# REVIEW® of Ophthalmology

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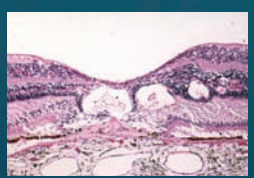


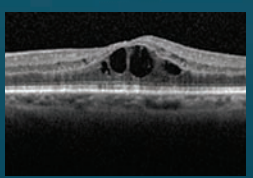

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*ANSI Z80.30-2010 requires that >90% of eyes experience a change in axis of ≤5° between two consecutive visits approximately three months apart.


**1.** TECNIS Toric 1-Piece IOL [package insert]. Santa Ana, Calif: Abbott Medical Optics Inc.
**2.** Novis C. Astigmatism and toric intraocular lenses. *Curr Opin Ophthalmol.* 2000; 11:47-50.




Abbott Medical Optics

REVIEW NEWS
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# Bascom Palmer Group Develops Gene Therapy for Leber's

**A multidisciplinary research team** of scientists, clinicians and biostatisticians led by John Guy, MD, professor of ophthalmology and director of the ocular gene therapy laboratory at the Bascom Palmer Eye Institute of the University of Miami Miller School of Medicine, has pioneered a gene therapy approach for Leber's hereditary optic neuropathy, an inherited genetic disorder that causes rapid, permanent and bilateral loss of vision in people of all ages, but primarily males ages 20 to 40.

The field of human mitochondrial genetics was born a quarter century ago and the list of neurodegenerative disorders associated with mutated mitochondrial DNA keeps growing. While many different experimental approaches have been proposed, development of a clinically effective therapy has been elusive until now. LHON is caused by genetic defects inside mitochondria, the energy factories inside cells. Through this trial, patients who have visual loss from LHON will receive an injection of a mitochondrial gene into the vitreous. While there have been approximately 1,800 reported clinical trials using gene therapy, all but one have targeted the nucleus, the home for most of the cell's DNA. This new trial is among the first to target a disease caused by a defective gene located inside the mitochondria.

"A wide range of other conditions, including aging, cancer and Parkinson's disease, are also caused by mutations in the mitochondria," said Dr. Guy. "This novel approach shows the vast potential for genetic-therapy applications, while helping to address a significant cause of blindness." About half of all patients with LHON have mutations in the mitochondrial gene ND4, and most other patients carry mutations in one of two related mitochondrial genes. The ND4 protein is part of Complex I, an essential protein that works as part of an assembly line for producing energy inside mitochondria.

The approach in the clinical trial for therapeutic intervention is to in,troduce a normal copy of the defective gene into retinal ganglion cells, the cell type exclusively affected in LHON. Replacing a defective gene has been the basis for more than 1,500 gene therapy clinical trials worldwide, but only one involving a mitochondrial disease. One of the major drawbacks for treating mitochondrial diseases by gene therapy has been a lack of availability of practical methods.

Dr. Guy developed an approach to deliver the normal ND4 gene into

## Dog Bites Man (SGR Kicked Down the Road) & ICD-10 Delayed

On Tuesday, April 1, President Obama signed the "Protecting Access to Medicare Act of 2014," HR 4302, which creates a one-year patch for the Sustainable Growth Rate (SGR) Medicare physician payment formula, to April 2015, the 17th such patch enacted since the SGR was devised in 1997. "That's a surprise," said no one.

Also included among many other provisions in the 45-page bill, however, was a delay in the conversion to ICD-10 by one year, to October 2015.

The ICD-10 delay caught many by surprise. "We knew there was legislation being drafted to stave off the reduction in reimbursement, and people chuckled that maybe they'll delay ICD-10, but I don't think anyone believed that would be part of this legislation," says Donna McCune, vice president at the Corcoran Consulting Group, who specializes in Medicare reimbursement issues.

"Some folks have invested a lot time and revenue into being prepared for October 1, especially large institutions like hospitals," says Ms. McCune. "I just met with a hospital's ICD-10 consulting team that's been on board for six or seven months. They're a hired force. Do they stop and come back next year, do they continue on and finish their project?"

The silver lining if there is one, says Ms. McCune, is that the delay may take the pressure and the focus off the deadline and the new codes and enable users to concentrate on the processes that need to change.

