are obvious potential downsides to it, although I'm very interested in studying it in the lab.

"Among the downsides, besides disturbing the zonules, is the fact that you have this milky material, the triamcinolone, which interferes with patient vision early after surgery," he continues. "Another concern is that you're injecting a long-acting steroid, which means you will occasionally encounter an uncontrollable IOP. We can titrate the effect of a steroid when using eye drops, but once you put a bolus into the vitreous, you can't titrate its effect.

"I agree fully with the concept of going dropless when we can," he says. "Imprimis is moving in that direction, but this requires a huge difference in the way we deliver medication, and it violates, to me, some of our surgical principles—specifically, to not disturb the zonules. My partner and I have spoken about participating in an investigation using it as a pars plana injection rather than a transzonular injection. However, we tried that in one case and ended up with a very milky

The Surgical Skill Factor

It's worth noting that many of the surgeons who are reporting positive results using intracameral antibiotics are highly experienced. This raises the question: Are their minimal rates of endophthalmitis really attributable to the use of this protocol, or simply to their level of skill and experience?

Samuel Masket, MD, a clinical professor of ophthalmology at the Jules Stein Eye Institute, UCLA School of Medicine in Los Angeles, admits that the positive results reported by some well-known surgeons using intracameral antibiotics might not be duplicated by less-experienced surgeons, but for reasons having nothing to do with the efficacy of the protocol. "Using intraocular antibiotics is not a substitute for careful attention to wound construction and management," he points out. "We know that leaking wounds are associated with a far greater risk of infection. We also know that complicated surgery, prolonged surgery and capsulorhexis rupture all increase the rate of infection. The point is that a lot of the surgeons who currently use intraocular antibiotics are also very experienced surgeons, so their rates of infection might be low even if they didn't use intraocular antibiotics.

"I have no doubt that intracameral antibiotics are beneficial, but you also have to manage other potential sources of infection as well," he continues. "You have to evaluate the lid margins carefully prior to surgery; treat blepharitis; use topical povidone iodine; do careful draping of the lid margins; make sure fluids don't accumulate on the surface; make sure the head is turned; and so on. There's a whole list of things surgeons need to do to reduce the likelihood of infection. But I firmly believe that among them is the intracameral use of antibiotics."

Francis Mah, MD, who specializes in cornea, external disease and refractive surgery at Scripps Health System in San Diego, agrees that an important factor in the effectiveness of intracameral antibiotics is good surgical technique. "Cases of endophthalmitis have been reported even when using intracameral antibiotics," he notes. "It's not a guarantee that you'll never see an infection. You still need to be careful, be smart and use good technique. You still need to use povidone iodine, which is another important method of preventing infection."

Does this mean it's riskier for a less-experienced surgeon to use intracameral antibiotics? "Not at all," says Dr. Masket. "If you're using nontoxic doses in an appropriate manner, that should not increase the risk of infection; just the opposite. In retrospective studies done back in 1997, the overall rate of endophthalmitis was seven in 10,000. When vancomycin was used the rate dropped to three in 10,000, a statistically significant difference. The point is simply that the best surgeons tend to pay more attention to detail, so their overall infection rates may be lower than those of less-skilled surgeons."

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vitreous and a complaining patient. So I'm not yet ready to accept that mode of delivery. I applaud Imprimis for what it's doing, and those doctors who are investigating it, but I think we need a very carefully designed study to look at the risks and benefits."

Dr. Wiley says he understands why surgeons would be concerned about these aspects of the TriMoxi protocol. "We are putting triamcinolone into the vitreous, and it's a whitish medication," he says. "It is visible floating in the vitreous, so for the first 24 to 72 hours patients do notice a fair number of floaters," he says. "However, we manage this by talking with the patient preoperatively and setting appropriate expectations. We were worried about the decreased 'wow effect' we might see, but in reality it hasn't been a concern.

"As far as potential issues with transzonular application, there are two approaches to placing the medication—transzonular and transcleral using a pars plana injection," he explains. "The latter is similar to what retinal specialists do when giving intravitreal injections for macular degeneration, which has become one of the most common procedures performed worldwide. It's very safe and effective. That's the approach I've chosen to inject the TriMoxi, because it's easier for me to perform than the alternative and there's no risk of disrupting the zonules. In any case, there are many different techniques regarding how much steroid people put in at the time of surgery and where they put it. Some people put it all in the vitreous; some put it in the vitreous or the anterior chamber; some put it in the vitreous, anterior chamber and/or sub-Tenon's."

Unanswered Questions

Not surprisingly, some important questions remain:

• ***Which antibiotic is best for intracameral injection?*** Dr. Mah notes that it's not yet clear which antibiotic is the best choice. "Most experience with this around the world has been with cefuroxime," he says. "Its effectiveness has been demonstrated in numerous studies. There have been some papers looking at moxifloxacin, though, as potentially having some superior characteristics. A United States study from Kaiser Permanente in northern California actually found moxifloxacin to be superior to cefuroxime or vancomycin. I believe there's also a Japanese retrospective study that found moxifloxacin to be at least as good as cefuroxime.

"One factor may have influenced the seeming superiority of moxifloxacin in the Kaiser study," he continues. "They did not use cefuroxime intracamerally if patients had a broken capsule; but they did use moxifloxacin if patients had a broken capsule. That could have influenced the results, because the literature supports the idea that patients with broken capsules are at increased risk of infection. Using moxifloxacin in higher-risk patients may have helped to reduce the statistical incidence of endophthalmitis, compared to not using any intracameral agent.

"In any case, the majority of prospective studies have involved cefuroxime," he says. "Which antibiotic is most effective is still debatable. But the biggest debate, initially, is going to be the concept of intracameral antibiotics. Many surgeons are not yet convinced that this approach can be trusted as their primary prophylaxis for infection. We're just beginning to try it in our own surgical center, but after reviewing all the literature, I believe the data, and the data indicates that this is a better method of preventing infections than the traditional protocol using drops. However, the issue of possible TASS must be incorporated to calculate overall positive vs. negative effects of the technique."

• ***Do patients need postop antibiotic drops after an intracameral injection of antibiotic?*** "That's an issue that has not been resolved," says Dr. Masket. "It depends in part on when the eye is at risk. We do our surgery, we put antibiotic in, we think the eye is sealed, we think we're safe. However, the eye is still susceptible to contamination postoperatively until the epithelium seals over the incisions. That can take two or three days, so during that period that patient is still potentially subject to infection from contamination—particularly if the wound is unstable. For that reason, I think we still have a potential need for eye drops in the early postoperative period. I typically keep patients on drops for five to seven days, even though I use intracameral antibiotics; I want to protect the patient from postop contamination, not just intraoperative contamination. Unfortunately, the half-life of moxifloxacin is very short, unless it's in repository form. If it's gone within 12 to 18 hours, then it's no longer protecting the patient."

Dr. Masket adds that a sealant like ReSure might solve this problem without postoperative drops. "A sealant may keep the incision closed for three to five days," he notes. "That could be a very excellent substitute for postop drops."

• ***Do patients need antibiotic drops before surgery?*** "I think most surgeons agree that using povidone iodine at the time of surgery should be standard," says Dr. Mah. "However, there isn't any data to support the use of topical antibiotics ahead of surgery as a way to prevent postop endophthalmitis—although some people look at the decrease in colony counts and see that as surrogate evidence that preop topical drops may help prevent postsurgical infections. Having said this, there isn't any evidence that it does not help, either."

The Coming Thing?

"There are many things we need to keep in mind in order to decrease

infections postoperatively," says Dr. Mah. "But I do think surgeons will be moving toward intracameral injection of antibiotics, whether it's sooner or later. It will happen sooner if we can get an FDA-approved medication for this purpose."

Dr. Wiley agrees. "In five years, I see the use of drops being drastically reduced or eliminated, unless studies find some problem with the alternatives," he says.

"It will be great when we can supply the patient with a single dose of medication at the time of surgery that manages prophylaxis against infection, as well as other issues such as inflammation," says Dr. Masket. "Everybody is moving toward drug-delivery systems that eliminate the need for drops. We all know that drops are really inefficient; they come with different rates of absorption, poor compliance, toxicities, and now, unfortunately, huge expense. So all of us would love to eliminate them.

"People out there are developing drug-delivery systems that will be safe and efficacious," he adds. "Given all the nanotechnology in the pipeline, I'm sure in the reasonable future we'll see agents that combat inflammation and infection that are placed inside the eye during surgery. At that point, eye drops will only be used under certain circumstances. I can't say how far off that is, but I know it's coming soon." REVIEW

Dr. Mah is a consultant to Alcon, Allergan, B+L/Valeant, Ocular Therapeutix and Polyactiva. Dr. Wiley does paid research for Imprimis and Ocular Therapeutix. Dr. Masket has no relevant financial ties.

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Is Bilateral, Same-Day Cataract the Future?

Walter Bethke, Managing Editor

Surgeons need some questions answered before they'll embrace the procedure.

Many decisions in life revolve around mitigating risk. Some parents take separate airline flights so that one of them will survive to care for their children in case of a plane crash; investors spread out their risk by investing in a variety of stocks rather than just one; and cataract surgeons perform surgeries with a delay in between the eyes to avoid potentially blinding the patient with a bilateral complication. There's a growing number of surgeons, however, both in the United States and abroad, who say that simultaneous, bilateral cataract surgery is better for patients and, potentially, for the health-care system. Here's a look at this controversial practice and what hurdles it needs to clear before it can become more popular.

Why Surgeons Do It

Surgeons who perform simultaneous, bilateral cataract surgery say it offers patients a number of benefits.

Toronto, Ontario, surgeon Steve Arshinoff says that, many years ago, he would usually only do SB cataract surgery on certain patients for whom two trips to the OR would be difficult, such as someone with Down's syndrome. In 1998, however, he performed his first SB case on someone who simply wanted it done for convenience's sake. He agreed to do it, and the patient signed a special consent form for it. "On the day of her surgery I operated bilaterally on her and did the first eyes of maybe 15 other people," Dr. Arshinoff recalls. "The next day in the office she was ecstatic, much more so than her fellow postop patients, because she could see well out of both eyes. The others had had one eye done and had the issues involved with waiting for the second eye to be done. When I realized how happy she was, I thought that maybe I'd loosen my criteria and do a few more people if they wanted to have it done." Now, 17 years and nearly 5,000 bilateral cases later, he performs it on 80 to 90 percent of his patients and has become one of the cofounders of the International Society of Bilateral Cataract Surgeons.

Dr. Arshinoff says the postop vision benefits really become important for patients with high refractive errors. "Let's say you have someone who has a refractive error of +8 D or -8 D," he says. "When you correct that in only one eye, he is really incapacitated until the second eye is done because he sees double. So, for all those types of patients, rather than try to compromise and make them highly myopic or highly hyperopic, you can aim for any refractive error you think is best for them by doing bilateral surgery. If you

implant multifocal lenses, you have fewer problems because, when you're done, both of the eyes can immediately see close and at distance; you don't have to worry about the patients comparing an eye with a multifocal to one without it. It's not that a multifocal IOL is bad—it's just different and it takes time to adapt. And people adapt to things better when their entire system is adapting to it, not just half of it."

Some patients need to travel a long distance for cataract surgery, and making that trip twice, in addition to all the extra follow-up visits for each eye, can be a hardship that many acknowledge is one of the main reasons for doing SB. Surgeons say, however, that this convenience can be enjoyed by any patient, not just rare hardship cases. Amarillo, Texas, surgeon Sloan Rush acknowledges the benefits of SB surgery, and is a member of the ISBCS. To help gauge the surgery's beneficial effect on the patient experience, he recently performed a prospective study of SB surgery vs. sequential cataract surgery. "With the surgeries separated, our patients averaged 7.1 visits to my office," he says. "With simultaneous, bilateral surgery, they averaged 3.3 visits. That's a significant feature for our patient population, more than half of whom travel from more than 60 miles away. In fact, the total distance traveled was 522 miles for the simultaneous surgery patients vs. 969 miles for the sequential ones, a difference that was statistically significant. Recovery time was much quicker also; simultaneous surgery patients recovered their best-corrected vision in 3.3 weeks, compared to 5.9 weeks for sequential patients."

Linköping, Sweden, surgeon Björn Johansson says doing the second eye on the same day as the first helps the surgeon manage the second case. "Should there be any small thing that makes the surgery more difficult than standard, it's actually better to do the second eye immediately," he says.

Björn Johansson, MD

Surgeons say the preop exam is crucial for ruling out anything that might increase the risk of a complication with simultaneous, bilateral surgery.

"This is because my plan for surgery can be refined based on the result of the first surgery. Of course, you could note the difficulty in the patient record to help plan a second surgery several weeks later, but I've found that most of the time it's an advantage to have the first surgery on your mind when you immediately carry on with the second eye, as long as there hasn't been a significant complication with the first. For a significant complication, you have to postpone the second eye's surgery."

As with any surgery, SB has contraindications. "We ask patients to sleep on their backs for the first couple of days," says Dr. Arshinoff. "This is to avoid lying on their eyes. However, some can't sleep on their backs because of arthritis, so we'll do one eye at a time. We're also concerned about people who appear to not be very clean and not able to take care of themselves. And if there are any concerns with the retina, lens, cornea or anything else, or they have a chronic infection of the conjunctiva or lids, we're more careful."

Dr. Johansson says it takes meticulous patient selection. "You need to be aware of any factors that increase the risk for a complication," he says. "This includes endothelial dystrophy or diabetic retinopathy with central changes. Also, be aware of the potential for patient noncompliance with postop care. And if you suspect addiction or dementia, it's still possible to proceed but make sure there's a network of care around the patient."

Why Surgeons Are Wary

Putting financial issues aside, from a patient-care standpoint surgeons' primary concerns with SB cataract surgery revolve around the surgery's ability to cause a problem for both eyes, and to lose the benefit of using the first eye's outcome to plan the second eye's surgery.

"One of the fears we all have is the fear of potential bilateral endophthalmitis," says Nick Mamalis, MD, professor of ophthalmology and visual sciences at the University of Utah School of Medicine. "This would be a potential disaster. Fortunately, the reported incidence of bilateral endophthalmitis is very low when proper techniques for preoperative patient preparation and intraoperative/postoperative antibiotics are used. Another area of concern is toxic anterior segment syndrome. This is an issue because when TASS occurs it tends to cluster in a surgical center or an operating room. The problem with TASS is you don't know it has occurred until the next day. TASS clusters have been caused by all kinds of things, including inadequate instrument cleaning and sterilization, endotoxin contamination and products that are mislabeled or mixed incorrectly. So, theoretically, there's a small risk you could get bilateral TASS in a patient. Again, it's not been reported, but is a theoretical concern. Even if you treated each eye as a separate procedure during a simultaneous, bilateral case, if there were a problem with TASS in your facility, from such causes as improper flushing of handpieces or inadequate sterilization, you could end up with a bilateral case of TASS. If it were significant TASS where you've got corneal edema and/or glaucoma,

that would be difficult to treat."

SB surgery proponents say they completely understand a surgeon's concern about bilateral complications, but are quick to point out that if certain strict surgical protocols are followed, the data shows that bilateral complications appear to be exceedingly rare. According to a paper on bilateral complications co-authored by Dr. Arshinoff, there have only been four documented incidences of bilateral complications of SB cataract surgery since 1952, and in each of those, some aspect of the aseptic protocol advocated by the ISBCS wasn't followed properly.[1] In the study, the researchers surveyed the members of the ISBCS about the incidence of postop endophthalmitis and any bilateral endophthalmitis. In 95,606 cases, there were no instances of bilateral infection. The overall rate of postoperative endophthalmitis occurring in just one eye after SB surgery was 1:5,759, which, the researchers said, compared favorably with 1:1,977 in the European studies of intracameral antibiotics and 0.028 percent in a large retrospective U.S. study using topical antibiotics.[2,3] With intracameral antibiotics, the rate of infection for the ISBCS surgeons went down to 1:14,352.[1]

The aseptic protocol referred to in the study, and which SB surgery proponents advocate, basically comes down to treating each eye of the same patient as if it is an entirely separate surgical event. "This means a new surgical drape for the patient, new gowns for the surgeon and nurse, new prep and cleaning of the skin, new supplies, new handpieces, new instrument tray, et cetera," says Dr. Johansson. "When we first started doing the procedure, we had the patient enter the room and have his first eye done. We'd then do a second patient's surgery, then bring the first patient back in to do his second eye. We did this for two to three months, just to make everyone aware that the surgeries are meant to be separate." Surgeons will even use BSS and viscoelastic from different lots or manufacturers just to be sure.

Another objection raised about SB surgery is that it doesn't allow the surgeon any time to learn from the first eye to improve the refractive outcome on the second. One study that looked at this issue found that by accounting for part of the first eye's deviation of the postop spherical equivalent refractive error from that predicted by the intraocular lens formula, the surgeon might be able to improve the refractive outcome of the second eye.[4] The study noted, however, that since IOLs are made in 0.5-D increments, this might mitigate any beneficial effect of adjusting for the first eye's error, since it would usually be smaller than 0.5 D. Dr. Arshinoff says newer lens formulas and biometry technology make it more difficult to squeeze any improvement out of the second eye if you wait between surgeries. "A study found that, if you look at different methods, the advantage for correcting for the second eye based on the first decreases as you use better and better techniques,"[5] he says. "Basically, if you do things accurately the first time, there's no benefit from correcting for the first eye's error because there's almost no error."

Intracameral Antibiotics

The use of intracameral antibiotics is one of the underpinnings of SB surgery but, since this method isn't widely used in the United States, it represents yet another hurdle. *(For an in-depth discussion of new trends in antibiotics, see the feature article on p. 28.)* Neal H. Shorstein, MD, an ophthalmologist and associate chief of quality with Kaiser Permanente health system in Walnut Creek, Calif., says the results of a study he performed, however, show intracameral is worth pursuing.

In the study, Dr. Shorstein and his colleagues used different antibiotic techniques in three different time periods. In 2007, cataract patients received postop antibiotic drops. In 2008 and 2009, in addition to the drops, they received intracameral cefuroxime, unless contraindicated. Then, in 2010 and 2011, all patients received intracameral cefuroxime, moxifloxacin or vancomycin, with the addition of topical drops left up to the surgeon. Ultimately, the rates of endophthalmitis were 3.13:1,000 in 2007, 1.43:1,000 in 2008/2009, and 0.14:1,000 in 2010/2011.[6] There was one case of endophthalmitis in 2,038 patients without a posterior capsule rupture who received only intracameral and no topical antibiotic (0.49:1,000). "With the advent of intracameral antibiotics, and with the marked reductions in endophthalmitis that we've seen at Kaiser Permanente, I think this opens the door, on a relatively short timeline, to start thinking about bilateral, same-day surgery," Dr. Shorstein says.

Financial Roadblocks

Even if the complication data eventually won the hearts and minds of surgeons in the United States, SB cataract surgery would come to a hard stop as far as reimbursement is concerned. To put it simply: Surgeons lose money every time they do it because the Centers for Medicare & Medicaid Services only pays half for the second eye if it's done in a simultaneous fashion.

"In the United States, it's ridiculous to pay 50 percent to the surgeon and the ambulatory surgery center for the second eye," argues Dr. Arshinoff. "When you do two eye surgeries like this, it's not as if you're doing the patient's cataract and then doing a combined cataract and filtration procedure, in which you use the same instrument and just change two more surgical steps. With simultaneous, bilateral surgery, you're changing all of the drapes, all of the instruments, using a different OVD—the costs are double. Furthermore, when the patient comes back for postop visits, he incurs more costs to

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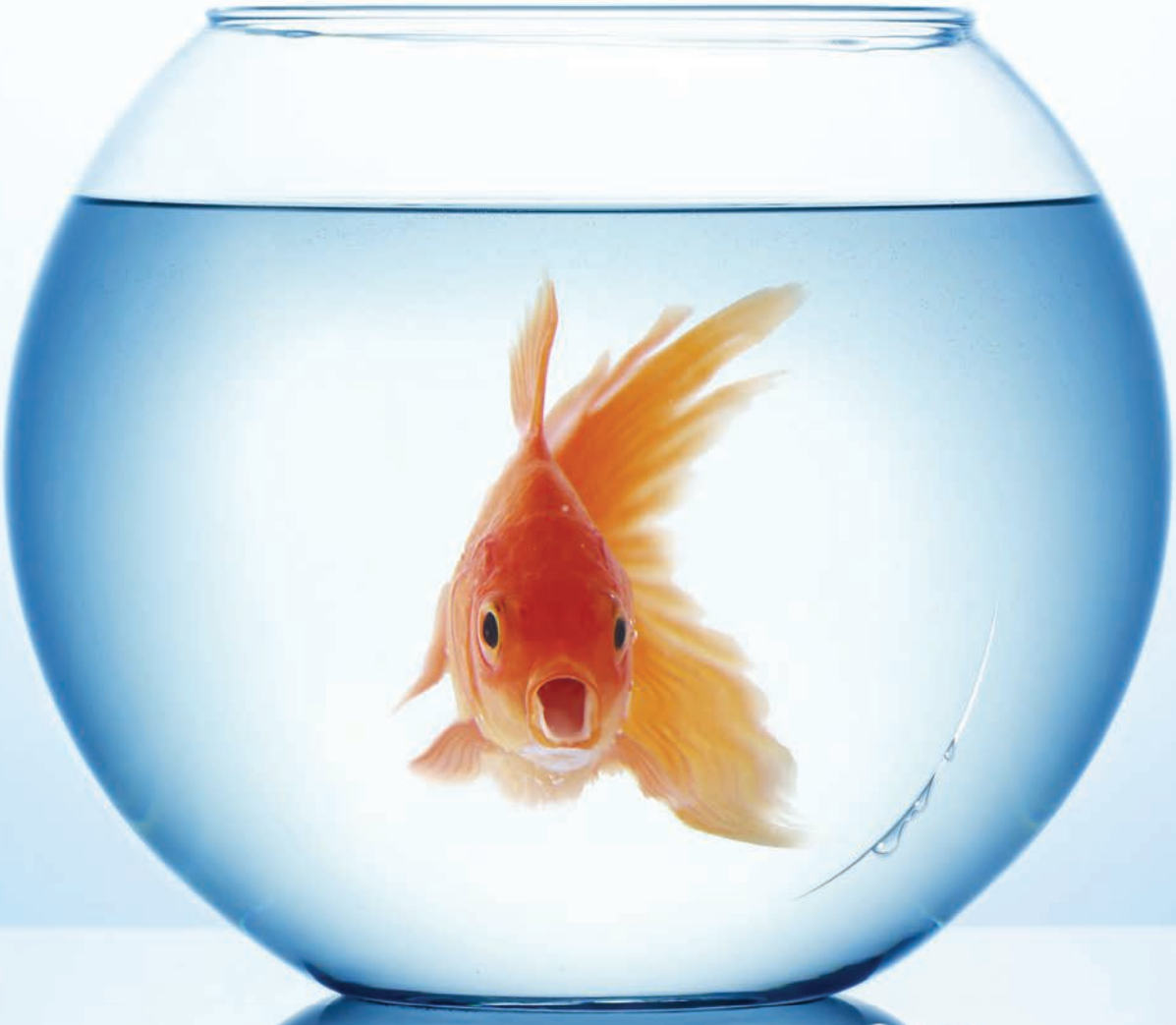

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the health-care system; no matter how it's structured, someone is paying."