Many of her clients, she says, are pressing on. "Several have said, please come, let's just do this. They'd like the doctors to see what this is all about because many of them still have no clue what it all involves. But they also said, if you can shift the focus away from the hard-core, this is how you find a code, and really focus on how much needs to be in your documentation. So you shift the focus to, these are changes you need to make, and the sooner you start making them the easier it's going to be."

Looks for further advice from Ms. McCune in a future edition of our bimonthly Medicare Q&A column.

retinal cells using a virus. But since viruses are designed by nature to infiltrate and take over a cell's nucleus, the next challenge was how to target the gene into mitochondria. Dr. Guy's solution was to create an ND4 gene that is delivered to the nucleus, but modified so that the ND4 protein carries a mitochondrial address label. In experimental models, they have found that this approach is safe and effective to replace the ND4 gene and that doing so prevents deterioration of the retinal cells that form the optic nerve. This research demonstrates that when efficiently introduced into mitochondria, normal DNA can correct a biochemical defect in cellular energy production and restore visual function.

"Other research studies have shown that LHON patients who have lost their vision still have some sensitivity to light," said Dr. Guy. "This indicates that if you can restore the functioning of those cells through gene therapy, those patients could see again." In conjunction with his research, Dr. Guy explored why only about 50 percent of male patients with the genetic mutation develop LHON. Known for exploring gene therapy as a potential treatment for diseases of the optic nerve, Dr. Guy holds several patents related to mitochondrial gene therapy. He and his team recently advanced their research significantly by demonstrating that the vector (the adeno-associated virus, AAV, with the ND4 gene) was made human-grade and proven safe in experimental models that are closest to the human eye. With the Food and Drug Administration having recently approved the investigational new drug (AAV-ND4 gene), a Phase I trial of the approach will begin in April 2014 and conclude five years later.

Louise Wideroff, PhD, a program director in the NEI Division of Extramural Research, stated, "The continuing progress in this research—especially its movement from the lab into human trials—is cause for excitement and optimism, not only for families with LHON but for families affected by other mitochondrial disorders."

## Immune System Targets Diseased Blood Vessels

**A new report published** online in *The FASEB Journal* may lead the way toward new treatments or a cure for proliferative retinopathies. Specifically, scientists have discovered that the body's innate immune system does more than help ward off external pathogens. It also helps remove sight-robbing abnormal blood vessels, while leaving healthy cells and tissue intact. This discovery is significant as the retina is part of the central nervous system and its cells cannot be replaced once lost. Identifying ways to leverage the innate immune system to "clean out" abnormal blood vessels in the retina may lead to treatments that could prevent or delay blindness, or restore sight.

"Our findings begin to identify a new role of the innate immune system by which endogenous mediators selectively target the pathologic retinal vasculature for removal," said Kip M. Connor, PhD, a researcher involved in the work from the Department of Ophthalmology at the Harvard Medical School and Massachusetts Eye and Ear Infirmary Angiogenesis Laboratory in Boston. "It is our hope that future studies will allow us to develop specific therapeutics that harness this knowledge, resulting in a greater visual outcome and quality of life for patients suffering from diabetic retinopathy or retinopathy of prematurity."

To make this discovery, Dr. Connor and colleagues compared two groups of mice, a genetically modified group which lacked activity in the innate immune complement system, and a normal group with a fully functional innate immune system. Researchers placed both groups in an environment that induced irregular blood vessel growth in the eye, mimicking what happens in many human ocular diseases. The mice that were lacking a functional innate immune system developed significantly more irregular blood vessels than the normal mice, indicating that the complement system is a major regulator of abnormal blood vessel growth within the eye. Importantly, in the normal mice, scientists were able to visualize the immune system targeting and killing only the irregular blood vessels while leaving healthy cells unharmed.

"Knowing how the complement system works to keep our retinas clean is an important first step toward new treatments that could mimic this activity," said Gerald Weissmann, MD, editor in chief of *The FASEB Journal*. "It's a new understanding of how proliferative retinopathies rob us of sight, and promises to let us see the path ahead clearly."