In Dr. Rush's analysis of SB surgery in his practice, he also performed a cost analysis to determine how SB surgery could be made to work in the United States. "We make recommendations in our study that, if CMS implemented a simple rule change, SB surgery would be economically advantageous not only for Medicare, but for patients, doctors and ASCs, alike. We found that the total reimbursement for the physician for both eyes done on the same day is $1,340. If the eyes are done on separate days the reimbursement is $1,705. The reimbursement for the ASC if the surgeries are done on the same day is $1,813, versus $2,369 when done on separate days. There was a significant loss there. An expense that wouldn't exist for SB eyes, however, is the preop assessment for the second eye, which averages $81.59.

"We recommend that if you do the surgeries on the same day Medicare pays you 190 percent," Dr. Rush continues. "This is because you're still providing postop care, though with fewer visits, so maybe the physician should be willing to take a small hit there. Based on Medicare's reimbursement for a unilateral, non-complicated cataract in 2013—$629.91—our suggestion would save Medicare $62.99 for each patient that underwent bilateral, same-day surgery. When this is added to the $81.59 saved from eliminating the intermediate exam, the total potential savings to Medicare is $144.58."

One situation in the United States where economics isn't an issue with SB surgery is in the Kaiser Permanente health system, especially in sections of Colorado and California. Kaiser Permanente's Dr. Shorstein says his system's surgeons are doing more and more SB surgery, with one surgeon's practice in particular doing between 40 and 50 percent of his 1,000 annual cases in this manner. The reason it's economically viable at Kaiser Permanente is because it's an integrated system in which individual physicians don't contract with Medicare, but instead are reimbursed by the health system, allowing them to perform the surgery they feel is best, with proper informed consent. "In our integrated health-care organization, there are none of the disincentives that are in place in the private sector in which bilateral, same-day surgeries aren't reimbursed fully," says Dr. Shorstein. "So, if the patient desires to have both eyes done on the same day as a matter of convenience and rapid recovery, the barriers to that really aren't there in our organization."

Sloan Rush, MD

Amarillo, Texas, surgeon Sloan Rush's staff is trained to make sure everyone knows which eye is being operated on. They also take intraoperative time-outs to confirm the lens.

With so many cases being done on an institutional level, surgeons would be eager to hear about the results of Kaiser Permanente's SB surgeries. Dr. Shorstein says that data is on its way. "We're looking at data such as bilateral complications right now," he says. "We have a team at my local hospital performing a failure modes and effects analysis. The FMEA is looking at all our processes in the clinic and the OR in order to identify any potential failures in the system of bilateral, same-day cataract surgery. We hope to report our findings in a study this year. Three of us at my hospital have been doing it for 12 to 18 months in a very controlled way. This is because with bilateral, same-day surgery there are a number of areas that can be potentially more prone to a mistake than with separate-day surgeries. When both eyes are done on the same day, you have two lenses in the OR, a sheet of paper with different lenses circled for each eye and extra data on each eye floating around that could potentially be confused. It's been a fairly exhaustive process to try to uncover every conceivable pitfall in the system, since we anticipate ramping up our bilateral cataract surgery offerings."

Dr. Arshinoff says he thinks surgeons could be successful with SB surgery if they gave it a chance and reimbursement issues fell into place. "There's always an argument about why not to do a procedure," he says. "And then, one day, you do a procedure such as bilateral, same-day surgery on the worst patients, such as someone with Down's syndrome who's confined to his bed, and find out that he does OK. But that type of patient is the one who probably had the highest risk. So if you can do him, why can't you do everybody? The truth is you can." REVIEW

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Classic beta blocker adjunctive therapy for the right patient at the right time[3]

The concomitant use of two topical beta-adrenergic blocking agents is not recommended[4,5]

Indications and Usage

ISTALOL® (timolol maleate ophthalmic solution) is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. It may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

Important Safety Information for Istalol® and Timoptic® in Ocudose®

- Both ISTALOL® (timolol maleate ophthalmic solution) and TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) are contraindicated in patients with: bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of the product.
- **The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Severe respiratory reactions and cardiac reaction, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate.**
- Patients with a history of atopy or severe anaphylactic reactions to a variety of allergens may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.
- Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.
- Beta-adrenergic blocking agents may mask signs and symptoms of acute hypoglycemia or certain clinical signs of hyperthyroidism. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving either insulin or oral hypoglycemic agents, or patients suspected of developing thyrotoxicosis, should be managed carefully, with caution.
- In patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta adrenergic receptor blocking agents because these agents impair the ability of the heart to respond to beta-adrenergically mediated reflex stimuli.
- The most frequently reported adverse reactions have been burning and stinging upon instillation. This was seen in 38% of patients treated with ISTALOL and in approximately one in eight patients treated with TIMOPTIC in OCUDOSE. Additional reactions reported with ISTALOL at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity.

Please see Brief Summary of Prescribing Information for ISTALOL and TIMOPTIC in OCUDOSE on the following pages.

For the patients who need incremental IOP reduction in a preservative free form[6]

Preservative-Free

TIMOPTIC® in OCUDOSE®
(TIMOLOL MALEATE 0.5% OPHTHALMIC SOLUTION) (DISPENSER)

For the patients who need incremental IOP reduction in a once a day form[6]

Istalol®
(timolol maleate ophthalmic solution) 0.5%

References: 1. Alm A, Stjernschantz J. Effects on Intraocular Pressure and Side Effects of 0.005% Latanoprost Applied Once Daily, Evening or Morning. *Ophthalmology*. 1995;102:1743-1752. **2.** Brubaker R. Flow of Aqueous Humor in Humans. *IOVS*. 1991;32:(13)3145-3166. **3.** Obstbaum S, Cioffi GA, Krieglstein GK, et al. Gold Standard Medical Therapy for Glaucoma: Defining the Criteria Identifying Measures for an Evidence-Based Analysis. *Clin Ther.* 2004;26(12)2102-2119. **4.** Istalol [package insert]. Bridgewater, NJ: Bausch & Lomb Incorporated; 2013. **5.** Timoptic in Ocudose [package insert]. Lawrenceville, NJ: Aton Pharma; 2009. **6.** Stewart W, Day DG, Sharpe ED. Efficacy and Safety of Timolol Solution Once Daily vs Timolol Gel Added to Latanoprost. *Am J Ophthalmol*. 1999;128(6)692-696.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use TIMOPTIC® 0.25% AND 0.5% (timolol maleate ophthalmic solution) in OCUDOSE® (DISPENSER) safely and effectively. See full prescribing information for TIMOPTIC in OCUDOSE.

PRESERVATIVE-FREE STERILE OPHTHALMIC SOLUTION
in a Sterile Ophthalmic Unit Dose Dispenser

TIMOPTIC® 0.25% AND 0.5% (TIMOLOL MALEATE OPHTHALMIC SOLUTION)

in OCUDOSE® (DISPENSER)

INDICATIONS AND USAGE

Preservative-free TIMOPTIC in OCUDOSE is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC in OCUDOSE may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

CONTRAINDICATIONS

Preservative-free TIMOPTIC in OCUDOSE is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Preservative-free TIMOPTIC in OCUDOSE should be discontinued.

Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which TIMOPTIC in OCUDOSE is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including Preservativefree TIMOPTIC in OCUDOSE.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

General: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Preservative-free TIMOPTIC in OCUDOSE, alternative therapy should be considered.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. TIMOPTIC in OCUDOSE should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients: Patients should be instructed about the use of Preservative-free TIMOPTIC in OCUDOSE.

Since sterility cannot be maintained after the individual unit is opened, patients should be instructed to use the product immediately after opening, and to discard the individual unit and any remaining contents immediately after use.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Drug Interactions: Although TIMOPTIC (timolol maleate ophthalmic solution) used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC (timolol maleate ophthalmic solution) and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Preservative-free TIMOPTIC in OCUDOSE should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as Preservative-free TIMOPTIC in OCUDOSE, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

CYP2D6 inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable epinephrine: (See PRECAUTIONS, *General, Anaphylaxis*)

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000 times, respectively, the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy: *Teratogenic Effects* — Pregnancy Category C. Teratogenicity studies with timolol in mice, rats and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. Preservative-free TIMOPTIC in OCUDOSE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE: Headache, asthenia/fatigue, and chest pain.
CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.
DIGESTIVE: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.
IMMUNOLOGIC: Systemic lupus erythematosus.
NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.
SKIN: Alopecia and psoriasiform rash or exacerbation of psoriasis.
HYPERSENSITIVITY: Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localized and generalized rash.
RESPIRATORY: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.
ENDOCRINE: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).
SPECIAL SENSES: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, *General*); and tinnitus.
UROGENITAL: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta blocking agents, and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura; agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

OVERDOSAGE

There have been reports of inadvertent overdosage with Ophthalmic Solution TIMOPTIC (timolol maleate ophthalmic solution) resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

Overdosage has been reported with Tablets BLOCADREN* (timolol maleate tablets). A 30 year old female ingested 650 mg of BLOCADREN (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment but approximately two months later developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate, and borderline first degree heart block.

An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION

Preservative-free TIMOPTIC in OCUDOSE is a sterile solution that does not contain a preservative. The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be guaranteed after the individual unit is opened, the remaining contents should be discarded immediately after administration.

Preservative-free TIMOPTIC in OCUDOSE is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent Preservative-free TIMOPTIC in OCUDOSE in the affected eye(s) administered twice a day. Apply enough gentle pressure on the individual container to obtain a single drop of solution. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) administered twice a day.

Since in some patients the pressure-lowering response to Preservative-free TIMOPTIC in OCUDOSE may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with Preservative-free TIMOPTIC in OCUDOSE.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above one drop of 0.5 percent TIMOPTIC (timolol maleate ophthalmic solution) twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted taking into consideration that the preparation(s) used concomitantly may contain one or more preservatives. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, *Drug Interactions, Beta-adrenergic blocking agents.*)

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Based on PI - 514266Z/069A-03/09/9689-9690
US/TOP/14/0018 Issued February 2009

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ISTALOL® (timolol maleate ophthalmic solution) 0.5% safely and effectively. See full prescribing information for ISTALOL.

Istalol® (timolol maleate ophthalmic solution) 0.5%

Initial U.S. Approval: 1978

STERILE

INDICATIONS AND USAGE

Istalol (timolol maleate ophthalmic solution) 0.5% is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

4.1 Asthma, COPD: Istalol is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease (see **WARNINGS AND PRECAUTIONS, 5.1, 5.3**).

4.2 Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock: Istalol is contraindicated in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure (see **WARNINGS AND PRECAUTIONS, 5.2**); cardiogenic shock.

4.3 Hypersensitivity Reactions: Istalol is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this product in the past.

WARNINGS AND PRECAUTIONS

5.1 Potentiation of Respiratory Reactions Including Asthma: Istalol contains timolol maleate; and although administered topically, it can be absorbed systemically. Therefore, the same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see **CONTRAINDICATIONS, 4.1**).

5.2 Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe failure. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Istalol should be discontinued (see also **CONTRAINDICATIONS, 4.2**).

5.3 Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease [other than bronchial asthma or a history of bronchial asthma in which Istalol is contraindicated (see **CONTRAINDICATIONS, 4.2**)] should, in general, not receive beta-blocking agents, including Istalol.

5.4 Increased Reactivity to Allergens: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

5.5 Potentiation of Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

5.6 Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

5.7 Masking of Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

5.8 Contamination of Topical Ophthalmic Products After Use: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see **PATIENT COUNSELING INFORMATION, 17**).

5.9 Impairment of Beta-adrenergically Mediated Reflexes During Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

5.10 Angle-Closure Glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This may require constricting the pupil. Timolol maleate has little or no effect on the pupil. Istalol should not be used alone in the treatment of angle-closure glaucoma.

5.11 Cerebrovascular Insufficiency: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Istalol, alternative therapy should be considered.

5.12 Choroidal Detachment: Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

ADVERSE REACTIONS

6.1 Clinical Trials 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 practice.

The most frequently reported adverse reactions have been burning and stinging upon instillation in 38% of patients treated with Istalol. Additional reactions reported with Istalol at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity. The following additional adverse reactions have been reported less frequently with ocular administration of this or other timolol maleate formulations.

Timolol (Ocular Administration): *Body as a whole:* Asthenia/fatigue and chest pain; *Cardiovascular:* Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon and cold hands and feet; *Digestive:* Nausea, diarrhea, dyspepsia, anorexia, and dry mouth; *Immunologic:* Systemic lupus erythematosus; *Nervous System/Psychiatric:* Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness and memory loss; *Skin:* Alopecia and psoriasiform rash or exacerbation of psoriasis; *Hypersensitivity:* Signs and symptoms of systemic allergic reactions, including angioedema, urticaria, and localized and generalized rash; *Respiratory:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections; *Endocrine:* Masked symptoms of hypoglycemia in diabetic patients (see **WARNINGS AND PRECAUTIONS, 5.6**); *Special Senses:* Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis, decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see **WARNINGS AND PRECAUTIONS, 5.12**); *Urogenital:* Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

6.2 Postmarketing Experience

Oral Timolol/Oral Beta-blockers: The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

DRUG INTERACTIONS

7.1 Beta-Adrenergic Blocking Agents: Patients who are receiving a beta-adrenergic blocking agent orally and Istalol® should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

7.2 Calcium Antagonists: Caution should be used in the co-administration of beta-adrenergic blocking agents, such as Istalol, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided.

7.3 Catecholamine-Depleting Drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

7.4 Digitalis and Calcium Antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

7.5 CYP2D6 Inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine) and timolol.

7.6 Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C: Teratogenicity studies have been performed in animals. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. Istalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers: Timolol has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from Istalol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

OVERDOSAGE

There have been reports of inadvertent overdosage with Istalol resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose. In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin. Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test. Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

PATIENT COUNSELING INFORMATION

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (see **CONTRAINDICATIONS, 4.1, 4.2**) Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (see **WARNINGS AND PRECAUTIONS 5.8**) Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart. Patients should be advised that Istalol® contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following Istalol® administration.

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Clinical Advances in Ocular Allergy

Mark Abelson, MD, CM, FRCSC, FARVO and Lisa Smith, Andover, Mass.

Researchers are exploring disease-modifying treatment options and not just symptomatic relief.

It is time to take stock of conditions that affect 25 percent of your patients: seasonal and panseasonal allergic conjunctivitis. While from one point of view, ocular allergy research and new treatments certainly know how to ride the coattails of research in other forms and sites of inflammation, interest in ocular allergy also stems from the fact that the ideal drug has not yet come to hand. In this article, we'll provide news about the more pragmatic clinical science of ocular allergy.

Our Methods

This article is the result of a comprehensive literature search of clinical studies from 2013 to 2015, combined with information from studies listed on clinicaltrials.gov whose results have yet to be published. Much of what has been reported has actually focused on chronic allergy with a proliferative component. While diseases such as vernal and allergic keratoconjunctivitis afflict a small percentage of allergy sufferers, the permanent damage to vision that can result from corneal involvement, sometimes in pediatric patients, lends weight to this discussion and warrants a complete investigation into the more disease-modifying treatment options. This year, our mainstays for symptomatic therapy are also being challenged, and the results of new head-to-head comparisons may surprise.

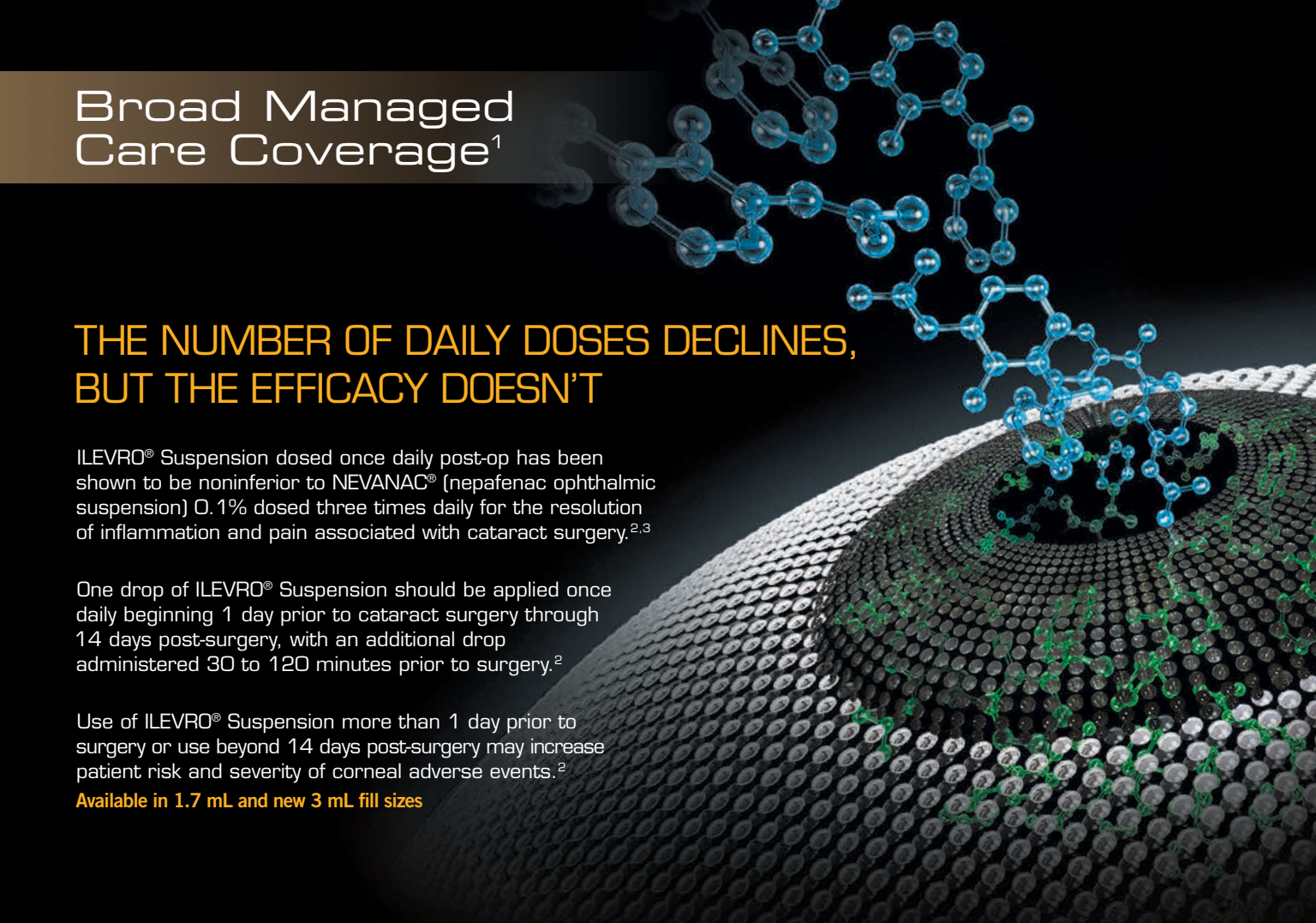
Severe Allergy

Several agents for severe cases of allergy have been the subjects of research this year.

• *Cyclosporine.* Cyclosporine has won a lot of press this year in allergy. Four peer-reviewed articles highlighted the efficacy of this immunomodulator in ocular allergic disease. While ophthalmologists overseas have treated severe ocular allergy with *ad hoc* formulations of cyclosporine for years, the results highlighted below, taken with the now-known safety of commercially available Restasis, may make revisiting this immunomodulator worthwhile, particularly in light of its steroid-sparing effect. In a Hong Kong study, researchers analyzed the efficacy of a three-month course of Restasis in 14 pediatric allergic conjunctivitis patients. Eleven were able to taper off steroid treatment after three months, and scores dropped for signs and symptoms ($p<0.0001$).[1] A review of VKC treated with cyclosporine and tacrolimus recently summarized the interest in these treatment options, particularly tacrolimus.[2] A clinical trial

This article has no commercial sponsorship.

Broad Managed Care Coverage[1]



THE NUMBER OF DAILY DOSES DECLINES, BUT THE EFFICACY DOESN'T

ILEVRO® Suspension dosed once daily post-op has been shown to be noninferior to NEVANAC® (nepafenac ophthalmic suspension) 0.1% dosed three times daily for the resolution of inflammation and pain associated with cataract surgery.[2,3]

One drop of ILEVRO® Suspension should be applied once daily beginning 1 day prior to cataract surgery through 14 days post-surgery, with an additional drop administered 30 to 120 minutes prior to surgery.[2]

Use of ILEVRO® Suspension more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.[2]

Available in 1.7 mL and new 3 mL fill sizes

INDICATIONS AND USAGE

ILEVRO® Suspension is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

IMPORTANT SAFETY INFORMATION

Contraindications

ILEVRO® Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

Warnings and Precautions

- Increased Bleeding Time – With some nonsteroidal anti-inflammatory drugs including ILEVRO® Suspension there exists the potential for increased bleeding time. Ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.
- Delayed Healing – Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO® Suspension may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- Corneal Effects – Use of topical NSAIDs may result in keratitis. In some 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.

  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.

  Use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.
- Contact Lens Wear – ILEVRO® Suspension should not be administered while using contact lenses.

Adverse Reactions

The most frequently reported ocular adverse reactions following cataract surgery occurring in approximately 5 to 10% of patients were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation.

For additional information about ILEVRO® Suspension, please refer to the brief summary of prescribing information on adjacent page.

References: 1. Formulary data provided by Pinsonault Associates, LLC, PathfinderRx, June 2014. **2.** ILEVRO® Suspension prescribing information. **3.** NEVANAC® Suspension prescribing information.

For more resources for eye care professionals, visit MYALCON.COM/ILEVRO

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
ILEVRO® Suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of ILEVRO® Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

Use with Other Topical Ophthalmic Medications
ILEVRO® Suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

CONTRAINDICATIONS
ILEVRO® Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

WARNINGS AND PRECAUTIONS
Increased Bleeding Time
With some nonsteroidal anti-inflammatory drugs including ILEVRO® Suspension, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that ILEVRO® Suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Delayed Healing
Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO® Suspension, 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.

Corneal Effects
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 ILEVRO® Suspension 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 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.

Contact Lens Wear
ILEVRO® Suspension should not be administered while using contact lenses.

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

Ocular Adverse Reactions
The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These events occurred in approximately 5 to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these events may be the consequence of the cataract surgical procedure.

Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO® Suspension 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 the ductus arteriosus), the use of ILEVRO® Suspension during late pregnancy should be avoided.

Nursing Mothers
ILEVRO® Suspension is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO® Suspension is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of ILEVRO® Suspension in pediatric patients below the age of 10 years have not been established.

Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice. Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

Avoiding Contamination of the Product
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

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

Contact Lens Wear
ILEVRO® Suspension should not be administered while wearing contact lenses.

Intercurrent Ocular Conditions
Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Shake Well Before Use
Patients should be instructed to shake well before each use. U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767.