## Drops Warrant Caution in ROP Examinations

**Eyedrops administered to infants** as part of routine outpatient retinopathy of prematurity screening can have life-threatening consequences. A case report published in the current issue of the *Journal of the American Association for Pediatric Ophthalmology and Strabismus* describes cardiopulmonary arrest in a 27-week-old infant following administration of three sets of cyclopentolate 0.2%/phenylephrine 1% (Cyclomydril) eyedrops.

"Cardiopulmonary arrest can occur from just instillation of eyedrops in a premature infant seen for ROP in an outpatient setting, and pediatric ophthalmologists should be prepared to handle such an emergency in their office," says Sylvia Kodsi, MD, profes-

sor of ophthalmology at Hofstra North Shore-LIJ School of Medicine. "This can be particularly perilous in outpatient offices where patient monitoring and emergency back-up is not as readily available as in the hospital setting."

ROP primarily affects premature infants who weigh 2.75 pounds or less who are born before 31 weeks of gestation. Each year, about 28,000 infants in the United States fall into this category and about half are affected to some degree by ROP. About 400 to 600 of these children with ROP become legally blind. ROP occurs when babies are born before blood vessels in the eye have had a chance to reach the edges of the retina. Abnormal blood vessels form, resulting in inadequate blood supply, retinal scarring and retinal detachment.

Professional organizations such as the American Association for Pediatric Ophthalmology and Strabismus, American Academy of Pediatrics and American Academy of Ophthalmology recommend that at-risk infants be regularly screened for changes associated with ROP.

In the case that was reported, a 27-week-old, low-birth-weight infant presented for a follow-up ROP screening examination at 41 weeks' corrected gestational age. The patient had previously undergone several such examinations, beginning at 30 weeks corrected gestational age and every two weeks thereafter. For all those examinations, the infant received three sets (one drop per eye) of Cyclomydril, a combination of cyclopentolate (an anticholinergic that blocks pupillary constriction and eye muscle contraction), and phenylephrine (an alpha-adrenergic agent that causes mydriasis).

Fifteen minutes after the last set of drops was administered, but prior to the eye examination, the baby suffered a cardiopulmonary arrest and was revived within a few minutes. After transport to the hospital, she experienced another episode of apnea and

# Ophthalmic Product Development Insights

Matthew Chapin, Van Sandwick and Aron Shapiro • Ora Inc., Andover, Mass.

## When Does an ex-U.S. Trial Make Sense?

Given the increasing pressure to make development programs more enticing to investors and partners, many innovators consider conducting clinical trials outside the United States. Doing so can enable them to reach value inflection points or to secure capital required to move R&D forward (e.g., demonstrating clinical proof of concept) especially in a time when capital is difficult to secure for early programs. In this installment of our ongoing column, we will review the considerations for early clinical trials that are conducted outside the United States. While this data can certainly add value in certain instances, it is important to align the designs of such studies with your target product profile (TPP) that we have discussed in prior columns, and consider the ability to rely on the data for decision-making and perceptions. Further, it is critical to set appropriate objectives for data acquired from ex-U.S. clinical trials to ensure it meets your goals and that conducting them is the right decision for your project and stage.

### When to Pursue an ex-U.S. Trial

When conducting clinical investigation outside the United States, remember that the goal is not to avoid the U.S. Food and Drug Administration or requirements it has for initiating a trial. Requirements for proper clinical conduct (GCP), toxicology, chemistry and manufacturing controls are meant to provide reliability of data for the developers and safety to patients. Ultimately the ex-U.S. data will still be submitted to the FDA, and it is important that the agency agrees that it will be supportive and reliable data.

Given that the goal of development is to provide a product the best chances for success, each component of the development program must add value by advancing the program toward financing, regulatory approval, partnering/acquisition or demonstrating safety/efficacy of the respective drug/device to help inform, design or define the TPP. The conduct of smaller ex-U.S. proof-of- concept (POC) studies should be aligned with one of these. A global regulatory strategy to reduce lag time between U.S. approval and other regions such as Europe and Japan, and integration of clinical sites or parallel studies in other regions to that path, is another topic of its own.