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of a four-week course of 0.05% cyclosporine in 62 VKC patients came out of Turkey this year, and both sign and symptom scores were significantly improved ($p<0.0001$).[3]

Also from Hong Kong was a meta-analysis of trials involving cyclosporine use for allergic conjunctivitis (and not VKC or AKC). Investigators identified seven qualifying studies, with 153 patients treated for at least two weeks. Topical cyclosporine was associated with lower composite scores in signs and symptoms compared to placebo, with a pooled standardized mean difference of -1.21. Two of the three studies also found a significant reduction in steroid dependency.[4]

• *Tacrolimus.* Another large-scale clinical trial investigated the efficacy of twice-daily 0.1% tacrolimus in 1,436 subjects with refractory allergic conjunctivitis with proliferative lesions and/or corneal involvement. At last observation, mean total sign (-9.4) and symptom (-6.3) changes were significant (both, $p<0.001$). A subpopulation of patients who were unresponsive to a previous treatment with cyclosporine (n=239) also showed significant improvement in signs and symptoms, including giant papillae and/or epithelial defects. A significant steroid-sparing effect was observed, with 53.4 percent successfully weaned off steroids after six months of tacrolimus treatment.[5]

Another recent trial of tacrolimus demonstrated that addition of olopatadine to the therapy regimen added no more efficacy than tear substitutes for symptom control.[6] In atopic blepharoconjunctivitis (ABC), a disease of similar mechanism to atopic dermatitis, tacrolimus was shown to be superior to an immunomodulating newcomer, pimecrolimus, in 338 patients.[7]

Closing the discussion of the more serious allergic diseases were some interesting case reports using subcutaneous omalizumab,[8] or supratarsal injections of triamcinolone[9] for successful treatment of recalcitrant VKC.

Itching is a useful parameter with which some new anti-allergic molecules are assessed.

Crossover Action

Another interesting case report touched on the use of rebamipide, recently approved in Japan for dry eye, in patients with both dry eye and refractory allergic diseases.[10] Results indicated that rebamipide might also be useful for both proliferative and non-proliferative allergic disease. Dry eye/allergy comorbidity is extremely common,[11] and might require creative approaches to treatment. It is not surprising really that dry-eye therapy is effective for allergy and perhaps some allergy therapy is effective for dry eye, when we consider the common threads from which ocular surface inflammation is woven.

Allergic Interplay

A meta-analysis was performed on clinical trials of allergic ocular disease involving the oral leukotriene antagonist, montelukast. In six comparable trials, oral montelukast improved ocular symptom scores better than placebo, but not better than oral antihistamine.[12] This is notable since we previously compared the effects of oral antihistamines versus topical ophthalmic anti-allergic agents, and found that topical therapy wins every time.[13]

Similarly, several papers were published this year on the eye-nose nexus. Allergic conjunctivitis was shown to have 95-percent comorbidity in patients with allergic rhinitis.[14] The possible anatomical and functional relationships between the eye and nose were reviewed, and a case made for bidirectional flow.[15] Conjunctival and tear inflammatory cells increased after nasal allergen provocation.[16]

As with oral therapy, we've investigated the claims that nasal anti-allergic therapy might be effective for ocular allergy.[13,17,18] While this concept is attractive, especially for allergists wanting to simplify therapies, it is unlikely to succeed given the magnitude of ocular anti-allergic response that's required.

Our literature review also revealed clinical trials of immunotherapy addressing "rhinoconjunctivitis." However, a closer look revealed that these studies do not address ocular endpoints in a well-controlled fashion. We shall see if more stringent requirements for allergic disease indications will translate in the years to come to better-controlled ocular endpoints in immunotherapy trials. One systematic review of 13 trials and 1,037 subjects concluded that sublingual therapy, not yet available in the United States, was moderately successful in improving conjunctival symptoms.[19]

Salve for Symptoms

Switching gears, let's discuss what's new in symptomatic relief of ocular allergy, particularly for relief of the itching that most of our patients suffer.

The pooled per-protocol results from the two pivotal conjunctival allergen challenge bepotastine trials re-

sponsible for the U.S. approval of this drug were published in 2014.[20] By way of nomenclature, per-protocol populations are those subjects who complete a clinical trial with no major protocol deviations, which is different from the intent-to-treat population, which is composed of all subjects treated, independent of how well the protocol was followed. Thus, the per-protocol population is usually a cleaner assessment of drug efficacy.

In the bepotastine trial, out of 157 subjects, 140 were identified as the per-protocol population. Differences in mean ocular itching scores were statistically significant ($p<0.001$) at all visits and time points. The onset and eight-hour duration data were also clinically significant, indicated by a one-unit minimal magnitude of difference from placebo. Differences in itch scores recorded at the 16-hour allergen challenge were highly statistically significant, at 0.8 (three minutes post-challenge), 1.0 (five minutes post-challenge) and 0.9 (seven minutes post-challenge) unit differences from placebo, but these were not considered clinically significant since two of the three time points did not demonstrate a full one-unit change.

Itching was also assessed as the percentage of subjects with complete resolution of itching. This is another useful parameter with which new anti-allergic molecules are assessed. The majority of subjects treated with bepotastine reported zero itching at three minutes post-challenge, the peak time for itching response. This total control was maintained at eight hours for one-third of the treated subjects. Since prevention of itching is the indication for which these antihistamines are approved, studying the itching effect from various perspectives has proven very useful in teasing out the benefits afforded of one antihistamine over another.[20] These itching results were then confirmed in an allergist-based trial in seasonal allergic conjunctivitis.[21]

International Research

Epinastine (Elestat, Allergan) is another antihistamine whose efficacy in the CAC was published last year, though it's been eclipsed in the United States by Allergan's subsequent release of alcaftadine (Lastacaft), which demonstrates superior efficacy and duration. Nevertheless, alcaftadine is not available as yet in Japan, and epinastine is still actively prescribed and investigated in Asia. In fact, many CAC studies are ongoing in Japan due to the alarming incidence and increasing severity of cedar pollen allergic conjunctivitis, considered a health hazard on a national level.

In the epinastine study, it was compared to placebo and olopatadine 0.1% (Patanol, Alcon), the only concentration available outside of the United States. Results showed epinastine to be superior to placebo for both itching and redness at four hours and eight hours, and non-inferior to olopatadine 0.1% when challenged at four hours after dosing.[22] A subsequent Japanese study overseen by our research firm, Ora, and sponsored by Alcon Japan, assessed olopatadine versus epinastine in a contralateral-eye CAC study. It demonstrated the superiority of olopatadine.[23] This latter study in a Japanese population confirmed the results of an earlier U.S. trial that demonstrated olopatadine to be superior to epinastine.[24] This finding also attests to the consistency of results across populations that can be expected when using the CAC model to assess ophthalmic anti-allergic agents.

Some other comparative studies in anti-allergics were completed outside the United States. Chronic allergic conjunctivitis is always a challenge, and was the subject of two peer-reviewed articles. In China, the efficacy of 1% fluorometholone was compared to the NSAID, 0.1% pranoprofen, both used q.i.d. for four weeks in 75 patients.[25] Signs decreased more significantly in fluorometholone-treated patients at day seven, after which time reductions tapered off. Fluorometholone also did better in symptomatic relief on day three. Interestingly, a better clinical outcome was observed in patients under 30 years of age, perhaps indicating that the disease itself becomes more complex with age, or that with accumulating co-morbidities it's harder to treat. Due to a slight IOP effect in the fluorometholone group, the authors advised initiating combination therapy for three to five days, followed by maintenance therapy with an NSAID alone in patients with chronic allergy.[25]

In Turkey, olopatadine 0.1% combined with fluorometholone 0.1% versus olopatadine with ketorolac 0.4% was evaluated in 52 seasonal allergic conjunctivitis patients. The unique study design involved instilling both drops in one eye versus placebo in the contralateral eye. Olopatadine was instilled b.i.d. and the steroid or NSAID q.i.d. for 10 days. Redness, mucus secretion, chemosis and eyelid edema were all statistically superior in the fluorometholone-olopatadine group than in the olopatadine-NSAID group.[26]

A French study in 75 subjects compared a preserved formulation of olopatadine to preservative-free ketotifen 0.025% in treating seasonal allergic conjunctivitis. Resolution of signs and symptoms was assessed with b.i.d. treatment for 28 days. The composite score for signs and symptoms improved significantly for ketotifen, and no significant difference was observed between this anti-allergic and olopatadine 0.1%.[27]

Exploring Alcaftadine

Alcaftadine (Lastacaft) is the newest chemical entity to be approved for prevention of ocular itching associated with allergic conjunctivitis, and two papers have been published investigating the comparative efficacy of olopatadine 0.2% to alcaftadine 0.25%.[28,29] These are the only two antihistamines

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Ophthalmologist and noted refractive and cataract surgeon.
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Table 1. Anti-Allergic Drugs Tested Clinically, 2014 to 2015

Drug/Sponsor	Mechanism of Action	Indication	Status
EB-101 Eleven Biotherapeutics	IL-1 antagonist	Chronic AC	• Phase II complete • did not meet primary endpoint of itching
Dexamethasone-Depo Ocular Therapeutix	corticosteroid	Chronic AC	• Phase II underway • punctal plug depot showed positive results
Fluorometholone non-sponsored studies	corticosteroid	Chronic AC	• Study 1: superior to pranoprofen, (n=75) • Study 2: superior in combination with olopatadine versus ketorolac + olopatadine (n=52)
Triamcinolone Non-sponsored study	steroid, supratarsal	Recalcitrant VKC	• two doses, 1 month apart; no additional anti-allergic meds • cobblestones, erosions completely resolved at 18 months
Cyclosporine Non-sponsored studies	immunomodulator calcineurin inhibitor	VKC chronic AC	• VKC study (n=62), AC meta-analysis (n=153) • improvements in signs and symptoms in both reports
Tacrolimus Non-sponsored studies	immunomodulator calcineurin inhibitor	refractive AC VKC	• refractive AC (n=1436), VKC: ± olopatadine (n=21) • all treatments showed improvements in signs/symptoms
Tacrolimus/Pimecrolimus Non-sponsored studies	immunomodulator calcineurin inhibitor	Atopic blepharo-conjunctivitis	• Both treatments were effective (n=338)
Omalizumab Non-sponsored study	imonoclonal antibody anti-IgE (systemic)	VKC	• marked improvements in signs and symptoms at 8 weeks • proliferative changes resolved at 18 months
Montelukast Non-sponsored study	leukotriene receptor antagonist (systemic)	SAC	• meta-analysis of six trials • improvements shown in ocular signs and symptoms
SLIT Immunotherapy Merck; Stallergenes	grass or ragweed immunogen	Rhinitis with AC	• FDA approved in 2014 • reduces ocular signs and symptoms in secondary endpoints
Rebamipide Otsuka Pharmaceutical	mucogenic	Proliferative AC	• Giant papillae were reduced in all cases
Cetirizine Aciex Therapeutics	antihistamine	AC	• Clinical trials completed • NDA filing is expected in 2015
Olopatadine 0.77% Alcon/Novartis	dual-acting agent	AC	• drug approved by the FDA for q.d. use February 2015 • superior effects on itching over 0.2% olopatadine
Bepotastine 1.5% Bausch & Lomb	dual-acting agent	AC	• b.i.d. dosing confirmed (n=140) • percentage with minimal or no itching was greater than placebo
Epinastine 0.05 % Santen Pharmaceutical	dual-acting agent	AC	• non-inferior to olopatadine at four hours (n=87)
Olopatadine 0.1% Alcon Japan	dual-acting agent	AC	• superior to epinastine's onset of action (n=50)
Olopatadine 0.2% Alcon/Novartis	dual-acting agent	AC	• Study 1: non-inferior to preservative-free ketotifen (n=75) • Study 2: ongoing trial in China compared to olopatadine 0.1% (n=250)
Alcaftadine 0.25% Allergan	dual-acting agent	AC	• pooled analysis (n=284) • superior to olopatadine 0.2% for itching and for percentage of subjects with minimal or no itching

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available with once-daily dosing, so this comparison was appropriate and necessary for us to understand if there are any benefits offered by treating with the newer compound. While olopatadine is recognized as a dual-acting mast cell stabilizer and antihistamine, the mechanism of alcaftadine appears to be predominantly potent antagonism of H1, H2 and H4 receptors,[30] with receptor affinities that are 10 times higher than that of olopatadine for H1 and H2 receptors. Further, olopatadine has no affinity for the H4 receptor.[31] It's unknown if alcaftadine's receptor antagonism is responsible for its known eosinophil chemotaxic inhibition and tightening of conjunctival epithelial tight junctions that have been shown preclinically.[32]

The earlier paper presented the results of one CAC trial in which alcaftadine went head-to-head with olopatadine 0.2% in 127 subjects.[28] Onset and duration of action at 16 and 24 hours after dosing were established. For the primary measure of ocular itching, both actives were statistically significantly superior to placebo at all time points post-CAC for both the 16- and 24-hour duration assessments ($p<0.0001$). This confirms that both olopatadine 0.2% and alcaftadine 0.25% are effective for symptomatic prevention of itching, all day for up to 24 hours, which is already a feat when we consider how far we've come in making our patients more comfortable. However, at three minutes after challenge, the peak time post-CAC for itching because histamine has exploded from mast cells, alcaftadine treatment resulted in significantly lower mean itching scores at the 16-hour duration assessment ($p=0.026$).[28]

The second alcaftadine versus olopatadine paper, published last year, was on a pooled analysis of two CAC studies (n=284) performed identically to the one described above. In it, patients rated their itch numerically, with 0 signifying no itch and 1 meaning serious itching. Again, at 16 hours after instillation, alcaftadine was superior to olopatadine 0.2% for the first explosive itching that occurs three-minutes after allergen challenge (0.50 vs. 0.87, respectively, $p=0.0006$). Alcaftadine also showed lower mean itching scores over all time points (0.68 vs. 0.92 respectively, $p=0.0390$) compared with olopatadine. Finally, minimal itching (a score <1) was reported in 76.1 percent of alcaftadine-treated subjects versus 58.1 percent of olopatadine-treated subjects ($p=0.0121$).[29]

Ongoing Trials

To round out these published offerings, let's look at whichß studies have been posted to clinicaltrials.gov.

In 2014, Nicox bought Aciex, and with it the rights to the antihistamine, cetirizine ophthalmic solution (AC-170), which has been evaluated in two pivotal CAC studies. Nicox's website states that successful pre-NDA meetings have been held with the Food and Drug Administration, and that a submission date of the NDA will be announced in the near future. Ocular Therapeutix has developed technology for encapsulating ophthalmic pharmaceuticals within a hydrogel to deliver sustained therapeutic levels of various drugs via punctal plugs. One of these, OTX-DP, is a dexamethasone depot that has been tested for treatment of chronic allergic conjunctivitis modeled by multiple CACs.

Alcon has developed a high-dose olopatadine 0.77%, and results of an Alcon-sponsored CAC trial were presented at the ARVO meeting last year (clinicaltrials.gov: NCT01743027).[33] *(McLaurin E, et al. IOVS 2014;55; ARVO E-Abstract 2488)* This formulation appears to have benefits to controlling itching at 24 hours that the 0.2% olopatadine concentration doesn't have. This high-dose olopatadine, named Pazeo, was just approved by the FDA in February 2015.

Eleven Biotherapeutics has completed a study on one of its lead candidate products, an interleukin-1 receptor antagonist, in a clinical model of moderate to severe allergic conjunctivitis using both an environmental exposure chamber and modified conjunctival allergen provocation test (clinicaltrials.gov: NCT02082899). The company recently announced that the primary endpoint of ocular itching wasn't demonstrated in the CAPT model.

Ultimately, reviewing the numerous reports on ocular allergy has shown us that interest in the topic is still very high, and has allowed us to draw some conclusions. Conventional immunomodulators like cyclosporine are being investigated anew for allergy; however, it's uncertain if the efficacy of this class compares favorably to the previous generation of mast cell stabilizing/antihistaminic drugs. At the same time, chronic allergic diseases such as VKC and AKC are still challenging clinicians. Elsewhere in the treatment realm, ocular anti-allergics are continually being compared to highlight possible benefits of one over the other, while alcaftadine (Lastacaft) is proving to be very effective in numerous cases of ocular allergy. REVIEW

Dr. Abelson is trustee of the Schepens Eye Research Institute, emeritus surgeon of the Massachusetts Eye and Ear Infirmary, and clinical professor of ophthalmology at Harvard Medical School. Ms. Smith is a medical writer at Ora Inc.

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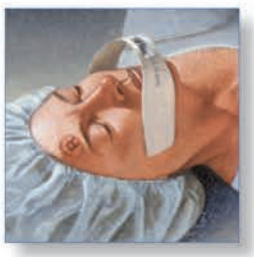

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How to Assess an Ophthalmic Start-up

William C. Stewart, MD, Jeanette A. Stewart, RN, and Lindsay A. Nelson, BS, Cheyenne, Wyo.

Your initial due diligence when considering a medical startup should include these steps.

Ophthalmologists are highly dependent on risk-taking entrepreneurs for new medicines and devices to assist in the battle against blindness. In turn, new companies are reliant mostly on private equity sources to fund their development, which CEOs of ophthalmic start-ups generally consider the hardest aspect of their job.[1]

Nonetheless, an investment in an ophthalmic start-up may be attractive because of the potential for financial payback, perhaps as much as seven to tenfold, if the product "makes it big."[2,3] However, investing in start-up companies in ophthalmology also carries risks as the overall success rate is low, and with failure comes the potential loss of the investor's funds.[4,5] Unfortunately, ophthalmologists are not trained, and it is difficult to find information, regarding how to evaluate an ophthalmic start-up to assess the investment potential.

The purpose of this article is to provide ophthalmologists with basics about how to perform initial due diligence for a potential investment in an ophthalmic start-up developing a medicine. This article is intended to be a primer and is not meant to replace the advice of legal counsel or other consultants/advisors who might help with such an investment decision.

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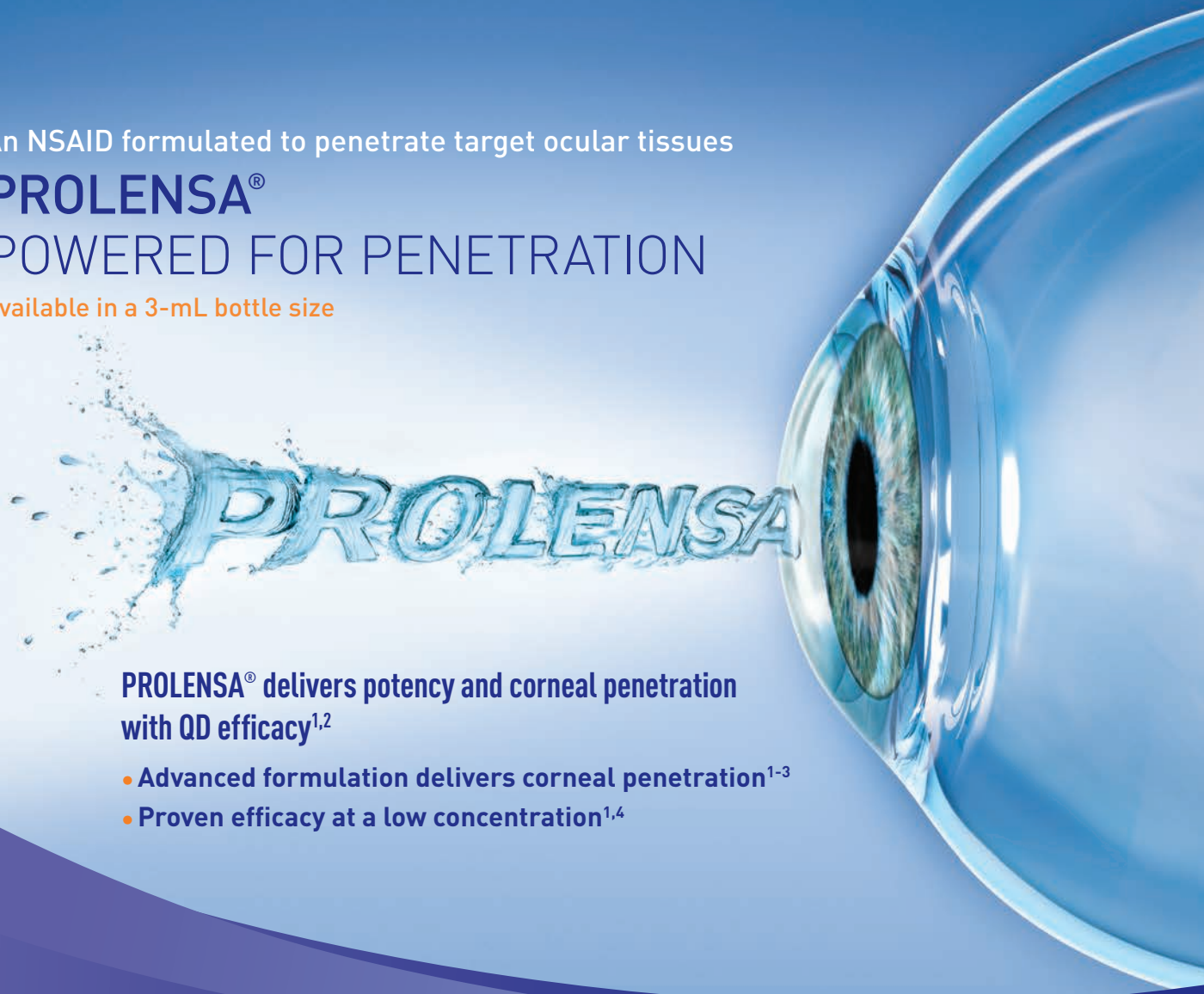

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INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% 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.

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

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 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

Please see brief summary of Prescribing Information on adjacent page.

References: 1. PROLENSA® Prescribing Information, April 2013. **2.** Data on file, Bausch & Lomb Incorporated. **3.** Baklayan GA, Patterson HM, Song CK, Gow JA, McNamara TR. 24-hour evaluation of the ocular distribution of 14C-labeled bromfenac following topical instillation into the eyes of New Zealand White rabbits. *J Ocul Pharmacol Ther*. 2008;24(4):392-398. **4.** BROMDAY® Prescribing Information, October 2012.

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Brief Summary

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.

DOSAGE AND ADMINISTRATION

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.

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.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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.

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.

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.

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.

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.

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.

ADVERSE REACTIONS

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® ophthalmic solution 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.

USE IN SPECIFIC POPULATIONS

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.

Nursing Mothers

Caution should be exercised when PROLENSA 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 PROLENSA differ in patients 70 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY

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 (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).

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

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

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® ophthalmic solution, be used to treat only one eye.

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.

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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Table 1. Initial Questions About the Function of a New Medicine

What is the mechanism of action (on a molecular basis)?
What is the exact indication?
What unique problem does the medicine solve?
What is the molecular biological link to treat the targeted disease?
Can this medicine be delivered to the target tissue in sufficient levels to initiate its therapeutic action?
What are the advantages over current therapies?
Are there any potential safety issues?

Modified from reference #5

Be Careful!

Even now you may know of a seemingly attractive start-up and feel enthusiasm about its prospects for success. However, be aware that your excitement might lead to a poor investment decision and loss of invested funds. The facts are somewhat scary! Generally, any new undeveloped medication has only a very low chance (one in 10 to 10,000, depending on the development stage) of reaching commercialization.[6] Specifically, in ophthalmology alone there are already more than 300 products (publically known) being developed by both large and small pharmaceutical companies (Internal data, PRN PharmaFarm). Consequently, despite your enthusiasm you should make a careful assessment of your potential investment and its chance for success. In doing so ask yourself some important questions.

Does the Medicine Work?

This assessment begins with a close consideration of several vital questions listed in Table 1. Importantly, the answers should be backed by data! The answers are necessary so you can become confident about the narrative your favored product will tell to any potential licensee.

The start-up should have identified a clear indication the medicine can treat. Further, the new medicine should be able to advance therapy for the intended indication in a measurable way, beyond foreseeable competition, that can be articulated succinctly and precisely.

In addition, the new medicine's mechanism of action should be known on a molecular basis either in reasonable theory derived from prior research, or from actual studies performed by the start-up. Further, how the new treatment alters the disease process also should be known on a molecular basis. Also, initial *in vivo* or *in vitro* studies should provide some idea of the safety profile.

The new medicine should have been prepared already in at least a simple formulation. In addition, the start-up should offer evidence from *in vivo* or *in vitro* studies that the medicine can reach its site of action by the chosen delivery route, at levels known to activate the protein or enzyme that affects the curative process consistent with the desired indication.

Is short, the new product should tell a clear story. You should be able to succinctly express your product's story to yourself and others as a safely deliverable medicine that clearly should advance therapy of a precise indication as suggested by animal studies and founded on a molecular basis of the therapy and the treated disease.

If you cannot answer clearly all the questions in Table 1 you probably should be hesitant to invest unless there is a very compelling reason and after consultation with appropriately knowledgeable colleagues. Warning: Do not be tempted to overlook these questions based on the enthusiasm of a CEO or because you feel foolish for not accepting the company's well-imagined assumptions.

Is It Regulatory Friendly?

This question is answered by considering several important issues. First, as noted already, identify the exact indication. This should be single and precise. Generally, start-ups should be focused on developing only one product for one indication at a time, as their personnel and money resources typically are limited. They may brag about their extensive pipeline but this additional product development should ideally be planned for the future.

Second, assure the planned indication has a known regulatory pathway. Ideally this pathway should include a short clinical trial duration (months not years) to prove therapeutic value to the regulatory agency. Further, the primary efficacy variable should be clear and reliably measured by a process accepted by the ophthalmic community. If the company does not have a precise indication or primary efficacy variable, or the medicine is too long or expensive to develop, think long and hard before investing.

Lastly, inquire if the appropriate section of the Food and Drug Administration has reviewed the start-up's plans in a formal meeting or at least in an informal conversation. If not, determine why and the plans to engage the agency. Regulatory agency approval of a company's development plans, emerging from a harmonious relationship, is vital for success.

Can the Product Be Made?

You should inquire with the start-up regarding potential manufacturing is-

sues. Making the new medicine can be the most difficult part of drug development. The manufacturing facilities are tightly regulated, and every step of the manufacturing process requires carefully planning.

The manufacturing process is roughly divided into two segments: the drug substance (the pure medicine without any additives) and the drug product (the drug substance formulated into its delivery medium).

The drug substance should have a readily available source of material. The synthesis or production of the new compound ideally should have been outlined and be relatively simple in design.

The drug product ideally should be developed into a relatively simple solution. If a more complex delivery system is required (e.g., gel, nanoparticles) then some explanation as to its need and advantage should be offered. All excipients (other materials in the solution apart from the active medicine) should have been used in ophthalmology before and be known to be safe. In addition, the starting compound for synthesis, as well as all reagents, excipients and synthesis steps used in the planned manufacturing process ideally should be described in the *United States Pharmacopeia* or a like compendium.[7]

For both the drug substance and product, some evidence of its stability and its ability to be purified and sterilized would be helpful even in early development. Inquire about anticipated manufacturing problems for both drug substance and drug product for clinical trials and scale-up to larger batches for commercial use.

Can It Be Sold?

Once you determine the medicine can function as intended, with a reasonable regulatory pathway, and can be manufactured, consider whether the start-up can actually sell it. Again, this assessment requires critical, realistic thinking. Do not assume that doctors will readily prescribe the new product only because it becomes commercially available. Table 2 provides for a summary of key questions.

Table 2: Market Assessment Questions

What is your potential market size?
What percent of the market can you capture?
At what stage of therapy will the medicine be used?
What is the SWOT analysis?
Who will pay for the medicine?
What are the backup plans should the primary plans fail?

Modified from reference #5

The initial question is the easy one—potential market size—or the number of people with the disease within the chosen treatment indication. These data generally are accessible from an Internet search. This is the point where many CEOs stop their analysis.

Therefore, you should consider several additional vital questions: What market penetration can the product realize within the existing patient population, and at what level of therapy will the product be used? These will help you project the rate at which the new product might be reasonably prescribed. Importantly, these questions should be answered by data (i.e., market research), not just the opinion of the CEO or several key opinion leaders.

Also important is a thorough SWOT analysis. Think through not only the Opportunities and Strengths of every product, but also the Threats and Weaknesses, both current and future. The company should provide you its SWOT analysis. Check to assure it is thorough and realistic.

Who will pay for the medicine? Will this be a self-paid product or is it for an indication and price level that will require private and government reimbursement? It may be too early for a detailed analysis but the start-up should have considered the potential payers as part of its profit projections.

If you are convinced that the start-up has a manufactural product, good market date and a good story, the next step is to review its business plan. Although this seems like an arduous task, it will help assure you have understood the company's perspective and plans regarding its product.

Is It Legally Safeguarded?

Intellectual property is a most important consideration and is typically the basis for creating the start-up itself. A start-up should have a relationship with a reliable pharma-experienced patent attorney to aid in protecting IP through a comprehensive and expanding legal strategy. Ask what patent types have been filed. Usually these are classified generally as composition of matter, a process (or method), or use patents.[3] In addition, how long is the remaining patent life? This should typically be 15 to 20 years. In what countries are the patents filed? They should be in the United States and ideally in other major worldwide markets as well. Have the patents been issued?

It is important that the start-up have an exclusive license to the product in the most important market countries for a suitable period to develop and market the medicine. The license should include the current indication and all potential associated indications sto prevent potential competition from a separate license to another company.

Post-op relief is affordable for your patients[1-3]

DON'T LET POSTOPERATIVE INFLAMMATION AND PAIN LEAVE A BAD IMPRESSION

3x more cataract patients achieved zero inflammation on postoperative Days 8 and 15 vs placebo
- 22%* vs 7% on Day 8; 41%* vs 11% on Day 15[1]

Nearly 2x as many cataract patients achieved zero pain on postoperative Days 8 and 15 vs placebo
- 58%* vs 27% on Day 8; 63%* vs 35% on Day 15[1]

WHEN TREATING ENDOGENOUS ANTERIOR UVEITIS, DUREZOL® EMULSION WAS NONINFERIOR TO PRED FORTE^ (DUREZOL® EMULSION 4X DAILY VS PRED FORTE^ 8X DAILY)[1]

- **BETTER** or comparable formulary coverage vs generic prednisolone acetate on some Medicare Part D plans[4-7]
- **NO** therapeutic equivalent to DUREZOL® Emulsion

*Pooled data from placebo-controlled trials in patients undergoing cataract surgery; $P<0.01$ vs placebo.
^Trademark is the property of its owner.

CORTICOSTEROID COVERAGE IS NOT THE SAME

LEARN MORE ABOUT DUREZOL® EMULSION FORMULARY ACCESS IN YOUR AREA AT MYALCON.COM/FORMULARY

INDICATIONS AND USAGE:
DUREZOL® Emulsion is a topical corticosteroid that is indicated for:
- The treatment of inflammation and pain associated with ocular surgery.
- The treatment of endogenous anterior uveitis.

Dosage and Administration
- For the treatment of inflammation and pain associated with ocular surgery instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.
- For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

IMPORTANT SAFETY INFORMATION
Contraindications: DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Warnings and Precautions
- Intraocular pressure (IOP) increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Cataracts—Use of corticosteroids may result in posterior subcapsular cataract formation.
- Delayed healing—The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Bacterial infections—Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Viral infections—Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections—Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Contact lens wear—DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

Most Common Adverse Reactions
- Post Operative Ocular Inflammation and Pain—Ocular adverse reactions occurring in 5-15% of subjects included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis.
- In the endogenous anterior uveitis studies, the most common adverse reactions occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis.

For additional information about DUREZOL® Emulsion, please refer to the brief summary of Prescribing Information on adjacent page.

For more resources for eye care professionals, visit MYALCON.COM/DUREZOL.

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Alcon®
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DUREZOL®
(difluprednate ophthalmic emulsion) 0.05%

DUREZOL®
(difluprednate ophthalmic emulsion) 0.05%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
Ocular Surgery
DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.
Endogenous Anterior Uveitis
DUREZOL® Emulsion is also indicated for the treatment of endogenous anterior uveitis.

DOSAGE AND ADMINISTRATION
Ocular Surgery
Instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.

Endogenous Anterior Uveitis
Instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

DOSAGE FORMS AND STRENGTHS
DUREZOL® Emulsion contains 0.05% difluprednate as a sterile preserved emulsion for topical ophthalmic administration.

CONTRAINDICATIONS
The use of DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

WARNINGS AND PRECAUTIONS
IOP Increase
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts
Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing
The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections
Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Viral Infections
Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections
Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Topical Ophthalmic Use Only
DUREZOL® Emulsion is not indicated for intraocular administration.

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

ADVERSE REACTIONS
Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects; posterior subcapsular cataract formation; secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Ocular Surgery
Ocular adverse reactions occurring in 5-15% of subjects in clinical studies with DUREZOL® Emulsion included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1-5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in < 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritus, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.

Endogenous Anterior Uveitis
A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 106 were exposed to DUREZOL® Emulsion. The most common adverse reactions of those exposed to DUREZOL® Emulsion occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2-5% of subjects included anterior chamber flare, corneal edema, dry eye, iridocyclitis, photophobia, and reduced visual acuity.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects
Pregnancy Category C. Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal) anomalies when administered subcutaneously to rabbits during organogenesis at a dose of 1–10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL® Emulsion, since DUREZOL® Emulsion is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL® Emulsion should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

Nursing Mothers
It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when DUREZOL® Emulsion is administered to a nursing woman.

Pediatric Use
DUREZOL® Emulsion was evaluated in a 3-month, multicenter, double-masked, trial in 79 pediatric patients (39 DUREZOL® Emulsion; 40 prednisolone acetate) 0 to 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL® Emulsion to prednisolone acetate ophthalmic suspension, 1%.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, and Impairment of Fertility
Difluprednate was not genotoxic *in vitro* in the Ames test, and in cultured mammalian cells CHL/IU (a fibroblastic cell line derived from the lungs of newborn female Chinese hamsters). An *in vivo* micronucleus test of difluprednate in mice was also negative. Treatment of male and female rats with subcutaneous difluprednate up to 10 mcg/kg/day prior to and during mating did not impair fertility in either gender. Long term studies have not been conducted to evaluate the carcinogenic potential of difluprednate.

Animal Toxicology and/or Pharmacology
In multiple studies performed in rodents and non-rodents, subchronic and chronic toxicity tests of difluprednate showed systemic effects such as suppression of body weight gain; a decrease in lymphocyte count; atrophy of the lymphatic glands and adrenal gland; and for local effects, thinning of the skin; all of which were due to the pharmacologic action of the molecule and are well known glucocorticosteroid effects. Most, if not all of these effects were reversible after drug withdrawal. The NOEL for the subchronic and chronic toxicity tests were consistent between species and ranged from 1–1.25 mcg/kg/day.

PATIENT COUNSELING INFORMATION
Risk of Contamination
This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the emulsion.
Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Risk of Secondary Infection
If pain develops, or if redness, itching, or inflammation becomes aggravated, the patient should be advised to consult a physician.

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Patients should be advised to remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

Revised: May 2013
U.S. Patent 6,114,319

Manufactured For:
Alcon®
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or
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Assure also that all patent holders have assigned their rights to the license to the start-up. In addition, check to assure any arrangements with a university and its claims to the patent have been included in a license.

Also inquire about the security arrangements for the IP against hackers. The IP should be protected behind a firewalled server with limited, secure access, central network control and encrypted communications with strong login profiles for both employees and external contractors.

Who Is the Boss?

The CEO is a vital part of your investment decision. Try to speak to him or her personally. The CEO should be personable, non-emotional, professional, perceptive and "hands on" in a prospective manner in directing the company. CEOs should be experienced, knowledgeable and competent enough to manage the fundraising, investors and the board of directors, as well as the various CROs and consultants needed to assist the product maturation. However, they should also be unpretentious enough to know they personally do not have all the answers as they face the inevitable development issues as their product matures. They should be a cheerleader for their product but in a realistic, ethical and thoughtful manner.

The CEO position generally is full-time and should not be undertaken by someone too distracted with other major activities. The CEO may be the only full-time employee and all other activities may be outsourced to companies or contractors to save costs.

In most instances the product inventor should not be the person to develop the product and a CEO should have been appointed. The inventor may lack connections in the investment and the development communities, as well as business experience and knowledge, to manage a start-up and mature the product to commercialization or licensing.

What Is the Funding Plan?

Importantly, the start-up should provide a clear and detailed budget to inform investors how their money will be spent, the development stage to which the current investment round should take the company, a description of the next steps to procure additional financing and why investors will be attracted to add financing at the next development stage. Inquire also about any plans and the timing to license or sell the product to a large pharma company. This information will tell you when you can reasonably expect to receive your invested equity from any successful financial deal.

Alternatively the start-up may plan to market the product itself, but this is unusual. If this is the plan you should ask about the logistics since marketing ophthalmics is expensive in cost and personnel. Also, inquire how the start-up's self-marketing affects your investment commitment.

A good CEO almost always is considering funding needs, not only for current development, but communicating with appropriate larger pharma companies for the potential future license of their product.

Often early investors are concerned about dilution of their ownership interest. Realize that if you are investing early in the development process other private equity hopefully will be enticed to meet future funding needs and so indeed will dilute your percent ownership. However, in a successful company the future investment rounds or an out-licensing agreement should cause your stock to increase in value. Consequently, your shares will be diluted, but with success the share price will appreciate.[3] You should discuss the possible extent of dilution versus anticipated stock price valuations with the CEO before investing.

When you decide to invest you should receive a clear term sheet with the investment details specified. Have this term sheet reviewed by a corporate attorney experienced in start-up funding. Don't be tempted to conduct a deal on a handshake. A detailed agreement will help maintain ordered, harmonious relationships between the start-up and investors in future years and help keep disputes to a minimum.

We hope this review has provided you with the first steps in considering whether to invest in an ophthalmic start-up with an established funding, legal and organizational basis. Persistent, careful attention to administrative and scientific details will help you decide if a new product is worthy of your attention and investment. REVIEW

Dr. and Mrs. Stewart are co-founders of PRN Pharmaceutical Research Network, LLC, an international ophthalmic clinical study management and consulting firm, as well as PRN PharmaFarm, LLC, which specializes in financing new ophthalmic start-up companies to assist towards product commercialization. Ms. Nelson is a research coordinator for both companies. *They received no financial support from any private or government funding source for this article.*

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Trade-offs in New Tech Decision-Making

Jan Beiting, Cary, N.C.

Balancing demands for cost-cutting while maintaining high quality requires keeping patients' interests front and center.

In the current health-care environment, ophthalmologists are being challenged to deliver quality care to more and more patients at reduced cost. That means practices have to approach new technology acquisition very carefully.

"In a sense, physicians are operating in a socialist environment in terms of our income, but a capitalist environment for our expenses, said Lisa Arbisser, MD, clinical adjunct professor at the University of Utah's Moran Eye Center. "That leaves a tremendous gap in our ability to invest in new technology." Dr. Arbisser and others quoted here spoke during a panel discussion hosted by Ophthalmic Women Leaders and Women in Ophthalmology during the 2014 American Academy of Ophthalmology meeting in Chicago.

Cost concerns aren't just about maintaining physician income, Dr. Arbisser said. "We also have to make sure we are providing a good livelihood for all the people who support us." The first time she operated during an international charitable trip, Dr. Arbisser said she realized just how dependent her own productivity is on her staff and their protocols for moving patients, sterilizing equipment and breaking down operating rooms between cases.

To ensure that she is able to maintain that infrastructure, Dr. Arbisser said she tries to make careful judgments about when the time is right to jump on a new technology bandwagon. That could mean passing up the chance to be an early adopter in favor of waiting for more evidence that something new truly carries advantages. It also means she needs to keep her knowledge base current to understand the physiology of a new technique or the impact of advanced technology. "For me, it's been a matter of seeing myself as a patient advocate first and foremost," she said.

Industry's Role

"Early adopters do take a little more risk, but they provide valuable input that helps us continue to improve products for their patients," said Nick Tarantino, OD, chief global clinical research and regulatory affairs officer for AcuFocus. Of the medical device industry, he said, "We understand that we need to be able to demonstrate a favorable risk-benefit ratio, and often, the best way to do that is by assessing the benefit to patients through patient-reported outcomes."

Such evidence of clinical benefit is not only key to convincing physicians of the value of new technology but also in justifying its cost to hospitals,

This article has no commercial sponsorship.

ambulatory surgery centers and payers.

"Industry also plays an important role in supporting physicians through patient and staff education," noted Candace Catanese, senior cataract account manager for Alcon. Additionally, she said, the affordability of new products is about more than just the price. "Sometimes the gains in efficiency or in outcomes make even an expensive new product affordable."

"It really does 'take a village' to provide the kind of care that all of us in health care want to provide," said Jane Rady, divisional vice president, business development at Abbott Medical Optics, OWL board member and moderator for this panel. "There are many opportunities for physician, staff, health-care policymakers and executives, and industry to work together to achieve the common goal of better patient outcomes," she said.

Pressure to Standardize

"Large provider networks in the health-care system are eager to standardize care," said Linda Christmann, MD, MBA, regional chief medical officer for Universal Health Services and president elect of WIO. She cites the cost efficiencies to be gained when networks are able to evaluate and approve bundles of equipment for a surgical procedure.

"That doesn't work very well for me as a surgeon," said Dr. Arbisser. "I try to determine, in a fact-based way, what are the best products to use for my patient." That might mean she chooses an intraocular lens from company A, a phaco machine from company B, and drops or instruments from company C. Additionally, what works best in her hands might not be exactly what works best in another surgeon's hands. "Best" might be defined differently from one patient to the next. "So while increased uniformity may lead to

Ophthalmic Women Leaders

Ophthalmic Women Leaders promotes and develops diverse leadership to advance ophthalmic innovation and patient care. The organization's mission includes working across ophthalmology to provide professional and personal development and create opportunities for collaboration. OWL regularly hosts discussions and speakers on topics, like the one featured here, that are of compelling interest to its members and stakeholders. For more information about OWL membership and upcoming educational and networking programs, visit owlsite.org.

Ophthalmic Women Leaders
leadership | advancement | community

Women in Ophthalmology

Women in Ophthalmology works to empower the aspirations of its ophthalmology and related members. The organization provides leadership training, networking and continuing medical information opportunities at its annual August meeting. The group partners with international and U.S. chapters to further career development of its members. They create collaborative relationships with industry through OWL and sponsorships to meet the needs of women in academia, practice and ophthalmic businesses. See wioonline.org for more details.

WOMEN IN OPHTHALMOLOGY
EMPOWERING ASPIRATIONS

products." That trend is happening in ophthalmic devices, too, although there is still a deep well of innovation in larger companies.

Come Armed

Dr. Christmann said that hospitals and ASCs are looking for an 80 percent solution. "No matter how much we want to standardize, we do understand that patients aren't widgets," she said. She encouraged surgeons to be open to using what they can in common with other surgeons when it makes sense for their patients. But when it doesn't make sense, ophthalmologists must advocate for themselves and their patients.

greater cost-effectiveness, I'm not convinced it will truly provide the best value," she said.

Large ophthalmic companies would certainly like to be able to provide a hospital or surgery center with nearly every product needed for a surgical procedure. "I try to bundle the majority of the products, but when it comes to specialty products like IOLs, no company can satisfy everyone. I wish there was one lens for every patient out there, but there isn't," said Ms. Catanese. She said she tries to satisfy clinical needs by providing data and trial experience, but sometimes she has to take the surgeon's guidance back to the company for further research and development. "Competition is healthy," she acknowledged. "Good products by other companies force all of us to stay on our toes."

Innovative new ideas and great single products often come from smaller companies. "The pharmaceutical world has become almost bimodal," said Ms. Rady. "Smaller, venture-backed companies provide the seed for innovation and then the larger companies often step in for the development mode and are able to provide a more global reach for those

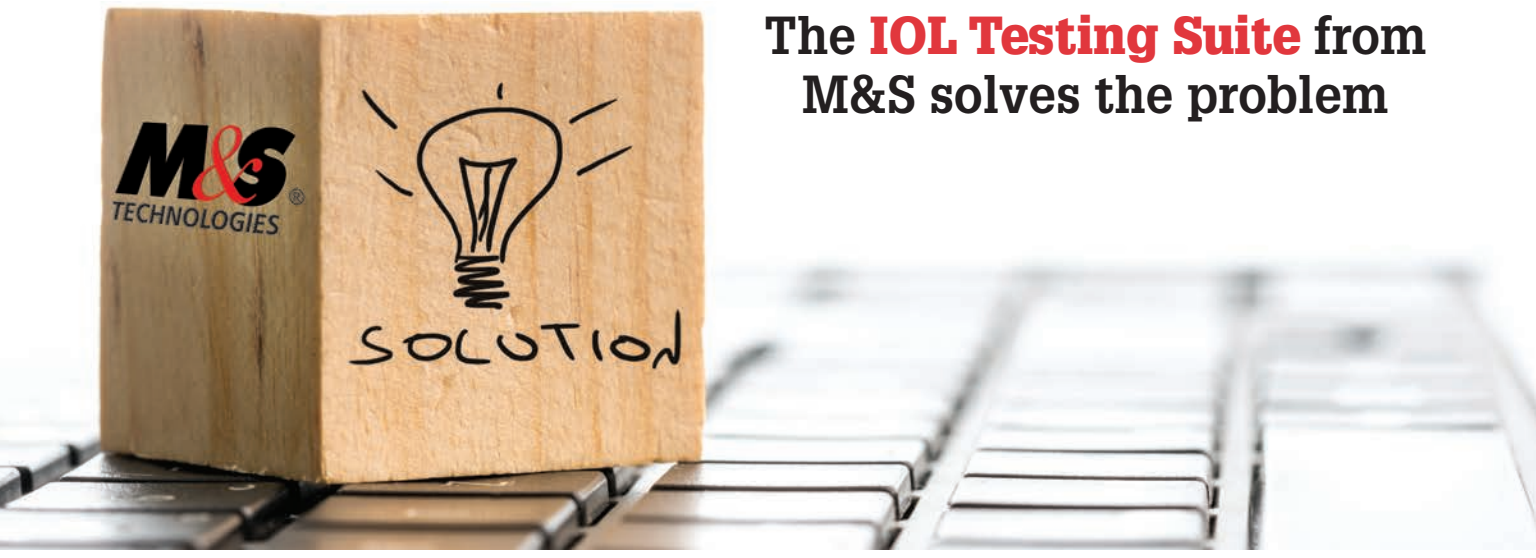
"The pharmaceutical world has become almost bimodal. Smaller ... companies provide the seed for innovation and then the larger companies often step in for the development mode and are able to provide a more global reach for those products."
—Jane Rady

"In the United States right now, we are poised to tip the scales in health care from a focus on v°olume to value," Dr. Christmann said. But value, she emphasized, doesn't necessarily mean the cheapest option. "We need for physicians to speak up and to speak from evidence, including evidence of the costs of bad care. Hospital CEOs can't factor that into their decision-making if they don't know what the true costs are." When it comes to purchasing expensive new surgical devices that can reduce complications, for example, that may mean coming to the table armed with facts about the incidence of complications and the financial impact of those complications. "We all need to champion the best care for patients," she said.