With that said, pursuit of clinical POC at ex-U.S. sites can allow innovators/entrepreneurs to:

• ***Access patient populations that are difficult to recruit in the United States.*** This includes rare disease, needing patients naïve to treatment, and when access to standard of care may impact recruiting. For example, a placebo control trial may not be ethical to conduct in the United Sates in certain cases; however given differences in access to care or accepted standard of care, it may be possible in other regions. In these cases, the ex-U.S. studies may expand beyond small POC, into the full Phase II and III trials.

• ***Gain insights that will guide decision-making and optimization of the product.*** Oftentimes we see ex-U.S. datasets that are significantly smaller than is common here, are non-randomized or lack other necessary features and controls of clinical trials designed to support a new drug application or premarket approval application. The strategy and future insights to be gained from these potential studies (and their value) should be interpreted on a case-by-case basis.

For devices, it is always helpful to take into account the different regulatory standards for safety and efficacy by different regions of the global market. Advancing safety considerations as well as potential surgical techniques for more significant-risk products can be very helpful when done in concert with FDA consultation through the Pre-Submission process. For example, as we look at new classes of surgically implanted devices such as MIGS (micro-incision glaucoma surgery) and intraocular pressure measuring devices such as Implandata Ophthalmic Products GMBH (Hannover, Germany) PRO-IOP monitoring, the development cycle includes several rounds of POC work. Companies like Implandata have taken the approach of demonstrating safety and surgical technique on a small scale. This can be very helpful before turning the focus to efficacy endpoints and final-product designs.

If this work can be done efficiently and allow for CE marking in Europe based on quality controls and safety, the companies can work to expand their approval base and allow the investment community to see progress toward milestones of global commercialization, and then focus on assessing efficacy for FDA.

It is paramount to engage potential partners or investors early in order to determine what are the relevant questions that will support value inflection and drive decision-making, in order to establish the most appropriate design and approach. For example, small POC data may not help if the key third parties you are targeting will discount the data because the supplies are not from GMP suppliers; if there is not a placebo or appropriate control; if the proper time points for assessments are not met because a clinical site did not have the right processes in place; or if proper monitoring and oversight were not in place.

• ***Potentially lower costs.*** The gap between clinical trial costs in the United States compared to other regions has narrowed in recent years in most cases. Many times, the anticipated slightly reduced costs of an ex-U.S. POC program may be swallowed up by the need for repeat testing, based on how the FDA, investors and partners interpret and use the results. Again, we emphasize the importance of engaging the FDA early. We have seen projects started ex-U.S. come back only to start again under the investigational new drug or investigational device exemption phases of FDA review.

### An Ex-U.S. Success Story

While the costs of proper controls and monitoring per Good Clinical Practice compliance would not necessarily be lower, clinical investigator costs can still certainly be reduced, at times. In addition, how a company is financed may also impact the strategy for utilizing an ex-U.S. POC trial.

For example, when a company is internally financed, then the objectives can be set to advance the understanding for the TPP, building early data sets, etc. The goal is to verify safety and efficacy and "fail early" if that's

going to be the outcome. Recognizing that this may potentially impact future partners' and investors' perceptions related to quality and reliability of the results, the goal is to have this data inform future, more formal U.S.-based studies under IND/IDE. If other potential investors/partners are involved, confirmation should be obtained on how such data will be used and perceived.

Allegro Ophthalmics has successfully used this approach. Allegro is developing ALG-1001, the first in a new class of drugs called integrin peptide therapy for the treatment of retinovascular diseases. Of course, only after determining that the drug was safe and effective in animals, Allegro began its international human clinical program with a primary endpoint of safety in the target population and a secondary endpoint of initial efficacy. They made the decision to conduct early human studies outside the United States because of efficiencies in recruitment time and expense (specifically around cost of the clinical investigators), without compromising the quality of clinical data. In an effort to ensure the highest-quality results, Allegro leveraged long-standing existing relationships with reputable ex-U.S. clinical sites with which the company had prior experience, and engaged its own scientific advisory board, an independent retinal reading center, and third-party clinical research oirganizations to monitor and evaluate the study.

The approach succeeded: A subsequent 2013 collaboration with Senju Pharmaceutical for Japan and a successful FDA IND filing in both vitreomacular traction and wet AMD demonstrate success in reaching their objectives with this strategy. Allegro acquired clinical Phase II data in less than four years from discovery, and answered important questions that added value to the ALG-1001 development program and enabled design of larger trials in the United States to be conducted under an IND designation.