Dr. Arbisser agreed. "As long as we always keep the patients' best interests at the forefront of our decision-making then we can't go too far wrong," she said. "I am very excited to see more collaboration, more vertical integration and more careful thought now going into how we can go forward to take care of our population properly." REVIEW

Ms. Beiting is past president of Ophthalmic Women Leaders and principal of Wordsmith Consulting, in Cary, N.C. Contact her at (919) 363-3727 or jan@wordsmithconsulting.com.

Ease the Burden of IOL Testing



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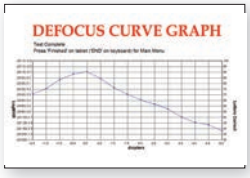

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Hopes and Hurdles for Stem Cell Therapy

The exciting world of stem cell therapy is the cutting edge of medical research. Here's how it intersects with ophthalmology.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and James McLaughlin, MD, Andover, Mass.

Stem cell technologies are now entering a third decade in the biomedical spotlight, with the potential for an accelerated therapeutic impact in the next few years. As often is the case, ocular disorders present some of the best opportunities to test and refine this latest advance in therapeutics. What's the potential for stem cell applications in the eye? This month we review the basics of stem cell biology, explore potential applications in the front of the eye and describe some recent progress. We conclude with a discussion of how this cutting-edge technology can move from an experimental protocol to an everyday therapy.

The Roots of Stem Cells

Stem cell research dates back to the early 20th century, but it wasn't until 1981 that embryonic stem cells were grown successfully in culture from mice; human cultured hESCs were first described in 1998.[1] The ethical issues of hESCs was one factor in the momentum that led to development of induced pluripotent stem cells, cells derived from somatic tissue, in which a combination of growth factors can induce a non-differentiated, pluripotent stem cell phenotype.[2,3] All of this work occurred against a background in which the parameters of bone marrow transplants for hematopoietic disease, the first true stem cell therapy, progressed from experimental treatment to standard of care.

At its core the principle of stem cell therapy is simple: Replace a tissue or organ that is failing with the means to rebuild itself. The eye is uniquely suited for this type of therapeutic approach, as demonstrated by the long-standing success of corneal transplants. In addition to the physical accessibility of ocular structures, corneal transplant benefits from the immune privilege that reduces the risks of rejection present with other organ transplant methods. Cadaver cornea transplant isn't appropriate for all corneal pathologies, however, and there are always patients for whom transplants simply don't succeed, but the clinical experience that we have gained from decades of allogeneic therapies has jump-started research into stem cell-based approaches to corneal disease.

Corneal Stem Cell Therapy

A normal cornea has its own supply of stem cells in the limbal epithelial stem cells. Localized to specialized niches at the corneal-scleral junction (the palisades of Vogt)[4,5] these cells supply the entire cornea with a source of progenitor cells that ultimately replenish the corneal epithelium. Limbal stem cells respond to environmental conditions or trauma by modulating the rate of turnover and differentiation into epithelial precursors and, eventually, terminal, postmitotic, corneal epithelium. When the health of the stem cells themselves is compromised, the ability of the cornea to repair itself is jeopardized. This limbal stem cell deficiency affects about 10 million people worldwide,[6] and can result in corneal erosion, corneal vascularization and, ultimately, in visual impairment or blindness. Nearly 70 percent of corneal blindness is due to some form of LSCD.[7,8]

Limbal cell defects can result from either inherited or acquired conditions, and they can be partial or complete. Rare genetic disorders such as aniridia or dyskeratosis congenita are

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associated with LSCD, but it is more commonly the result of a trauma such as chemical exposure, fire, repeated ocular surgery involving the limbus or adverse responses to contact lens use. Diagnosis is made by clinical presentation and impression cytology.[4,8,9] The presence of goblet cells on the corneal epithelium is suggestive of conjunctival epithelial ingrowth.[8-10]

The first step in managing LSCD is assessment and optimization of the health of the ocular surface. Surface debridement may be required, and artificial tears and topical corticosteroids may also be needed. In cases of partial and asymptomatic LSCD, this approach along with examinations may be all that is needed.[8-10] When more aggressive approaches become necessary, surface debridement coupled with limbal stem cell transplantation may be necessary in order to restore the stem cell populations and reestablish a healthy, functional corneal surface.[8,10]

Limbal stem cell transplant is the second most common form of stem cell-based therapy; only bone marrow transplantation is more common.[11] Stem cells can be harvested from the fellow eye and transplanted directly into the diseased eye in a procedure known as conjunctival limbal autograft. This approach is useful for cases of unilateral LSCD where the nondiseased eye has a healthy stem cell population. However, care must be taken not to induce LSCD in the donor eye.[7-11]

If the patient is not a candidate for autologous transplantation due to conditions such as bilateral LSCD, other transplant therapies may be used. A living, related donor can provide donor limbal cells or they can be harvested from otherwise healthy cadaver corneas. Both of these techniques require topical and systemic immunosuppression, and both have had only modest long-term (beyond two years) success.[5,11]

Patients with the most severe ocular surface disease (such as those with Stevens-Johnson syndrome) seem to have better outcomes with another approach: the combined conjunctival and keratolimbal allograft. In this procedure the patient receives tissue from a living related donor and a cadaver. This approach is useful for patients with severe ocular scarring; Stevens-Johnson patients in particular don't respond well to traditional corneal cadaver transplants.[5,6,11,12]

In order to avoid the risks of immune rejection associated with allografts as well as the need for lifelong immunosuppression therapy, *ex vivo* expansion of autologous cells has been carried out and remains the only clinically validated stem cell-based therapy that is routinely performed in ophthalmology.[6]

Cultured limbal epithelial transplantation is a two-step process in which a small graft is harvested from the donor eye and then expanded in the laboratory using a tissue matrix to increase the number of progenitor corneal cells.[5,12] After this *ex vivo* expansion, the cells are seeded onto carriers such as fibrin gels or human amniotic membrane, which can be used as a natural matrix to be transplanted into the patient.[6-8] Amniotic membranes have become the most common carrier substrate used for this procedure; the membrane appears to create niche-like conditions for the donor cells, and also exhibits anti-inflammatory properties once positioned in the recipient eye. Variations on this approach of graft harvesting, cellular expansion and transplant using a donor membranous matrix show promise for LSCD; for example, seeding an expansion can be done directly on the membrane, reducing the amount of tissue needed for allografts and therefore reducing the risk of iatrogenic LSCD. This intermediate step has also improved graft success rates.[5]

Manufacturing Stem Cells

If autologous limbal stem cells are not available, as is the case with total LSC deficiency, another source of stem cells must be found. Alternative cell sources being investigated include: oral mucosa; hair-follicle stem cells; mesenchymal stem cells (e.g., umbilical cord lining stem cells, dental pulp stem cells and adipose tissue-derived stem cells); and embryonic stem cells.[4,6-8,12-14] All of these alternative sources of stem cells have been shown to differentiate into corneal epithelium-like cells when exposed *in vitro* to characteristics resembling an LSC niche-like environment, but only oral mucosa cells have been evaluated clinically.[12,13]

Cultivated oral mucosal epithelial transplantation uses autologous cells obtained from the inferior buccal mucosa. Short-term results have been positive, but long-term efficacy has yet to be assessed.[12,13] Most commonly described methods include *ex vivo* expansion of excised mucosal tissue, with culture conditions designed to select for epithelial progenitor phenotypes. Cell expansion occurs in culture plates or using an amniotic membrane. Success with the *ex vivo* LSC expansion means that regardless of the autologous cell donor tissue, some variation on the *ex vivo* expansion paradigm is likely to be part of treatment protocols going forward. The exception to this will be protocols employing embryonic or induced pluripotent donor cells.

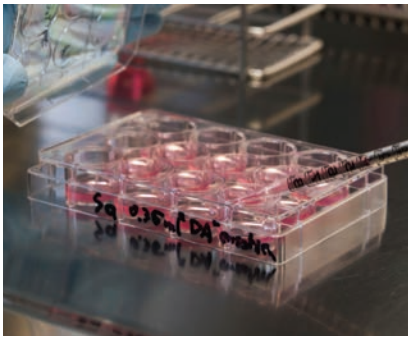
Human embryonic stem cells are derived from the inner cell mass of a 3- to 5-day-old embryo. Embryonic stem cells are more robust than adult somatic stem cells and they have a theoretically unlimited capacity to divide, and are by definition pluripotent: They can differentiate into all cell and tissue types given the correct sequence of differentiating stimuli. The establishment of hESC lines, as

well as the ability to obtain single-cell biopsies without harming embryos has eliminated some of the religious and ethical concerns that surrounded earlier stem cell research.[14] Objections exist, for example, over the use of established hESC lines in research.

The task of promoting appropriate differentiation has been addressed by growing hESCs on a collagen matrix using a nutrient broth similar to what is found *in vivo* in the limbal stem cell niche. When these cells are transplanted onto human corneas *in vitro*, they behave according to the normal corneal epithelial developmental process, forming corneal epithelial-like cells.[15]

While these studies provide useful insights into how hESCs may be used for corneal disease, the use of embryonic cells may eventually give way to cells derived from the reprogramming or inducing of non-embryonic stem cells into becoming pluripotent, undifferentiated stem cells. Induced pluripotent stem cells are adult somatic stem cells that have been reprogramed to return to an embryonic state, and so would provide tissue necessary for allografts of any tissue type.[16]

The reprogramming has been possible using combinations of transcription factor cocktails; most of these mixes include transcription factors Oct4 and Sox2 in combination with several other factors. Somatic cells engineered to express these mixes regress to an undifferentiated state; stable expression maintains this iPSC state, which can then be directed toward a new path of differentiation. Several reports have described a method that successfully produced corneal epithelial cells from iPSCs.[17,18] In one of these studies, mature human dermal epithelial cells were harvested from a donor and reprogrammed into iPSCs by a cocktail of transcription factors including Oct3/4, Sox2, c-Myc and Klf4. They were then differentiated into corneal epithelial cells using a stromal cell-derived inducing activity. Immunofluorescent staining of corneal epithelial markers was absent at the iPSC stage, but returned when cells were induced to differentiate.[18] This proof-of-concept study demonstrates the potential for iPSCs to provide the tissue needed for an inexhaustible supply of transplantable cells.



Ex vivo expansion of limbal cell grafts can improve outcomes in cases of limbal stem cell deficiency.

What Cost Pluripotency?

Although researchers have demonstrated that reprogramming somatic cells to pluripotency is possible, significant challenges remain. Some of the factors used to induce the iPSC state are associated with oncogenic transformation (such as c-Myc), and the risk of teratoma formation needs to be evaluated. The ability of iPSC to differentiate into cells that are able to work in concert with existing cells also needs to be determined.[16] It turns out that getting iPSCs to successfully differentiate has been more difficult than expected. A promising method that may help in predicting (and therefore, achieving) success involves the expression of a specific cell marker, p63, in the iPSCs.[5,19] Several studies established that the likelihood of transplant success is positively correlated with the number of p63-positive cells in the culture. This observation may lead to an ability to predict iPSC transplant success,[6] and has been an important factor in the early efforts to commercialize corneal stem cell therapies.[20]

The use of animal products in cell culturing, such as mouse feeder cells and fetal calf serum, is another area of concern. The risks of xeno-contamination and zoonotic disease transmission are unknown, so animal-product-free systems are being explored. Similar efforts are being applied to the *ex vivo* expansion techniques described earlier. To circumvent these issues, one study employed autologous limbal stem cells grown in the patient's own serum on an FDA-approved contact lens instead of using mouse feeder cells and human amniotic membranes. Early results are promising.

The clinical experience with corneal transplants and the availability of donor tissue have given anterior segment stem cell research a sizeable head start on posterior segment efforts, but a strong focus on stem cell therapies for congenital retinal diseases and on conditions such as dry AMD will soon level the playing field. As an example, a Phase I/II study of hESC therapy for macular degeneration was recently published, with promising safety and graft survival data providing an encouraging outlook for the future.[21] Look for a discussion of stem cell therapeutics beyond the cornea in a future column.

Finally, it's important to recognize that, like all new therapeutic strategies, the viability of these promising technologies depends upon the ability to refine the techniques to the point where they can be economically viable. Efforts to address this issue are focusing on the technologies required to create a consistent supply of high-quality iPSCs that are safe and respond to reprogramming in a reliable, predictable way.[22] We have no doubt that the last remaining hurdle can be cleared, however, and that more clinical trials and approved indications for ocular stem cell therapies will be part of our future. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical

School. Dr. McLaughlin is a medical writer at Ora Inc.

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Outer Retinal Layers as Predictors of Vision Loss

Advances in optical coherence tomography reveal correlations between retinal anatomy and vision loss in several retinal diseases.

Marco A. Bonini Filho, MD, and Andre J. Witkin, MD, Boston

Optical coherence tomography is a well-established diagnostic imaging technique that allows both qualitative (morphology and reflectivity) and quantitative (thickness, mapping and volume) analyses of the retinal architecture.[1,2] Since OCT has become available, correlations between anatomy on OCT and visual function have been investigated in a number of retinal diseases.[3-8] Retinal thickness parameters as assessed by OCT have been studied extensively in clinical trials, however only modest correlation between these quantitative parameters and visual acuity among a variety of retinal diseases has been established.[3,4,9-11]

Advanffces in OCT technology, most importantly the advent of spectral-domain OCT, have enabled retinal images to be acquired at higher speed and resolution, making it easier to identify boundaries between subtle intraretinal layers[2] and details of retinal microstructural changes associated with various retinal conditions.[12] In particular, the integrity of the photoreceptor layers as visualized using OCT has been demonstrated to have a more robust correlation with visual acuity than retinal thickness measurements alone, which has drawn attention to the continuity of these layers as possible predictive indicators of visual acuity in a wide variety of ophthalmic diseases that affect the macula.[6-8,13-15] This review will cover the most current understanding of the identities of these outer retinal layers, or ORL, and how disruption of these layers on OCT may correlate with visual function.

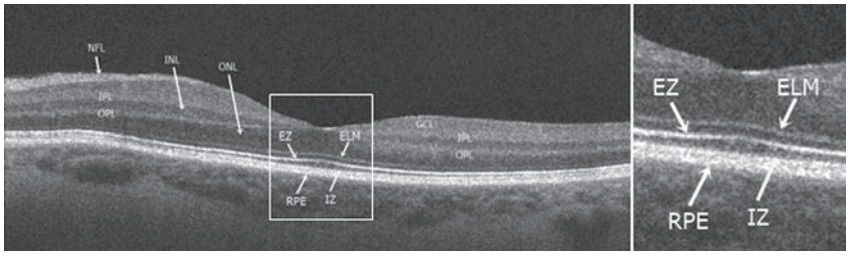

Figure 1. Spectral-domain optical coherence tomography image from the macula of a normal eye. The following retinal layers are labeled: nerve fiber layer; ganglion cell layer; inner plexiform layer; inner nuclear layer; outer plexiform layer; outer nuclear layer; external limiting membrane; ellipsoid zone; interdigitation zone; and retinal pigment epithelium.

Normal Anatomy of the ORL

Commercially available SD-OCT instruments have axial resolutions between 4 µm and 7 µm and transverse resolutions of approximately 15 µm, enabling the delineation of four hyperreflective bands in the outer macula. These bands have been extensively studied and their identities have been debated in an attempt to establish terminology that could facilitate communication in the field of ophthalmology. In 2014, an international panel of OCT experts came to a consensus on the most proper terminology for the retinal layers as visualized on OCT, and this terminology is currently commonly used among experts in the field.[12] The term "zone" was used to define anatomic regions without recognized histopathological correlation to a specific retinal layer.[12] The recent nomenclature of the outer retinal bands and their anatomic feature attributions are described below, from the innermost

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to the outermost *(See Figure 1)*.[12,13,15]

1) The external limiting membrane band (ELM) is located at the boundary between the cell bodies (nuclei) and the inner segments of the photoreceptors, and comprises clusters of junctional complexes between the Müller cells and the photoreceptors.

2) The ellipsoid zone (EZ), which was previously referred as the photoreceptor inner segment/outer segment (IS/OS) junction, is now thought to be formed mainly by mitochondria within the ellipsoid layer of the outer portion of the inner segments of the photoreceptors. In a normal fovea, the distance from the EZ line to the ELM is shorter than that from the EZ line to the RPE.

3) The interdigitation zone (IZ) corresponds to the contact cylinder represented by the apices of the RPE cells that encase part of the cone outer segments. This layer was previously referred to as cone outer segment tips (COST) or rod outer segment tips (ROST), and it is not always distinguishable from the underlying RPE layer, even in normal subjects.

4) The retinal pigment epithelial band is formed by the RPE and Bruch's membrane (indistinguishable from each other in a normal state using current SD-OCT systems). In the fovea, this band is thicker, which indicates that choroidal structures may also contribute to the hyper-reflectivity of the RPE band at this location.

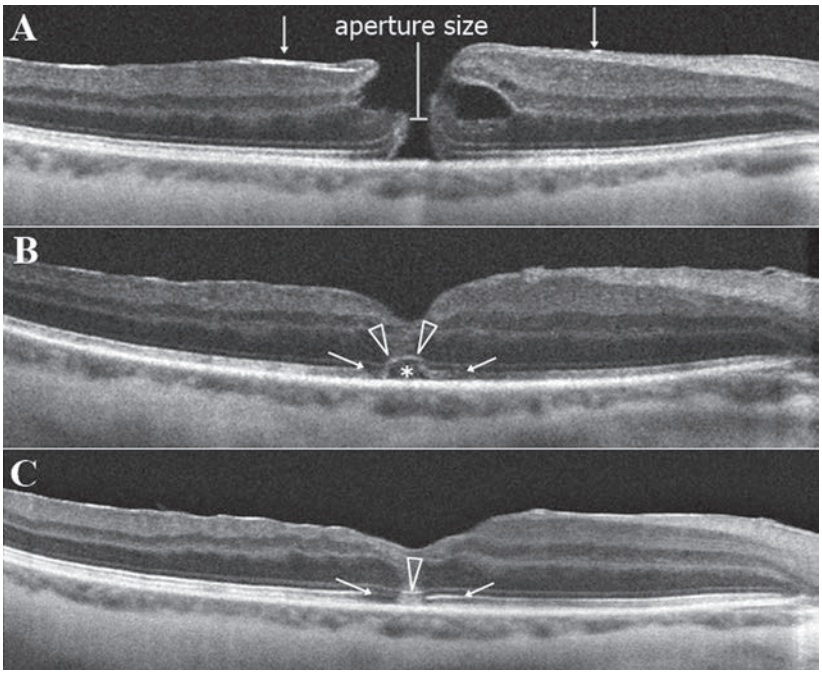

Figure 2. Sequential spectral-domain optical coherence tomography images of a successfully treated macular hole demonstrating initial restoration of outer retinal bands. A) At the initial presentation, best-corrected visual acuity was 20/100. SD-OCT image showed a full-thickness macular hole with perilesional cystoid spaces and an epiretinal membrane (arrow). The narrowest hole aperture size was 160 µm. B) Fifteen days after vitrectomy surgery, closure of the MH with restoration of the external limiting membrane and an outer foveal defect (star) are observed. Although ELM seemed to have recovered (arrowheads), the ellipsoid zone adjacent to outer retina is still irregular (white arrows). C) Thirty days after surgery, BCVA was 20/70. On SD-OCT, the ELM is continuous (arrowheads) and the EZ has recovered a more normal OCT appearance (white arrows).

Disruption of ORL Integrity

It is widely believed that damage or disruption of the photoreceptors can be visualized on OCT as loss of integrity of the ELM, EZ and IZ bands.[13,14] Attenuation, discontinuity or disruption of these bands have been reported as likely hallmarks of photoreceptor dysfunction or damage in a variety of retinal diseases.[6,14,16] These changes are better assessed in the absence of features that could weaken the signal intensity of the outer retinal layers, such as retinal edema, hemorrhage or media opacity.

Various stages of photoreceptor damage over time have still not been clearly correlated histopathologically with OCT findings. However, OCT of retinal degenerative diseases over time has demonstrated that ELM, EZ and IZ lengths are highly correlated with each other, and disorganization seems to occur in a stepwise order: first at the IZ, followed by the EZ and finally the ELM line.[16-18] The hypothesis that the photoreceptor outer segment layer is the first one to be affected in degenerative conditions, followed by damage of photoreceptor cell bodies occurring later in the process, is supported by histopathological evidence of decrease in outer segment length after retinal detachment in eyes with RD,[19] and shortening of cone outer segments and death of neighboring cones following rod cell death in eyes with retinitis pigmentosa.[20]

On the other hand, photoreceptor restoration as observed after macular surgery seems to occur in the opposite order. The ELM zone has been reported as the first structure to recover after macular hole closure, and its recovery has been considered a sign of intact photoreceptor cell bodies and Müller cells *(See Figure 2)*.[21] Additionally, OCT findings showed that EZ recovery is restricted to areas with intact ELM, and IZ recovery is observed only in eyes with an intact EZ and ELM line after macular hole and epiretinal membrane surgeries.[22,23] These findings suggest that an intact ELM at the fovea is necessary to complete restora-

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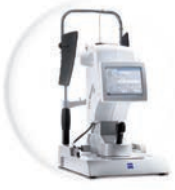	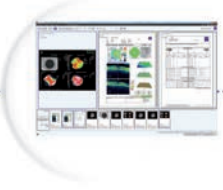		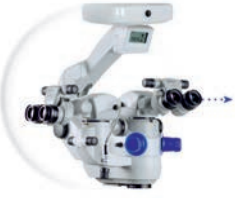
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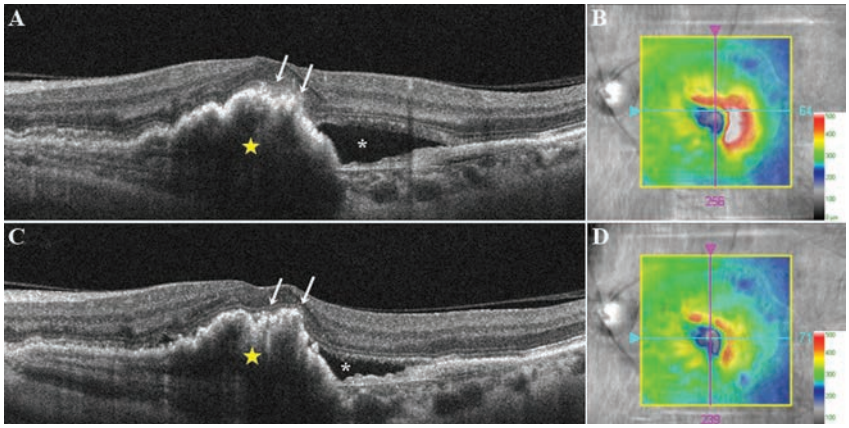

Figure 3. Sequential spectral-domain optical coherence tomography images of a treated choroidal neovascular membrane secondary to age-related macular degeneration demonstrating restoration of outer retinal bands after one intravitreal injection of anti-vascular endothelial growth factor. A) Initial presentation showed a multilayered retinal pigment epithelial detachment (yellow star) surrounded by subretinal fluid (white star). Outer retina layers on SD-OCT are disrupted and disorganized (arrows). B) Pre-treatment central thickness map showed central retina thickening in internal subfields. Baseline visual acuity was 20/80. C) Thirty days after anti-VEGF treatment, SD-OCT showed persistence of RPED (yellow star) and partial regression of subretinal fluid (white star). However, the ELM was restored in the area of the CNV. D) Although the post-treatment central thickness map showed only slight change, visual acuity improved to 20/50.

tion of the other photoreceptor microstructures.