While details are beyond the scope of this particular column, for certain products, we would point out that there may be differences, for example, in requirements for toxicology to support early clinical trials.

### Setting the Proper Expectations

Assessing external expectations (those of the FDA, investors and potential partners) for studies conducted outside of the United States is integral to maximizing the value of these trials. Ascertaining whether investors/potential partners will view clinical POC in an ex-U.S. trial as a value inflection point before planning or conducting ex-U.S. trials should be a precursor to any development work. Again, we emphasize that proper study design and controls (GCP) must still be followed to support reliability of the data.

There is little value in conducting studies that do not demonstrate safety/efficacy in well-designed trials or with proper controls, ending with data that can't be interpreted. We have seen some external parties (investors and partners) be open to well-controlled and executed ex-U.S. trials, whereas others are suspicious of it and don't give the data full value. The key is to set expectations on how that data will be viewed and used.

Managing internal expectations on timelines and the ability to conduct your trial ex-U.S. is also paramount. In the interest of establishing and preserving reputations and protecting their population, many regional regulatory authorities are strict. In some cases there have been more complications and longer submission timelines to prevent companies from simply attempting to use local citizens as the sole research subjects in studies.

While you can plan for a 30-day review by the FDA of an IND and IDE, review timelines can be unpredictable in emerging countries. We recently saw more than a year review of a submission in one country due to structural volatility. In another, multiple delays arose due to political changes followed by changes to local regulations, which caused additional delays with re-submissions, and rework of documents and procedures in the middle of a study. While a local institutional review board may approve a project, there may be critical elements missing on the toxicology, manufacturing and controls that can create issues when you do file in that region for approval, or with the FDA. This relates to so-called "IRB shopping" to find, for example, an IRB that will approve an IND as "non-significant risk" to allow proceeding with a trial, when the FDA may take a more conservative stance, creating review issues later.

*Mr. Chapin and Mr. Sandwick are with the Corporate Development Group, and Mr. Shapiro is a vice president at Ora, Inc. Ora provides a comprehensive range of product development, clinical-regulatory and product consulting, and clinical trial services in ophthalmology. They welcome comments or questions related to this or other development topics. Please send correspondence to mchapin@oraclinical.com.*

bradycardia and was found to have new-onset pulmonary hypertension.

These serious events are most likely attributed to an adverse drug reaction to cyclopentolate. According to co-author Jung M. Lee, MD, an ophthalmology resident also affiliated with Hofstra North Shore-LIJ School of Medicine, the phenylephrine would have mostly been cleared by the time the patient experienced the second event of apnea and bradycardia three hours after instillation of the eye drops. She cautions that other anticholinergic drugs such as tropicamide may have a similar side effect profile. For this child, subsequent dilated ROP examinations performed with tropicamide 1% and phenylephrine 2.5% were performed without incident.

"Eyedrops used for mydriasis and cycloplegia can be systemically absorbed and cause serious side effects, including oxygen desaturation, apnea, bradycardia, transient hypertension, delayed gastric emptying and transient paralytic ileus. These effects can be more serious in infants because of their lower body mass and immature cardiovascular and nervous systems," says Dr. Kodsi. "Pediatric ophthalmologists should be equipped to handle this type of emergency, either personally or with ancillary services that are immediately available."

## Early Warning For DR Vision Loss

**Indiana University researchers have** detected new early warning signs of the potential loss of sight associated with diabetes. This discovery could have far-reaching implications for the diagnosis and treatment of diabetic retinopathy, potentially impacting the care of more than 25 million Americans.

"We had not expected to see such striking changes to the retinas at such

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early stages," said Ann Elsner, PhD, professor and associate dean in the IU School of Optometry and lead author of the study. "We set out to study the early signs in volunteer research subjects whose eyes were not thought to have very advanced disease. There was damage spread widely across the retina, including changes to blood vessels that were not thought to occur until the more advanced disease states."

These important early-warning signs were invisible to existing diagnostic techniques, requiring new technology based on adaptive optics. Stephen Burns, PhD, professor and associate dean at the IU School of Optometry, designed and built an instrument that used small mirrors with tiny moveable segments to reflect light into the eye to overcome the optical imperfections of each person's eye.

"It is shocking to see that there can be large areas of retina with insufficient blood circulation," he said. "The consequence for individual patients is that some have far more advanced damage to their retinas than others with the same duration of diabetes."

Because these changes had not been observable in prior studies, it is not known whether improved control of blood sugar or a change in medications might stop or even reverse the damage. Further research can help determine who has the most severe damage and whether the changes can be reversed.

The changes to the subjects in the study included corkscrew-shaped capillaries. The capillaries were not just a little thicker, and therefore distorted, but instead the blood vessel walls had to grow in length to make these loops. This is visible only at microscopic levels, making it difficult to determine who has the more advanced disease among patients, because these eyes look similar when viewed with the typical instruments found in the clinic. Yet, some of these patients already have sight-threatening complications.

Diabetes also is known to result in a variety of types of damage to capillaries. The more commonly known changes, such as microaneurysms along the capillaries, were also present in the study, but seen in much greater detail. In addition to the corkscrew appearance and microaneurysms, along with the hemorrhages in the later stages of the disease, there is also a thickening of the walls of blood vessels. This is thought to be associated with poor blood flow or failure to properly regulate blood flow.

In the study, patients with diabetes had significantly thicker blood vessel walls than found in controls of similar ages, even for relatively small-diameter blood vessels. The capillaries varied in width in the diabetic patients, with some capillaries closed so that they no longer transported blood within the retina. On average, though, the capillaries that still had flowing blood were broader for the patients with diabetes. These diabetic patients had been thought to have fairly mild symptoms. In fact, the transport of oxygen and glucose to the retina is already compromised.

Previous diagnostic techniques have been unable to uncover several of these changes in living patients. Simply magnifying the image of the retina is not sufficient. The view through the imperfect optics of the human eye has to be corrected.

The study was published in *Biomedical Optics Express*.

# Alimera Moves Forward With Iluvien Review

**Alimera Sciences announced that** its recent resubmission of the New Drug Application for Iluvien has been acknowledged as received by the Food and Drug Administration as a complete class 2 response to the FDA's October 2013 letter and that a Prescription Drug User Fee Act (PDUFA) goal date of September 26, 2014 has been established.

In the resubmission, Alimera responded to questions raised in the FDA's October 2013 letter and provided data from Iluvien patients and from physician experience with the applicator in the United Kingdom and Germany, where Iluvien is currently commercially available.

"We are pleased to have achieved our goal of resubmitting our NDA in the first quarter and to have a PDUFA goal date set for a decision from the FDA," said Dan Myers, Alimera's president and chief executive officer. "We look forward to the FDA's response to our NDA and hope that we will be able to make Iluvien available to patients in the United States who are suffering from chronic DME." REVIEW