Correlation: ELM Integrity & VA

A relationship between the pre-treatment status of the ELM and post-treatment visual outcomes has been described for epiretinal membranes,[24-26] age-related macular degeneration[27] and diabetic macular edema.[28] Although the presence of undisturbed ELM was considered a positive predictor of visual outcome in these diseases,[26-28] there was only a weak correlation between the pre-treatment length of ELM at the fovea and post-treatment visual outcomes. In AMD patients, shorter pre-treatment ELM length was associated with a lesser degree of change in VA after treatment, however longer ELM length did not guarantee significantly greater visual improvement.[27] In ERM eyes, no statistically significant association between the preoperative length of ELM and postoperative VA was found.[24,25]

Recovery of ELM after treatment has been more robustly correlated with visual acuity outcomes for retinal detachment,[18] macular holes[22,29] and age-related macular degeneration *(See Figure 3)*.[30] In eyes with retinal detachment, preservation of the ELM postoperatively was correlated with better postoperative visual acuity. After successful macular hole restoration, presence of disrupted ELM was associated with poor visual acuity[31] and restoration of the EZ was restricted to areas where the ELM was also fully recovered, suggesting that restoration of the ELM is closely associated with that of the EZ.[21,32] In retinal detachment eyes, preservation of the ELM postoperatively also seems to predict the subsequent restoration of the photoreceptor layer.[18]

Correlation: EZ Integrity & VA

Disruption or absence of the EZ has been studied extensively and has been ascribed to a variety of retinal conditions. Absence or disruption of this layer has been shown to correlate with visual outcomes and disease severity.[15] In non-neovascular (dry) AMD, disruption of the EZ has been associated with visual impairment and may occur with progression of drusen or regression of subretinal drusenoid deposits; however, only moderate correlation between disruption of outer retina substructures in the foveal central subfield and visual acuity was reported.[33-36] Moreover, retinal sensitivity in eyes with geographic atrophy was significantly higher in areas with an intact EZ.[37] In neovascular (wet) AMD, integrity of the EZ at baseline was reported as a positive prognostic factor for visual outcome following three monthly injections of intravitreal anti-vascular endothelium growth factor medication.[30] In DME eyes, EZ disruption at the fovea was reported as an important predictor of visual acuity.[38,39] Increase of serum VEGF and intercellular adhesion molecule-1 (ICAM-A) levels were associated with severity of diabetic retinopathy and EZ disruption, indicating that loss of photoreceptor integrity may be a predictor of visual acuity and progression of diabetic retinopathy.[39]

After vitrectomy for full-thickness macular holes, outer foveal photoreceptor disruptions are typically apparent on OCT, and are associated with cystic spaces in the outer retinal layers of the fovea. Over time, these disruptions get smaller, although often they do not disappear completely.[40,41] In one study, recovery of visual acuity after macular hole repair was better correlated with the area of EZ disruption than linear measurements of EZ disruption.[42] In eyes with ERM, preoperative disruptions of the EZ were also associated with poorer visual acuity results postoperatively.[24,26,43,44] Moreover, recovery of the EZ after ERM surgery is more likely to occur in areas with disrupted EZ but normal autofluorescence[25] which has also been associated with recovery of visual acuity.[25,45]

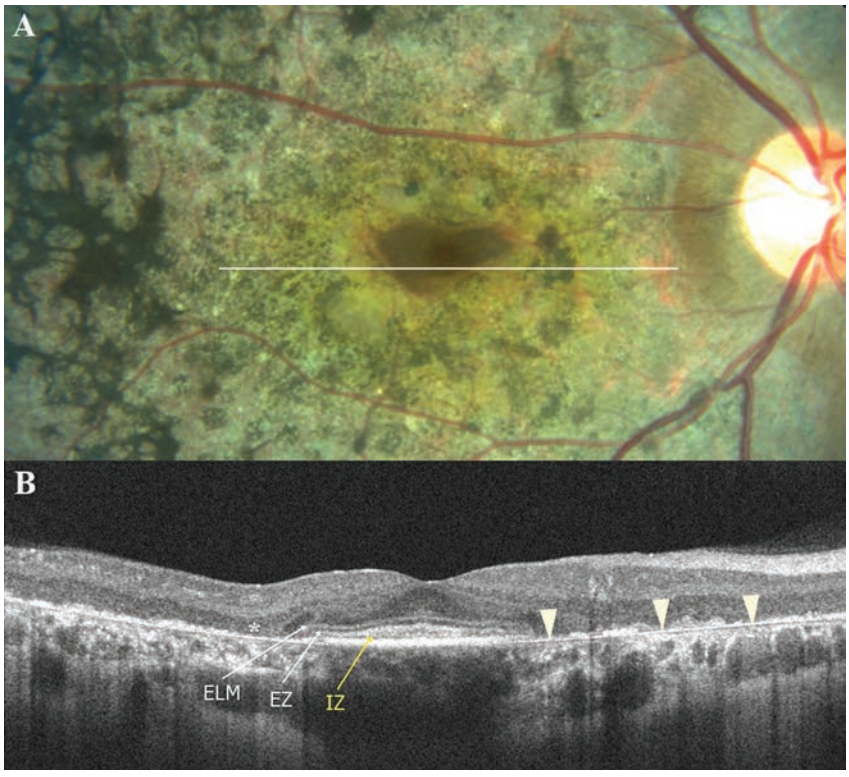

Figure 4. Right eye of a 38-year-old woman diagnosed with retinitis pigmentosa. Best-corrected visual acuity was 20/30. A) The color photo showed typical pigment retinal epithelium atrophic abnormalities sparing the central macula. B) Spectral-domain optical coherence tomography showed that there was an extensive perifoveal region where outer retina layers (stars) were absent and the RPE was irregular or absent (arrowheads). However, the outer retinal bands were preserved in the foveal region, which correlated with the relatively normal visual acuity. Arrows indicate the end points of the ELM, EZ and IZ, respectively.

Correlation: IZ Integrity & VA

The IZ is visible on OCT as a more subtle hyper-reflective line between the EZ and the RPE. A relationship between the postoperative status of IZ and visual acuity has been described for ERM,[24] RD[46] and macular hole.[22,31] In one report, integrity of the IZ was determined to be the most robust predictor of visual acuity outcome after primary RD repair.[46] After macular hole surgery, eyes with a distinct or irregular IZ had significantly better visual acuity outcomes compared with those with a disrupted or absent IZ line at the one-year visit follow-up, suggesting that restoration of the IZ line may indicate recovery of foveal photoreceptor microstructure.[30]

Masurement of ORL Thickness

Quantitative thickness analysis of the outer retinal layers has also been performed. The Outer Retinal Layer Thickness (ORLT)[37,47] can be measured between the inner edges of the outer plexiform layer and inner boundary of the RPE. In conditions where the outer plexiform layer cannot be delineated, as in some retinal dystrophies, ORLT can be represented by the value obtained from Retinal Thickness minus the Inner Retinal Layer Thickness. At the foveal center, since there are no inner retinal layers, IRLT would be zero and the foveal RT would be equal to the ORLT. In a comparative study featuring outer retinal changes on OCT, there was a significant difference in foveal ORLT between retinal dystrophy patients and normal age and gender-matched controls (92.2 ±34.2 µm versus 199.6 ±14.1 µm, respectively).[47]

In another study, Foveal Outer Segment/Pigment Epithelium Thickness (FOSPET) was defined as the distance between the inner border of the highly reflective line representing the EZ and the outer border of the RPE, measured at the center of the fovea. FOSPET was thought to represent a quantitative parameter of foveal photoreceptor loss on ultra-high-resolution OCT and was found to be significantly reduced in patients with retinitis pigmentosa compared to normal patients (52.8 ±18.3 µm vs 78.6 ±5.1 µm, respectively).[48]

Correlation: ORT Integrity & VA

Both ORLT and FOSPET significantly correlated with visual acuity in the studies listed above.[37,47,48] However, the EZ is often absent in advanced cases of retinal dystrophy, which may hamper the measurement of outer retinal thicknesses in these patients. In patients with RP, ORLT profiles averaged over 5 mm (macular) and 1.5 mm (fovea) showed more thinning of the macular ORLT than the foveal ORLT early in the disease process, which is consistent with the visual field losses beginning peripherally and then contracting concentrically later in the disease course of RP *(See Figure 4)*. In contrast, an early loss of foveal ORLT is observed in cone-rod and Stargardt disease with relative preservation of the macular ORLT, which is consistent with the central visual loss occurring earlier in these diseases.[47]

In summary, photoreceptor disruption can be visualized on OCT as loss of integrity or absence of the outer retinal layers: the ELM, EZ and IZ. Disruptions of these layers on OCT have been shown to correlate with visual acuity and retinal sensitivity in many retinal diseases. The higher speed and resolution of SD-OCT has improved the

accuracy and reproducibility of macular imaging and has allowed improved assessment of the integrity of the outer retina hyper-reflective bands. Further studies may enable new imaging and measurement protocols to enhance assessment of these outer retinal layers, which promises to greatly enhance the understanding of the relationship between morphologic changes in these layers and visual function in a variety of retinal diseases. REVIEW

Dr. Bonini Filho is a research fellow and Dr. Witkin is an assistant professor at the New England Eye Center, Tufts Medical Center, Boston. Dr. Filho is also on faculty at Capes Foundation at the Ministry of Education of Brazil in Brasilia, Brazil. *This work was supported in part by a Research to Prevent Blindness challenge grant to the NEEC/Department of Ophthalmology–Tufts University School of Medicine, National Institutes of Health contracts and Air Force Office of Scientific Research contracts.* *Dr. Witkin may be reached at: ajwitkin@gmail.com.*

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IOP Control: Know Your Surgical Options

The advent of MIGS may change the equation about what's the best initial therapy for patients with open-angle glaucoma.

Shakeel Shareef, MD, Rochester, N.Y., and Ike Ahmed, MD, Toronto

Just over a decade ago, treatment options in controlling intraocular pressure for patients with open-angle glaucoma were limited initially to topical medical therapy requiring daily multiple eye drops followed by laser trabeculoplasty. If the IOP lowering was still refractory despite maximal tolerated medical therapy or due to drug intolerance, they were then subjected to the other extreme of treatment: more effective but potentially sight-threatening filtration surgery with either trabeculectomy or tube shunt.

It has been estimated that approximately 60 percent of patients who seek treatment are on two or more medications with asymptomatic mild-to-moderate glaucoma. *(Ahmed I. MIGS: Unmet needs and opportunity assessment. Presented at: Ophthalmology Innovation Summit, Chicago, April 19, 2012)* As such, they do not demand a significant drop in IOP; nor does it seem reasonable to subject them to the short- and long-term risks associated with filtration surgery, including choroidal effusions, shallow anterior chamber, persistent corneal edema, bleb dysesthesia, blebitis and diplopia.[1] Therefore, surgical decision-making needs to take into account not only the desired percentage drop in IOP to retard glaucoma progression based upon the amount of optic nerve damage and visual field loss, but also the patient's quality of life including duration of the postoperative recovery period, follow-up office visits and resumption of daily activities.

Although trabeculectomy is the most commonly performed incisional surgical procedure,[3,4] attempts to provide safer alternatives have led to *ab externo,* blebless non-penetrating surgeries including viscocanalostomy and canaloplasty. This trend was noted in Medicare fee-for-service data from 1996 to 2001, with a 53-percent decline in trabeculectomy in patients without prior surgery, and doubling of trabeculoplasties from 2001 to 2004. Researchers have suggested that trends to lower IOP more aggressively in early glaucoma account for increased use of laser trabeculoplasty.[2] They also note that during this period, other than trabeculectomy, other fistulization procedures became very uncommon.

Pharmacotherapy is usually the primary initial treatment modality for OAG. However long-term, medical therapy is associated with non-compliance, especially in those taking multiple eye medications; potential ocular and systemic side effects; and financial hardship impacting a patient's overall quality of life.[3-5] One study evaluated the direct cumulative cost of *ab interno* surgical intervention vs. medical treatment of glaucoma projected over a six-year period in the Canadian Ontario Health Insurance Plan.[6] The study suggested a potential cost savings of those undergoing surgery ranging from $1,272.55 to $2,924.71 vs. patients taking two or three medications, respectively. This trend of surgical intervention as primary therapy for OAG was noted among patients undergoing argon laser trabeculoplasty.[7] More than 67 percent (n=93) were drug-free after an eight-year follow-up. Finally, the chronic use of topical medications results not only in ocular surface disease[5] but also, ironically, decreases the success rate of the other treatment arm, trabeculectomy.[8]

The advent of micro-invasive glaucoma surgery (MIGS), with Food and Drug Administration approval of Trabectome (Neomedix) in 2006 and iStent (Glaukos) in 2012, has created a

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way to bridge the gap between pharmacotherapy and filtration surgery *(See Figure 1)*. Additional devices are in clinical trials. This group of surgical procedures provides patients with mild-to-moderate OAG an alternative treatment option with a number of favorable characteristics:[9]

- MIGS represents not only a new trend in angle surgery but a shift from a traditional *ab externo* surgical approach to an *ab interno* one with the goal of re-establishing physiologic drainage of aqueous through the conventional outflow pathway via the trabecular meshwork, or enhanced outflow via the uveoscleral pathway or subconjuntival filtration. This approach has several advantages: sparing of the conjunctiva without compromising the option of undergoing a later *ab externo* incisional surgery should additional IOP control become necessary; surgical precision, given a direct view of the angle structures being manipulated; a stable anterior chamber with minimal impact on the post-refractive state; and ability to combine with cataract surgery via a common corneal incision.
- There is minimal trauma to the eye. Advantages include minimization of inflammation leading to a shortened postoperative recovery period and averting hypotony in the presence of a physiologic distal episcleral venous pressure resistance in the case of Schlemm's canal procedures.
- The efficacy of the procedure should be sufficient to reduce IOP to the desired target level and/or dependence upon glaucoma drugs. This has the advantage of eliminating the physical burden and associated side effects of administered multiple eye drops.
- MIGS is associated with a high safety profile, eliminating the short- and long-term vision-threatening complications associated with filtration surgery as noted above. This also forms the basis for earlier surgical intervention in the glaucoma disease spectrum.

Surgical Decision Making As a Function of Glaucoma Severity

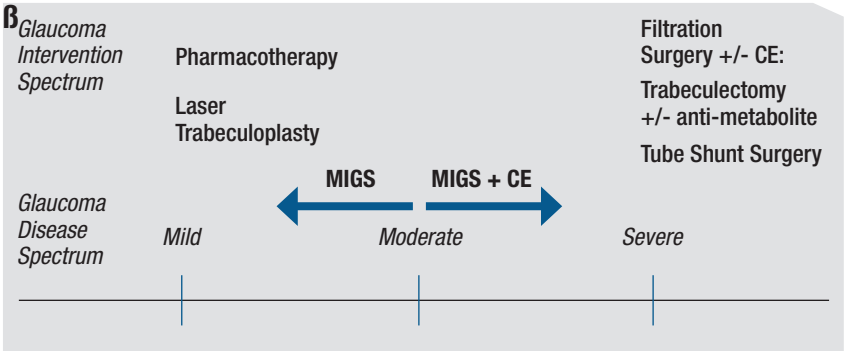

Figure 1: MIGS = Micro-invasive Glaucoma Surgery; CE = Cataract Extraction

- Rapid recovery results in minimal disruption in the patient's quality of life with resumption of daily activities in a relatively short period of time.

New Considerations

Surgeons who wish to embrace this new class of surgeries face two requirements: Not only is there a need to become familiar with angle anatomy in the office setting and for preop planning,[11] but also the key to successful angle surgery will be acquisition and mastering of a new skill set—intraoperative direct gonioscopy.[10] Surgical microscope and patient head positioning with increased working distance can initially pose a challenge in this setup versus traditional eye surgery performed in a supine position. Some other variables to consider when planning to perform MIGS include: the selection of an appropriate surgical goniolens to ensure good visualization of angle structures; globe stability, particularly with topical anesthesia to counter involuntary eye movements and avoid intraocular complications; and accessibility of surgical instruments via the peripheral cornea.

What is the role of MIGS in surgical glaucoma management? MIGS is a work in progress. Randomized control trials are necessary to determine the efficacy of these angle surgeries in comparison to an established alternative to help in clinical decision-making.[4,9,11] Although trabeculecomy has been suggested as the gold standard comparison arm, this may not be appropriate when MIGS is meant to lower IOP modestly in those with mild-to-moderate glaucoma while avoiding complications associated with *ab externo* filtration surgery.[9] The appropriate comparative study arm such as perhaps laser trabeculoplasty, should have comparable IOP-lowering effect and parallel the safety and efficacy of MIGS.

To date, MIGS studies combined with cataract surgery versus cataract surgery alone have shown an overall decreased dependence by one to two medications.[13] Two-year data on iStent implantation combined with phacoemulsification versus cataract surgery shows not only a lowering but also maintenance of IOP <21 mmHg on no medications with one iStent vs. control by 53 percent vs. 44 percent, respectively.[14] Additionally, the use of multiple iStents (two or three) resulted in a mean IOP < 15 mmHg with a 74 percent decrease in the mean number of drugs (from 2.7 to 0.7) at one year.[15]

This class of angle surgeries is welcome not only from the patient's perspective with respect to safety and quicker recovery but also from the surgeon's standpoint in decreasing the number of planned and unplanned

(continued on page 105)

Get the Eye Ready For LASIK Surgery

As the most powerful refracting element of the eye, the air/tear interface deserves a lot of preoperative attention, surgeons say.

Walter Bethke, Managing Editor

American businessman and wit Coleman Cox once wrote, "I'm a great believer in luck; the harder I work, the more luck I have." This also applies to a surgeon's probability of avoiding an unsatisfactory LASIK outcome. Experts say that the harder you work ahead of time getting the patient's ocular surface as pristine as possible, the higher your probability of avoiding problems postop. Here, several refractive surgeons share their methods for rehabilitating patients' ocular surfaces preop.

Catching the Problem

Assessing the extent of a patient's ocular surface issues will point you toward potential solutions, surgeons say.

"The ocular surface is very important in refractive surgery," says Sioux Falls, S.D., surgeon Vance Thompson. "The air/tear interface is the most powerful refracting element of the eye, and if it's deficient due to aqueous deficiency or is breaking up early due to meibomian gland dysfunction, it will affect our laser vision correction results. In our clinic, every patient has dry eye until proven otherwise."

A good patient history is an important aspect of the diagnosis. "I want to find out anything that might lead me to believe the patient could develop dry eye," explains Norfolk, Va., ophthalmologist Elizabeth Yeu. "So, I look for any risk factors such as contact lens intolerance, an erratic sleep schedule, prolonged hours spent on computer devices and even seasonal or perennial allergies. Age is also a factor. We also look for comorbidities and ask what medications they're on. Younger patients—especially those telling me that they're dry—who disclose the use of psychotropic medications, sleep aids or anxiolytics raise my index of suspicion for how aggressively I need to treat for potential dry-eye disease in the postop period."

Working in tandem with the history are the results of a thorough exam. "I look at the tear meniscus, fluorescein staining and will occasionally do rose bengal staining if it looks severe and the conjunctiva looks very dry," says Aurora, Colo., surgeon Rich Davidson, medical director of the faculty ophthalmology practice and vice chair for quality and clinical affairs at the University of Colorado Hospital Eye Center. "Then, looking at the lids themselves is important. It's common for patients to get pigeonholed as dry-eye sufferers but sometimes, when you really look at them, you find they may have floppy eyelids or lower-lid laxity instead. So, it's important to look at the lid position and make sure there's no lagophthalmos or any type of exposure that can result in ocular surface issues.

"We then look at the ocular surface itself," Dr. Davidson continues. "It's important to ascertain if patients have any meibomian gland disease. If they have such elements as crusting of the lashes or inspissated glands, that will help steer us in a certain direction. Also, depending on the severity of the ocular surface disease, it can even affect the diagnostic tests we do. If a patient has a cornea that's really dry, it'll affect our keratometry reading and our topography. I'll do some cursory evaluations just to tell them whether I think they're a candidate or not, but I won't take any measurements for planning the actual surgery until the ocular surface has improved."

Dr. Thompson says you can sometimes catch ocular surface problems

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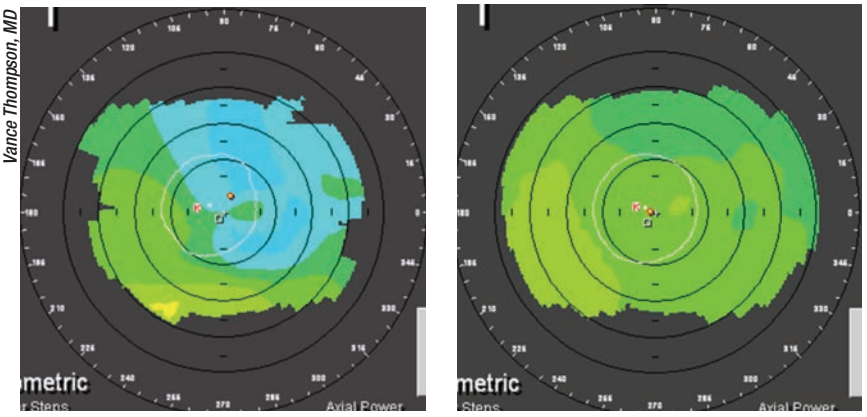
by noting how well the patient reads the Snellen chart. "When people concentrate, their blink reflex can go down 30 percent," he says. "So, if the patient finds that the chart is clear, gets blurry, but then clears with a blink, we already know that there are tear-film issues present, and that we're going to want to normalize them." In addition to the tests already mentioned, Dr. Thompson plans to add LipiView to his practice to help catch patients with problematic ocular surfaces.

Finally, Dr. Yeu likes to gauge the patient's risk for dry-eye problems based on how much tissue is going to be removed. "I look at the actual refraction," she explains. "This is because it appears that the higher the error being corrected the greater the risk of developing ocular surface disease. This appears to be related to the difference in the new contour of the cornea that could potentially lead to instability in the patient's tear film."



This patient's topography showed irregularity in the image along with an irregularity index of 4.2 at the 3-mm zone (left). After a good blink, however, the topography normalized and the irregularity index changed to 1.5 D at the 3.0-mm zone (right).

Proper Treatment

Surgeons will adjust their therapy based on the cause and severity of the ocular surface problem.

"For patients with aqueous deficiency, our approach depends on the level of the deficiency," says Dr. Thompson. "If it's mild, we'll just use lubricants and potentially Restasis. If it's moderate to severe, however, we'll start by using punctal plugs, lubricants and Restasis. We'll also inquire about their home humidity. If it's very dry, then we'll ask them to turn it up. If their home isn't conducive to that, we'll ask them to get a humidifier. We ask if they're using a ceiling fan, which can contribute to dryness. We also talk to them about computer use or if they're a truck driver, because both situations require concentration, and blink reflexes go down when you concentrate. We'll talk to them about the importance of blinking and using tear supplements in those situations."

Dr. Yeu likes to work in oral supplementation. "We'll start with artificial tears, and if they have more telangiectasia and poor mucin quality, I'll move down the list and add oral omega 3 fatty acids, with or without the addition of an oral tetracycline," she explains. "In this way, I'm tailoring the treatment for what seems to make up the majority of the disease. Everyone deserves oral supplementation, especially anyone who might be at risk for dry eye postop, but especially if they do have some form of staining. Once you start seeing corneal epithelial breakdown, however, it's more than just revitalization. In that case, you're actually having apoptosis and epitheliopathy. Any patient like that deserves to be on Restasis for the long haul, and should at least have a chronic course of it preop to prepare for the postop period. I will also use topical steroids to try to stabilize the surface as soon as possible and stop the destructive cycle of whatever's causing the ocular surface breakdown. For mild to moderate thinning, I'll start with something in the range of Lotemax or FML."

In cases of meibomian gland dysfunction or lid problems, Dr. Davidson says he first rules out any anatomic lid abnormalities that might need to be corrected surgically. If those aren't present, he'll address the MGD. "We do the normal things like lid scrubs and warm compresses," he says. "If it's really inflamed, I'll start the patient on a combination antibiotic/steroid drop such as Tobradex. I think this really helps kill the bacteria on the lid and reduce the ocular surface inflammation. Doxycycline can be helpful, as well." Surgeons say that the LipiFlow treatment can also be helpful in some patients with MGD.

When gauging the effects of treatment, most surgeons like to see an absence of staining before moving forward with refractive surgery. "I'll give patients three to four weeks before I bring them back," says Dr. Davidson. "If things start to look better at the three to four week visit, I'll want to get at least one other consistent reading two weeks after that. Then, I'll do the surgery two weeks after that final measurement visit. So we're looking at a two-month process to get things resolved, on average. At the follow-up visits, if a patient is symptomatic I want to reduce his symptoms, and I don't want to see any staining, or at least markedly reduced staining. I'm looking for less lid inflammation, and I want to see the meibomian glands cleared up, if it's MGD. If it's aqueous-deficient dry eye, I want to make sure the patient's tear meniscus and cornea are looking better." REVIEW


The Pros and Cons of Preservatives

Preservatives such as BAK can be hard on your patients' corneas, but the alternatives sometimes raise practical concerns.

Malik Y. Kahook, MD, Aurora, Colo.

As you know, preservatives are a mixed blessing. The Food and Drug Administration requires that multidose bottles of medications include a preservative to kill bacteria and fungi that may contaminate the fluid in the bottle; as a result, for several decades our medications have contained preservatives specifically designed to keep the medications sterile during patient use and the life cycle of the bottle.

Unfortunately, while these preservatives are very effective against pathogens, they were not specifically designed to be friendly to the eye. They tend to consist of harsh chemicals that stop bacterial growth but also harm corneal and conjunctival epithelial cells. After chronic use of medications containing these preservatives, the deleterious effect on anterior segment epithelial cells leads to poor production and maintenance of the tear film, resulting in problems such as dry-eye syndrome. Long-term use can also roughen the surface of the cornea and conjunctiva because of loss of epithelium and inflammation, which can then lead to foreign body sensation and deteriorating vision. So there's a good and bad side to preservatives—especially the older, soap-like preservatives in the quaternary ammonium family of chemicals, which include benzalkonium chloride, or BAK. These preservatives do a good job of protecting the multidose bottle of medication, but they have the potential for long-term deleterious effects on the eye.

Alternative Options

Partly for that reason, we've seen an influx of several new types of preservatives into glaucoma medications over the past few years. Some of these preservatives are well-known in the dry-eye world. For example, Polyquad (Polyquaternium-1) has historically been used in artificial tears; it was originally formulated by Alcon to replace BAK in contact lens solutions. (BAK concentrates in contact lenses during lens storage; Polyquad does not.)

Now Polyquad has found its way into several glaucoma formulations that are available outside the United States, including Travatan and a product that combines travaprost and timolol. Like BAK, Polyquad falls into the soap-like quaternary ammonium preservative family, but it's a much larger molecule. As a result, it's not internalized by the epithelial cells on the eye, so it doesn't cause the kind of toxicity that BAK causes. At the same time, it's just as effective against pathogens, altering the stability of the bacteria's cell wall, so it kills the pathogens but does not kill the epithelial cells.

Other new preservatives include SofZia, an ionic-buffered preservative that's found in Travatan-Z, and Purite, a preservative that breaks down upon contact with the air, found in Alphagan P. They act in a much different way than the quaternary ammonium compounds; Purite oxidizes microbial cellular components, but has no significant effect on human ocular tissues. SofZia causes oxidative damage and subsequent death in bacteria that lack the enzymes cytochrome oxidase or catalase. (Human cells possess these enzymes and are thus not similarly harmed.) These preservatives are

This article has no commercial sponsorship.

effective enough to pass all of the FDA requirements for preserving a multidose bottle of medication, and it's been proven both in cell cultures and clinical trials that they are much gentler to the eye than alternatives such as BAK.

Another approach to avoiding contamination is to eliminate the need for a preservative via single-dose packaging. Some medications are now available in unit doses that are intended to be used once and then thrown away; this eliminates any concern about contamination of the contents after the unit has been opened. There has been a significant increase in the number of medications available in this type of format, including Cosopt Preservative Free and Timolol Preservative Free.

Why Is BAK Still So Popular?

The existence of these alternatives raises an important question: If these alternative preservatives are equally viable options, why don't more medications use them instead of relying on BAK? There are a number of reasons, ranging from a few positive side effects of BAK to a lack of universal damage to patient convenience. Despite the downsides of BAK, manufacturers, ophthalmologists and patients all have reasons for not rushing to replace it.

For example, in some situations, BAK does have a positive effect. When the first medications for the treatment of glaucoma appeared, such as beta-blockers, it was understood that the penetration of these medications into the eye would be enhanced by something like BAK. BAK affects the cell-to-cell junctions on the cornea and conjunctiva, allowing more of the active ingredient to get into the eye. This results in a greater concentration of the drug in the aqueous humor, enhancing its effect. This effect encouraged companies to keep BAK in the drug formulation.

Many companies still view this as a positive and a reason to continue using BAK, despite the drawbacks associated with it. Consider the recent introduction of the higher-BAK formulation of Lumigan. The concentration of the active ingredient has been lowered from 0.03% to 0.01%, but the amount of BAK in the solution has been quadrupled. This allows more of the drug to get into the eye, even though the product has a lower concentration of the active ingredient.

It's possible that after some amount of exposure to a preservative like BAK the damage will become irreversible; we simply don't know. That's all the more reason to keep a close eye on your patients' corneas.

This same rationale explains different levels of BAK in other products. For example, Vigamox (moxifloxacin) is preservative-free while Zymar (gatifloxacin) contains BAK. That makes sense because moxifloxacin has been shown to penetrate the cornea better than some of the other fluoroquinolones, including gatifloxacin.[1-3] The BAK in some multidose antibiotic formulations, in addition to acting as a preservative, enhances the penetration of the active ingredient into the eye.

Another reason BAK remains widely used is that the alternative preservatives don't always meet all countries' preservative requirements, which in some cases are more stringent than those in the United States. Since most companies are global in their reach, they choose preservatives that can be used anywhere around the globe, and that's true of BAK. Another factor discouraging companies from venturing into milder alternative preservatives is the cost of developing them. Creating new preservatives and getting them through the different approval processes takes money and effort. BAK, in contrast, is familiar and inexpensive, so companies continue to opt for using it.

Ophthalmologists also have not been rushing to move patients off of BAK-preserved drops, for several reasons. For one thing, it's extremely difficult to clinically quantify the differences between the version of a given drug that incorporates BAK and the version that doesn't. We don't have very sensitive methods for measuring and comparing the differences that might exist. Basic science research shows that a quaternary ammonium compound like BAK can have an effect on the cells on the eye; but when you try to measure that effect clinically, it's not always measurable and reproducible. That lack of clinical differentiation helps to keep the message from getting through to physicians: Patients who are being treated with chronic drops might very well benefit from avoiding BAK-preserved drops.

Another reason BAK remains widely used is that the problems it may cause are not seen in every patient. Many of our patients who have been using BAK-preserved drops for multiple years seem to tolerate it very well, so there's little incentive to switch them over to a drug that's alternatively preserved. In addition, the reality is that when it comes to treating glaucoma, intraocular pressure con-

trol is king. If we're seeing the IOP reduction that we want to see, and the patient is stable and not exhibiting any noticeable signs of a problem with BAK, we typically don't change the medication.

Last but not least, drugs that do use alternative preservatives have a few downsides from the patient's perspective. First of all, these drugs are not generics, so they force the patient to pay brand-name prices. Also, the packaging of the single-dose, nonpreserved formulations may cause practical problems for some patients. The unit doses are small, and I've had patients complain about misplacing some of them and not being able to find them. Some patients with physical limitations have a hard time using them. Furthermore, in an attempt to save money, some patients will attempt to save an opened single-dose unit in order to get a second or third dose out of it later, which may lead to contamination of the contents, defeating the purpose of the single-dose packaging.

Working With What We've Got

Given that we're likely to have patients using drops that contain BAK for some time to come, here are a few strategies that may help you minimize the problems that can accompany its use:

• ***Examine your patients carefully for signs of ocular surface damage***. Because we tend to be so focused on IOP, I advocate for examining our patients carefully to see what the ocular surface looks like. If a patient has significant ocular surface disease and is showing signs of epithelial breakdown, that's a patient I would switch from a BAK-preserved drop to an alternatively preserved or nonpreserved drop. It's important to take that added stress on the ocular surface out of the equation. After a few weeks I would bring the patient back in for an IOP check and re-evaluation of tear breakup time and surface staining.

In our practice, when we note that a patient is having this problem and switch him to a different drop, we frequently see a measurable improvement in the ocular surface status. If the cornea doesn't improve, it may require a more intensive treatment for dry eye like Restasis or a mild steroid.

• ***Remember that it may take weeks to reverse BAK-related corneal damage.*** We don't know how long it will take a given eye to recover once the patient is switched to a drop without BAK. We conducted a study in which it took eight weeks to see the reversal of the effects on the eye. (The difference was measurable.) At the same time, other studies have found that it took 12 weeks to see a measureable change in tear-film breakup time and staining of the corneal epithelium. Either way, it's clear that it may take multiple weeks before the patient notices any difference and before the physician can actually measure any improvement.

It's also possible that after some amount of exposure to a preservative like BAK the damage will become irreversible; we simply don't know. That's all the more reason to keep a close eye on your patients' corneas, so none of them end up with potentially irreversible damage.

• ***If a patient will be undergoing glaucoma surgery such as a trabeculectomy, consider stopping BAK-preserved drops before the surgery.*** It's a good idea to do this when a glaucoma patient has a very hyperemic and inflamed conjunctiva with evidence of ocular surface disease. In this situation, it's not unusual for us to stop all glaucoma drops (if possible) before doing the filtration surgery, and place the patient on mild steroids for a week or two in order to reduce the conjunctival inflammation.

Remaining Vigilant

Of course, the use of topical drops comes with many problems besides preservative toxicity, among them the well-known issue of patient compliance. So it's likely that at some point in the future we'll be getting away from the use of topical drops as a mainstay of glaucoma treatment, eliminating concerns about preservative toxicity. Options such as laser trabeculoplasty, minimally invasive glaucoma surgeries (MIGS), new long-term drug delivery depots and other developments will hopefully allow us to move away from relying so heavily on drops.

Unfortunately, developments that might lead to eliminating drops have been slow in coming, and the regulatory approval process is long. Given those realities, topical therapies will probably be a key part our glaucoma treatments for years to come, and that means we'll be dealing with the issues surrounding preservatives such as BAK for the foreseeable future. But as long as we stay on the lookout for signs of trouble, and switch patients to alternatives when necessary, the benefits of drops should continue to outweigh the pitfalls. REVIEW

Dr. Kahook is a consultant for Alcon and Allergan and has patent interests with Abbott Medical Optics, Oasis, New World Medical, Glaukos, ClarVista and Mile High Ophthalmics.

1. Chung JL, Lim EH, Song SW, Kim BY, Lee JH, Mah FS, Seo KY. Comparative intraocular penetration of 4 fluoroquinolones after topical instillation. Cornea 2013;32:7:1046-51.
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3. Holland EJ, Lane SS, Kim T, Raizman M, Dunn S. Ocular penetration and pharmacokinetics of topical gatifloxacin 0.3% and moxifloxacin 0.5% ophthalmic solutions after keratoplasty. Cornea 2008;27:3:314-9. doi: 10.1097/ICO.0b013e3181608561.

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IOP Changes After Refractive Surgery

California doctors utilized a Scottish database of patients receiving refractive surgery to describe the factors that influence intraocular pressure change after myopic and hyperopic LASIK and photorefractive keratectomy. Myopic procedures lowered measured IOP more than hyperopic procedures; this decrease was proportional to the amount of refractive error corrected. Independent of the refractive error correction, the creation of the lamellar LASIK flap decreased IOP by 0.94 mmHg. The doctors also developed a best-fit model for IOP change that may allow better interpretation of post-laser vision correction IOP values.

The doctors searched the Optical Express database for all patients undergoing primary PRK or LASIK with a refractive target of emmetropia between January 1, 2008 and October 5, 2011. Data were extracted on procedure specifics; preoperative central corneal thickness; IOP (using noncontact tonometry); manifest refraction; average keratometry; age; gender; and postoperative IOP at one week, one month and three months. A linear mixed methods model was used for data analysis, and the main outcome measure was any change between preoperative IOP and IOP up to one month postop.

A total of 174,666 eyes of 91,204 patients were analyzed. Hyperopic corrections experienced a smaller IOP decrease than myopic corrections for both PRK and LASIK ($p<0.0001$). Patients who underwent LASIK had a 0.94 mmHg greater IOP decrease than patients who underwent PRK (95 percent confidence interval, 0.89 to 0.98; $p<0.0001$), reflecting the effect of the lamellar flap. The decrease in IOP was linearly related to preoperative manifest spherical equivalent for myopic PRK and LASK ($p<0.0001$), weakly correlated with preoperative MSE after hyperopic LASIK and not related to preoperative MSE after hyperopic PRK. The single greatest predictor of IOP change was preoperative IOP across all corrections. By using the available data, a model was constructed to predict postop IOP change at one month; this was able to explain 42 percent of the IOP change after myopic LASIK, 34 percent of the change after myopic PRK, 25 percent of the change after hyperopic LASIK and 16 percent of the change after hyperopic PRK.

Ophthalmology 2015;122:471-479.
Schallhorn J, Schallhorn S, Ou Y.

Ologen vs. MMC: Wound-healing Modulators in Trabeculectomy

A 12-month retrospective review of outcomes between patients undergoing trabeculectomy with an Ex-PRESS mini glaucoma device using mitomycin-C and those undergoing the same procedure using a subconjunctival collagen matrix device (Ologen) suggests that Ologen provides similar rates of surgical success.

All patients underwent a trabeculectomy using an Ex-PRESS shunt. A total of 49 eyes of 37 patients received Ologen and 50 eyes of 48 patients received MMC. Postoperative data were reviewed over 12 months. Outcomes included mean intraocular pressure, rate of success in achieving target IOP (with and without antiglaucoma medication), number of medications used and rates of complications/reoperations.

The mean preoperative IOP was 24.98 mmHg for the MMC group and 23.94 mmHg for the Ologen group ($p=0.3$). At 12 months postop, the mean IOP was 12.1 mmHg for the MMC group and 13.12 mmHg for the Ologen group ($p=0.34$). At 12 months, the rate of achieving an IOP ≤21 mmHg off medications (unqualified success) was 84 percent for the MMC group and 86 percent for the Ologen group. There was no statistically significant difference between the groups for the rates of achieving a specified postop IOP either with (qualified success) or without medications. There was no statistically significant difference between the two groups in the mean number of postop medications required. Both groups had similar rates of complications and

one patient in the MMC group lost light perception after a suprachoroidal hemorrhage.

J Glaucoma 2014;23:649-652.
Johnson M, Sarkisian S.

Choroidal Thickness in Pseudophakic CME

Polish researchers studying the subfoveal choroidal thickness in the acute symptomatic cystoid macular edema patient after uncomplicated cataract surgery, using enhanced depth imaging optical coherence tomography, discovered that the choroid in eyes with CME was thinner than in fellow eyes, suggesting that reduced choroidal blood flow in the choriocapillaris is also a possible factor in CME.

The mean subfoveal choroidal thickness measured in 28 eyes with CME was 229.14 ±62.61 µm and 280.82 ±79.09 µm in fellow eyes. At any point (subfoveal and 1.5 mm nasal; 1.5 mm temporal; 1.5 mm inferior; 1.5 mm superior from the center of the fovea) the choroidal thickness of the affected eye was significantly ($p<0.01$) thinner than that of the fellow eye.

Retina 2015;35:136-140.
Odrobina D, Laudanska-Olszewska I.

A Retrospective Analysis of Change in IOP after DSAEK

Researchers have concluded that the occurrence of postoperative IOP elevation is common after Descemet stripping automated endothelial keratoplasty, and that a significant number of patients will need IOP-lowering treatment. Pseudoexfoliation syndrome and PXF glaucoma are serious risk factors for an increased IOP after DSAEK. In most cases, IOP will remain controlled with conservative management, but some patients will require glaucoma surgery.

This study was a retrospective assessment of 211 consecutive DSAEK cases (176 patients), with a minimum one-year follow-up, performed by one surgeon between January 2007 and November 2010. Salient patient characteristics, IOP and type of anti-glaucoma treatment registered in postoperative visits up to 36 months were extracted from patient medical records. IOP elevation and its associations with glaucoma, PXF and a combination of the two were assessed using multivariate ordinal logit models.

Of the 211 eyes, 97 eyes (45 percent) showed at least one increase in IOP >25 mmHg after DSAEK. Of these 97 eyes, 17 eyes (17.5 percent) had a history of glaucoma alone; another 17 eyes (17.5 percent) had a history of glaucoma combined with PXF; 10 eyes (9.7 percent) had PXF alone; and 53 eyes (54.6 percent) were steroid responders only. To control elevated IOP, steroid reduction alone was performed in six eyes (6.2 percent) and IOP-lowering medication as the only measure was performed in 26 eyes (26.8 percent). In 46 eyes (47.4 percent), steroids were reduced in combination with IOP-lowering medication, while 16 eyes (16.5 percent) required surgery. In three eyes (3.1 percent), no action was required. The presence of PXF (odds ratio: 1.71; 95 percent CI, 0.62 to 2.81; $p=0.002$) and PXF glaucoma (r: 1.14; 95 percent CI, 0.06 to 2.21; $p=0.038$) required a more intensive IOP-lowering management than patients without PXF with IOP problems.

Cornea 2015;34:271-274.
Müller L, Kaufmann C, Bachmann L, et al.

Aflibercept in Recurrent or Persistent Neovascular AMD

California researchers retrospectively evaluated the six-month and one-year visual and anatomic outcomes of every-eight-weeks intravitreal aflibercept injections in patients with ranibizumab- or bevacizumab-resistant neovascular age-related macular degeneration, finding that more than half of their patients had an excellent anatomic response with injections every eight weeks. However, with longer follow-up to one year, symptoms tended to recur and a third of eyes needed monthly aflibercept injections.

The study cohort consisted of patients with resistance (multiple recurrences or persistent exudation) to every-four-weeks ranibizumab or bevacizumab that were switched to q8w aflibercept. Sixty-three eyes of 58 patients had a median of 13 (interquartile range, seven to 22) previous anti-VEGF injections. At six months after changing to aflibercept, 60.3 percent of eyes were completely dry, which was maintained up to one year. The median maximum retinal thickness improved from 355 µm to 269 µm at six months ($p<0.0001$) and 248 µm at one year ($p<0.0001$). There was no significant improvement in visual acuity at six months ($p=0.2559$) and one year follow-up ($p=0.1081$) compared with baseline. The mean difference in visual acuity compared to baseline at six months was -0.05 logMAR (+2.5 letters) and 0.04 logMAR at one year (-2 letters).

Am J Ophthalmol 2015;159:426-426.
Arcinue C, Feiyan M, Barteselli G, Sharpsten L, et al.

Genetic Type May Influence Treatment Response to AMD

An analysis of current literature evaluating the pharmacogenetics of treatment response in patients with neovascular age-related macular degeneration suggests that a patient's genetic background may influence individual response to treatment with anti-VEGF agents. Multiple studies demonstrate associations between various genotypes and response to intravitreal anti-VEGF injections. Lower-risk genotypes of the *CFH*, *ARMS2*, *HTRA1* and *VEGF-A* genes may be associated with improved visual outcomes. Additionally, frequency of injections may be associated with certain genotypes.

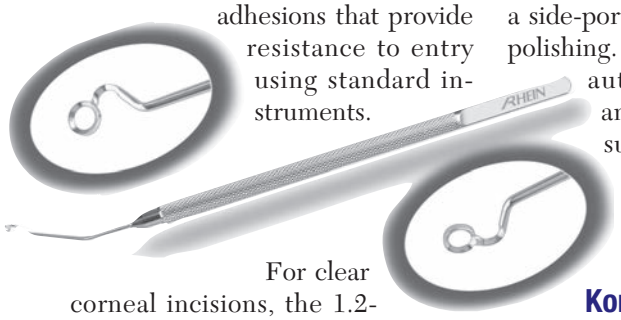
Retina 2015;35:381-391.
Dedania V, Grob S, Zhang K, Bakri S.

New Tools Ease Femto Surgery, Capsule Polishing

Here are two new surgical instruments offerings from Rhein Medical.

• The Folden Femto Dissector is a single instrument designed for smooth opening of all femtosecond laser-created corneal incisions during cataract surgery. Developed in coordination with David Folden, MD, the double-ended instrument measures 0.7 mm at one end and 1.2 mm at the other.

The polished, semi-blunted leading tip allows for "scoring" of the epithelium and provides easy, glided entry into the femtosecond laser-created corneal incision. The unique sharp-edge design cleanly separates residual tissue bridges and stromal adhesions that provide resistance to entry using standard instruments.



For clear corneal incisions, the 1.2-mm end provides easy entry into standard small incisions as well as sub-2.0 mm micro-incisions. The 0.7-mm end provides adequate clearance for entry into the paracentesis. Arcuate incisions for astigmatism are opened quickly and cleanly down to their base without risk of perforation. The polished semi-blunted leading tip glides smoothly along the base of the arcuate incision, while the sharp edge provides smooth opening of stromal tissue bridges and maintains clean epithelial edges. Fewer surface abrasions results in less foreign body sensation and improved patient comfort postoperatively, the company says.

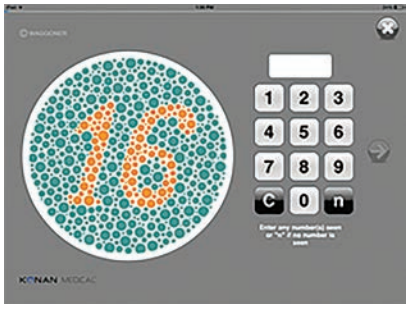
• The Younger 360 Degree Capsule Polisher features a special angulated shaft that allows quick and easy polishing of both anterior and posterior capsules with one instrument.