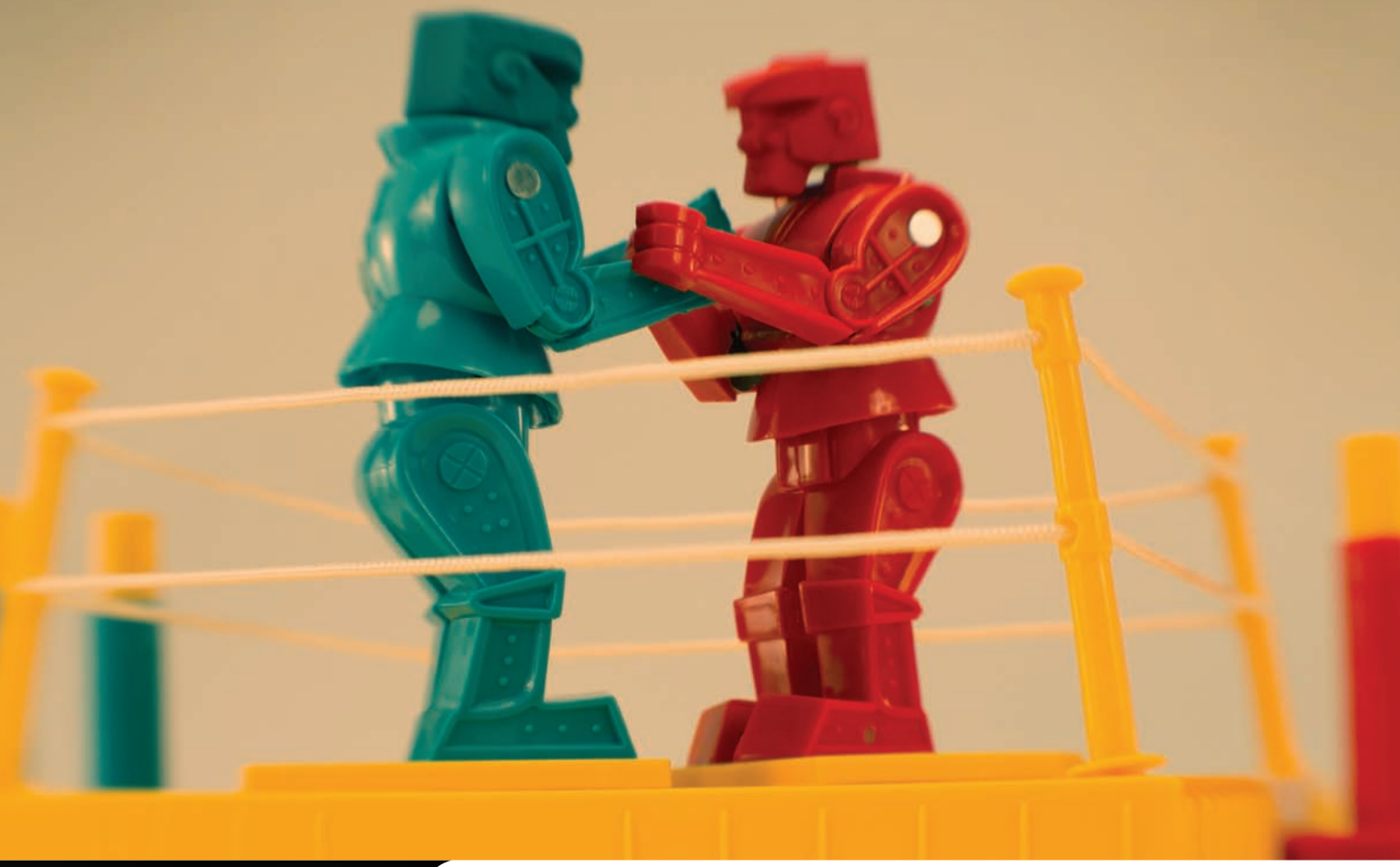
To the Editor:

It is a shame that your recent article on compounded ophthalmic drugs *[Compounded Drugs: Keeping Patients Safe, March 2014]* discussed only one of these drugs, intravitreal bevacizumab. Ophthalmologists rely on pharmacy compounding for a wide array of topical and intravitreal medications such as fortified antibiotics and mitomycin C. Pharmacy compounding also plays an important role in clinical research.

The American Academy of Ophthalmology, American Glaucoma Society and American Association for Pediatric Ophthalmology and Strabismus have published statements reminding lawmakers that compounding pharmacies supply essential ophthalmic medicines to patients. Few if any of these medicines have involved the kinds of risks publicized for intravitreal bevacizumab.

*Sincerely,*
*Michael S. Singer, MD, PhD*
*Topokine Therapeutics Inc.*
*Boston, MA 02111*

# The Rock ‘em Sock ‘em Glaucoma Instrument



## The Octopus 600 Perimeter

It’s working. Thanks to doctors like you and early diagnosis, the risk of blindness due to glaucoma has been cut by 50%. But Octopus can do better. It’s the all-in-one early detection and management device with the most accurate and reproducible data. Take your best shot at one soon.