Rhein says the unique angulation eliminates the need for using two instruments or using one instrument but having to exit and enter through a side-port incision to complete the polishing. The polisher is reusable, autoclaveable, U.S.-made and available for a 30-day surgical evaluation without obligation. Call (727) 209-2244 for more information on either product.

Konan Debuts Military-Grade Color Vision Test App

Konan Medical has released ColorDx Pro, a military-grade, extended color-vision diagnostics app for iPad. ColorDx Pro is available from iTunes for an introductory price of $699.99.

ColorDx is routinely used at the



Naval Aerospace Medical Institute for qualifying naval aviators and the FAA has recommended its use for qualifying civil aviation pilots. ColorDx has other test strategies for vocational color vision assessment that are also self-administered and automatically scored.

ColorDx apps test for both genetic (protan/deutan) and acquired (tritan) color-vision deficiencies and are used extensively in clinical practices to aid decision making for a variety of neurological and ocular disorders, or substance toxicities that can cause a tritan deficiency.

ColorDx is also available for Android tablets, Windows and Mac computers as well as online and print. For information, visit konanmedical.com/colordx.

Coburn's HOM-700 Surgical Microscope Streamlines Flow

Coburn Technologies introduces its latest addition to its diagnostic product line, the HOM-700 Surgi-

This article has no commercial sponsorship.

cal Microscope. Coburn says the HOM-700 streamlines all surgical workflow and maximizes surgery efficiency. This state-of-the-art product has a smooth system handling and superior performance with an optical system that is unequaled.

It has high-resolution imaging for improved visuals and enhanced ergonomics to improve comfort and performance.

Among its key features:

• an optical system that provides enhanced images even in low-intensity illumination situations, enabling sharp, crisp, high-resolution 3D observations;

• fatigue-free surgery with its 10 x 21 mm visual field;

• an optimized halogen illumination system that reduces shadowing in deep cavities, provides high-quality illumination and prevents heating and UV transmission;

• optimized red reflex allows instant and perfectly stable red reflex from the illuminator providing the optimum brightness and observation angle;

• foot pedal control for hands-free surgery;

• a built-in, rotatable 7-inch color TFT LCD control panel;

• two onboard lamps allow the lamp to be changed instantly without interruption;

• custom settings allow up to four surgeons' individual parameters to be saved and recalled effortlessly; and

• it's fully compatible with industry-leading peripheral lens systems.

For more information, visit coburntechnologies.com. REVIEW

REVIEW

Product Research News

Study of Artificial Tear Reveals Positive Effect on Dry-Eye Subjects

With still just one Food and Drug Administration-approved treatment for dry eye, researchers in the field continue to generate novel artificial tears with the hope of relieving patient symptoms and lessening signs of the disease. To date, emulsions are the latest and most innovative generation of dry eye therapy. Anionic oil-in-water nanoemulsions, while excellent vehicles for lipophilic drugs, have a poor retention time on the ocular surface. Cationic oil-in-water emulsions extend the benefits of anionic oil-in-water nanoemulsions by taking advantage of the negatively charged ocular surface, thus improving the residence time of the drop.

Recently, a single-center, open-label study was conducted to evaluate the efficacy of Retaine ophthalmic emulsion, a novel preservative-free artificial tear option, in patients diagnosed with dry eye. Retaine (marketed outside the United States as Cationorm, Santen, Osaka, Japan) is a proprietary, cationic oil-in-water nanoemulsion technology with novel bioadhesive properties.

In this Phase IV, two-visit study, 42 moderate to severe dry-eye subjects received one to two drops of Retaine b.i.d. for two weeks. Subjects were dispensed a diary with which they were to score their symptoms prior to each self-administered instillation (morning and night).

Following two weeks of dosing, study subjects demonstrated improvements in both signs and symptoms. At visit two, subjects had significantly less corneal fluorescein staining in the superior, central and the corneal sum regions. In the superior region, the mean score decreased from 2.2 to 1.93 (p=0.002) from visit one to visit two; in the central region, the mean score decreased from 1.25 to 0.95 (p=0.017); and in the corneal sum region, the mean score decreased from 5.55 to 4.95 (p=0.011). For all regions combined (i.e., the score of both corneal and conjunctival fluorescein staining), the mean score decreased from 9.36 to 8.67 (p=0.038). The reduction in central staining is clinically relevant, as the central cornea is critical to visual function *(Ousler III G, et al. IOVS 2007;48:ARVO E-Abstract 410)*, while the improvement in the sum of the corneal regions indicates a global treatment effect.[1-4]

Additionally, significant reductions were observed in three ocular symptoms. Reductions were observed in discomfort (2.55 on the first visit versus 1.95 on the second visit; p=0.0017); dryness (2.88 versus 2.02; p<0.001); and grittiness (1.40 versus 1.02; p=0.0217). Also of note, the overall reduction of all ocular symptoms (i.e., the scores for all five symptoms combined) was significant (8.71 on the first visit versus 6.67 on the second visit; p<0.001).

Tear-film instability is a key feature of dry eye, one traditionally assessed by tear-film breakup time. This study employed a video-based technology (OPI2.0, Ora Inc.) that standardizes the measurement of corneal exposure. Across the study population, corneal exposure was reduced by 40 percent on the second visit between the pre-dose and the post-dose time points (p=0.026), indicating that Retaine has the ability to provide immediate corneal coverage.

Dry-eye sufferers often complain of impaired visual function during everyday tasks like reading, using a computer and driving, and perhaps more specifically, while completing these activities at night. The impact of the study drug on visual function was assessed by testing corrected visual acuity degradation between blinks; the time at CVA (time to one-line loss of CVA) was 41-percent higher on the second visit than the first (p=0.0697). Improved visual function also correlated with improved quality of life. Study subjects reported a significant improvement in their ocular discomfort when they worked at a computer at night (1.67 on the first visit versus 1.38 on the second visit; p=0.044). Quality of life scores also decreased for reading at night, eye sight issues, watching television at night and driving at night.

In this two-week study, Retaine offered relief from both the signs and symptoms of dry-eye sufferers. The reduction in corneal exposure and in corneal fluorescein staining, coupled with the symptomatic relief and improvements in subject quality of life, equates to a product that provides total dry-eye relief.

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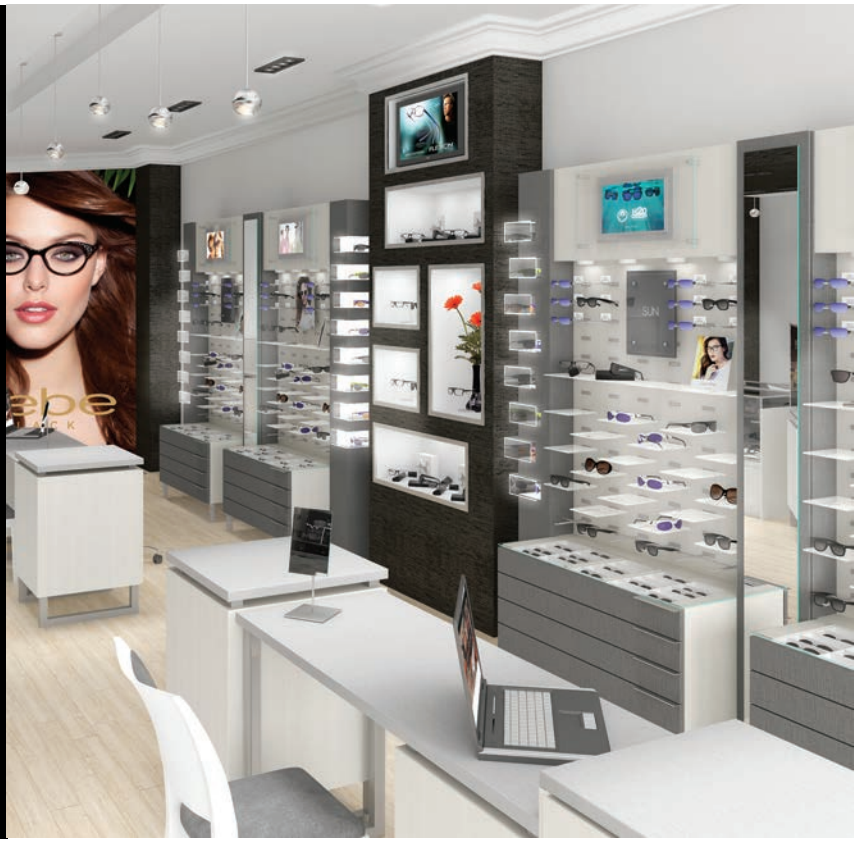

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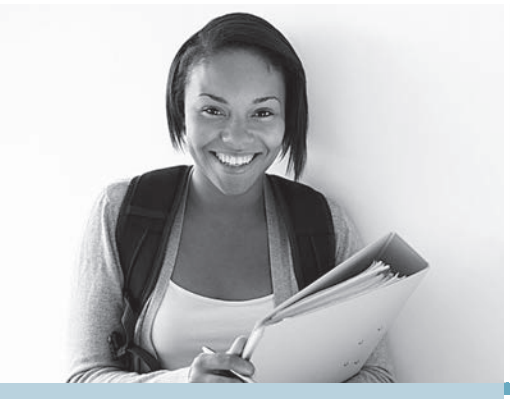

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A young infant is brought to Wills for evaluation of increased pigmentation and associated nodular lesions in her right eye.

Jinali Patel, MD, Carol Shields, MD, and Ralph Eagle, MD

Presentation

A 2-year-old Caucasian female presented for evaluation of increased pigmentation of her right iris. This was associated with nodular lesions in the same eye. Per the patient's parents, the darker iris color and iris lesions had been present since birth. However, the iris lesions appeared to be enlarging in size. On review of systems, there was no history of trauma, weight loss, poor feeding, abnormal bowel or bladder function, fever, rash or recent illness.

Medical History

The patient was otherwise healthy and with normal development. There was no relevant medical, ocular or surgical history. She was not taking medications. Family history was noncontributory.

Examination

Vital signs were within normal limits. Ocular examination demonstrated a visual acuity of fix and follow OU. Pupils were equal and reactive to light without a relative afferent pupillary defect. Extraocular motility was full bilaterally and intraocular pressures were normal by finger tension.

External examination revealed normal eyelids with no evidence of pigmentation, edema or ptosis. Heterochromia was detected with a dark brown right iris and light brown left iris *(See Figure 1)*. The left eye was normal anteriorly and funduscopically.

Evaluation of the right eye disclosed diffuse ocular melanocytosis involving the sclera and iris, but sparing the 1 o'clock meridian. The iris crypts were camouflaged with pigment. Additionally, there were multiple, large iris pigment epithelium (IPE) cysts at the pupillary margin and within the mid-zonal region. Funduscopically, diffuse choroidal melanocytosis was noted, with sparing from 10 o'clock to 2 o'clock *(See Figure 2)*. There was no evidence of tumor, orange pigment or subretinal fluid. Fluorescein angiography demonstrated a mildly "silent" choroid in the right eye from the extensive pigmentation.

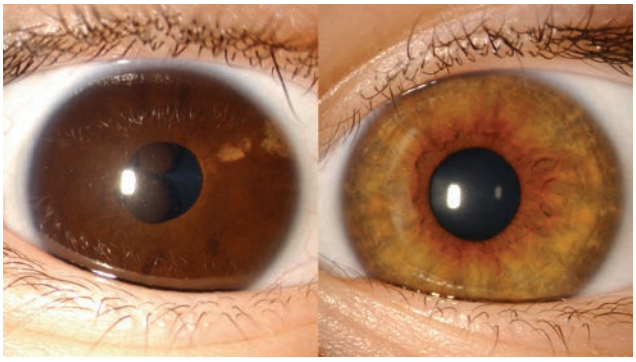

Figure 1. Heterochromia from iris melanocytosis OD with sparing from 1 o'clock to 2 o'clock in comparison to the normally pigmented OS. Also note iris pigment epithelium cysts at the pupillary margin OD.

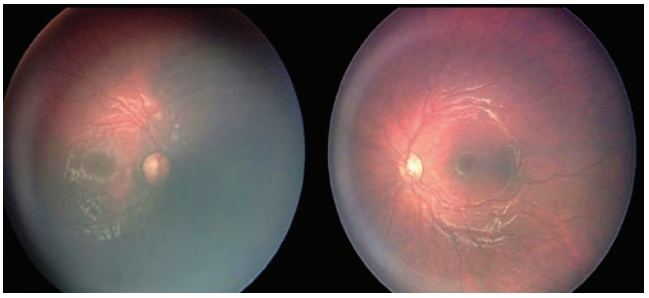

Figure 2. Fundus photos demonstrate sectoral melanocytosis of the choroid OD, with sparing from 10 o'clock to 2 o'clock in comparison to the normal fundus OS.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 86

Diagnosis, Workup and Treatment

Given the patient's clinical findings, she was diagnosed with ocular melanocytosis and recommended to have twice-yearly dilated fundoscopic examinations to monitor for the occurrence of melanoma. Over the next three years, examination findings remained stable. By 6 years of age, the IPE cysts had enlarged with iridocorneal touch and shallowing of the anterior chamber. Ultrasound biomicroscopy revealed numerous IPE cysts involving the pupillary margin, mid-zonal region and iridociliary sulcus junction as well as thickening of the ciliary body along the 6 and 9 o'clock meridians. The two largest cysts touching the endothelium were reduced using fine needle aspiration. Cytopathologic examination revealed cyst contents and no malignancy.

At this time, systemic evaluation revealed a normal echocardiogram to rule out aortic dissection that can be associated with pupillary margin IPE cysts, and normal brain and orbits MRI scan to rule out intracranial or meningeal involvement of the melanocytosis. The MRI did show a slightly smaller right globe with asymmetrical slight thickening and enhancement involving the ciliary body region OD, suspected to represent melanocytosis and consistent with the UBM findings. Observation was advised.

Two years later, the patient noted swelling and a mass-like lesion in the right temporal fossa. MRI revealed a soft-tissue mass in the right temporal fossa involving the temporalis muscle and measuring 3.5 x 1.4 x 2.7 cm. A suspicion for neoplasm was raised. Biopsy and histopathologic examination of this lesion revealed a diagnosis of malignant melanoma in the setting of a blue nevus. In addition, a mass was noted in the right eye by MRI.

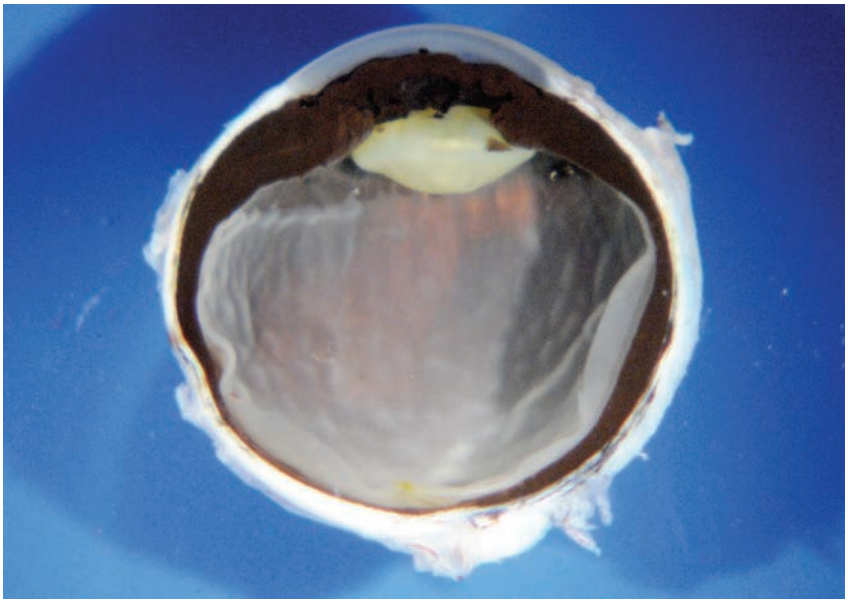

Figure 3. Gross pathologic section of the enucleated right eye showing extensive thickening of the iris, ciliary body and posterior choroid from melanocytosis admixed with spindle melanoma.

Ocular examination at this time showed large coalescent IPE cysts OD, precluding a view of the fundus. In-office B-scan ultrasonography disclosed a large choroidal mass, measuring 15 x 13 x 9.6 mm, and the entire uvea appeared thickened. Emergent MRI confirmed lack of orbital mass, but a clear-cut enhancing mass within the right globe, suggestive of a uveal malignant melanoma.

Enucleation was advised for the tumor, especially due to her young age, presence of melanocytosis, large tumor size and poor fundus view. Histopathologic examination of the globe revealed ocular melanocytosis involving the entire uvea and sclera, numerous IPE cysts, as well as low grade spindle melanoma *(See Figure 3)*. Orbital biopsies taken at the time of enucleation were negative for tumor. She further underwent complete resection of the temporalis tumor followed by high-dose interferon alpha 2b therapy. Genetic testing showed no mutations in the BRAF, KIT, GNAQ or NRAS genes.

Discussion

Oculodermal melanocytosis is defined as a congenital pigmentation of the periocular skin, episclera, uveal tract, and sometimes the orbit, meninges and hard palate.[1] Melanocytosis affects <1 percent of the Caucasian population, and it can be bilateral in 10 percent of cases.[1] Clinically, this condition appears as a flat, gray dermal pigmentation along the distribution of the 1st and 2nd divisions of the trigeminal nerve, although hard palate and temporal skin involvement can occur. The sclera assumes a blue-gray discoloration and the iris and choroid appear dark brown, often with iris mamillations and occasionally with elevat-

ed intraocular pressure from angle pigmentation.[2] Histopathologically, melanocytosis represents an excess of dendritic melanocytes in affected tissues, which can give rise to malignant melanoma, typically in the uvea, orbit or brain.[3]

The cutaneous component of oculodermal melanocytosis is a form of flat blue nevus. Blue nevus is generally categorized into congenital or acquired types and appears as a blue to black nodule within the dermis. There are two varieties of blue nevus: common and cellular. The common blue nevus has no potential for evolution into melanoma, while the cellular blue nevus carries low potential to undergo malignant transformation.[4] Most cutaneous blue nevi appear thicker and more irregular than oculodermal melanocytosis.[1]

Management of patients with oculodermal melanocytosis entails periodic examination for early detection of malignant melanoma. Dilated fundoscopic examination should be performed every six months. Surgical removal of patches of cutaneous or scleral melanocytosis is generally not advised.[1]

The overall lifetime risk for development of uveal melanoma in an eye with ocular melanocytosis has been calculated at one in 400 for Caucasians.[5] A study on sectoral melanocytosis by Carol Shields, MD, and colleagues revealed that male gender; related cutaneous or palatal melanocytosis, particularly in the temple region; scleral melanocytosis in the superior, nasal or temporal quadrants; sector or diffuse choroidal melanocytosis; and diffuse iris melanocytosis were associated with a clinically significant higher odds ratio for the presence or development of melanoma.[6]

Further analysis of this relationship disclosed that patients who develop melanoma in association with oculodermal melanocytosis carry a worse prognosis than those without melanocytosis. Melanoma in the setting of melanocytosis has approximately double the risk for metastasis.[7] Increasing tumor thickness was found to be predictive of both metastasis and death.[7] This was confirmed in a matched study that compared melanoma patients with oculodermal melanocytosis to those without this association. Even when cases were matched for patient age, tumor location, basal diameter and thickness, those with oculodermal melanocytosis still carried double the risk for metastasis.[8] While the etiology of this difference is unknown, it could be due to a subtle cytologic or genetic difference between the tumors.

In conclusion, oculodermal melanocytosis is congenital pigmentation that predisposes the patient to a low risk for uveal melanoma. When realizing the relatively aggressive nature melanoma and understanding the importance of detection when the malignancy is small, we suggest that screening of all patients with melanocytosis twice yearly and imaging of the eye annually is the mainstay of management. REVIEW

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Dr. Shareef is an associate professor at the University of Rochester School of Medicine and Dentistry. Dr. Ahmed is an assistant professor at the University of Toronto and clinical assistant professor at the University of Utah.

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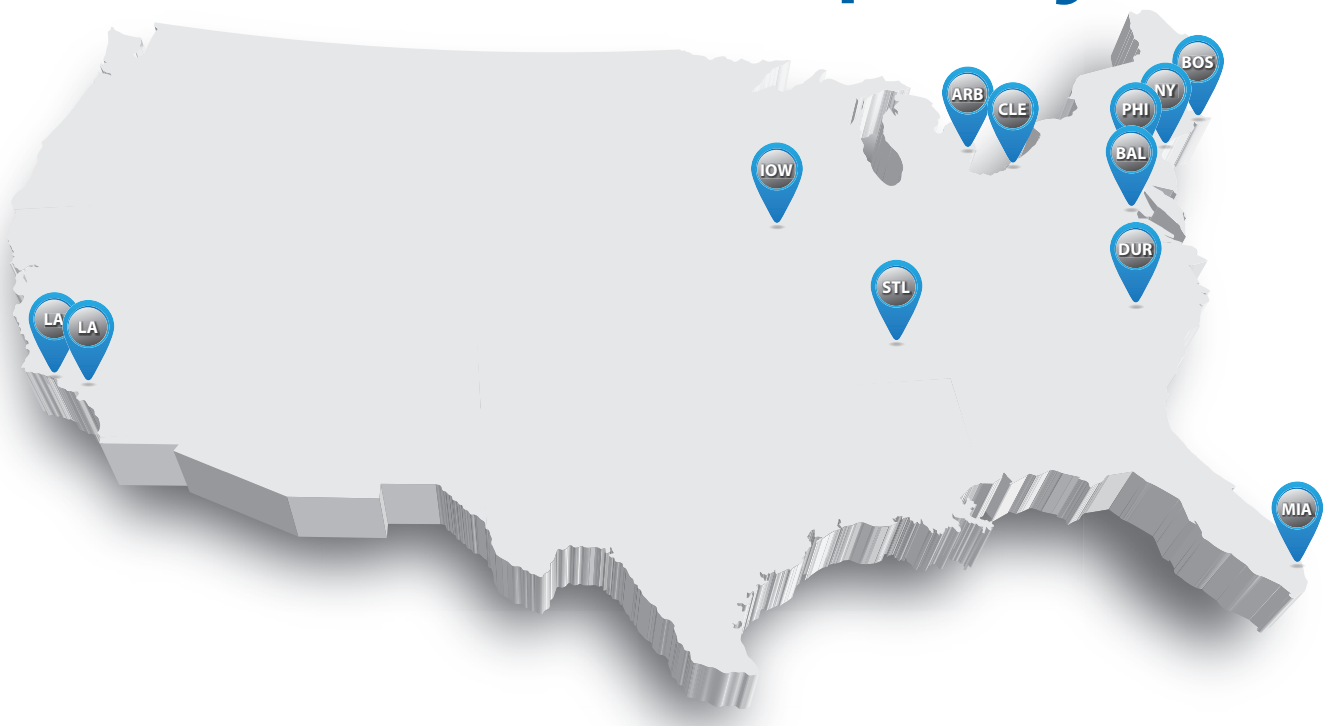

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