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# Cover Story

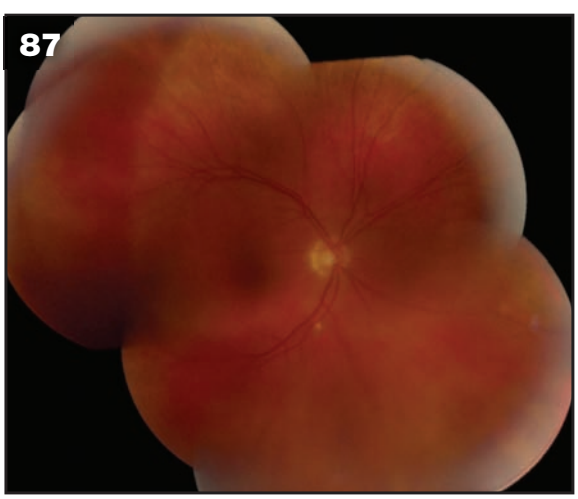


# Feature Articles

# Departments







The Quintessential

# Antibiotic™


## BACITRACIN OPHTHALMIC OINTMENT USP

## Proven therapeutic utility in blepharitis, conjunctivitis, and other superficial ocular infections

- **Profound bactericidal effect against gram-positive pathogens**[1]
- **Excellent, continued resistance profile**—maintains susceptibility,[2,3] even against methicillin-resistant *Staphylococcus aureus*[4]
- Ointment provides **long-lasting ocular surface contact time** and **greater bioavailability**[5]
- **Anti-infective efficacy** in a lubricating base[6]
- **Unsurpassed safety profile**—low incidence of adverse events[6]
- **Convenient dosing**—1 to 3 times daily[6]
- **Tier 1 pharmacy benefit status**—on most insurance plans[7]

Bacitracin Ophthalmic Ointment is indicated for the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

### Important Safety Information

The low incidence of allergenicity exhibited by Bacitracin means that adverse events are practically non-existent. If such reactions do occur, therapy should be discontinued.

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].

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REVIEW® of Ophthalmology



REVIEW Editor's Page

Christopher Glenn, Editor in Chief

# Yes, That's What It Costs. Glad You Asked

**Ophthalmologists around the country** found themselves in the headlines this month thanks to the decision by the Centers for Medicare & Medicaid Services to release Medicare payment data that has been private for more than three decades. While I don't envy the position in which they unfairly found themselves, those doctors, along with their professional societies, who chose to respond to media inquiries had appropriate responses at the ready, and the coverage for the most part seemed fair. You can't educate the public about health-care financing overnight, and the complaint from medical societies and doctors—that the data dump, with no context and nothing more than raw dollars reimbursed, risked unfairly portraying physicians as bilking the system—was indisputable. Again, I didn't have a microphone in my face, but those who did had pretty legitimate answers.

In an ideal world, those who set out to cover this story would first have read an excellent article this month by Drs. Melissa and Gary Brown and their coauthors, of the Center for Value-Based Medicine.[1]

The authors propose that medical expenditures comprise three types: direct medical costs (e.g., a drug, physician cost for examination, diagnostic testing); direct nonmedical costs (residence costs such as moving to a new home due to vision loss, caregiver costs); and indirect medical costs (impact on employment and earnings).

They evaluated the return on investment for three procedures: ranibizumab for AMD, timolol for glaucoma, and first-eye cataract. The respective ROIs were 450 percent, 3,957 percent, and 4,567 percent.

A hypothetical regarding the cataract ROI was especially illuminating: An investment of $1 in 1964 in Warren Buffett's Berkshire Hathaway stock would be worth $5,868 in 2012. The same investment in the S&P 500 Index over the same time period would be worth $74. If first-eye cataract surgery were considered an investment, the theoretical ROI of $1 from 1964 through 2012 would be $4,350,403 to society.

"The majority of the costs returned to society is returned to patients," say the authors, "but there is also a considerable financial ROI to health-care insurers. For the cataract surgery in the first eye for example, approximately 64 percent of dollars returned by the intervention over the direct ophthalmic medical costs went to patients, 29 percent to Medicare and 7 percent to secondary insurers."

Ophthalmology has been very effective in recent years at broadening the conversation from a narrow focus on what procedures cost. As the Medicare data dump showed, there is still much work to be done, but as the politicians like to say, that's a conversation we'd love to have.

1. Brown M, et al. Financial return-on-investment of ophthalmic interventions: A new paradigm. Curr Opin Ophthalmol 2014 May;25(3):171-6.


# Working With the Visian Toric ICL

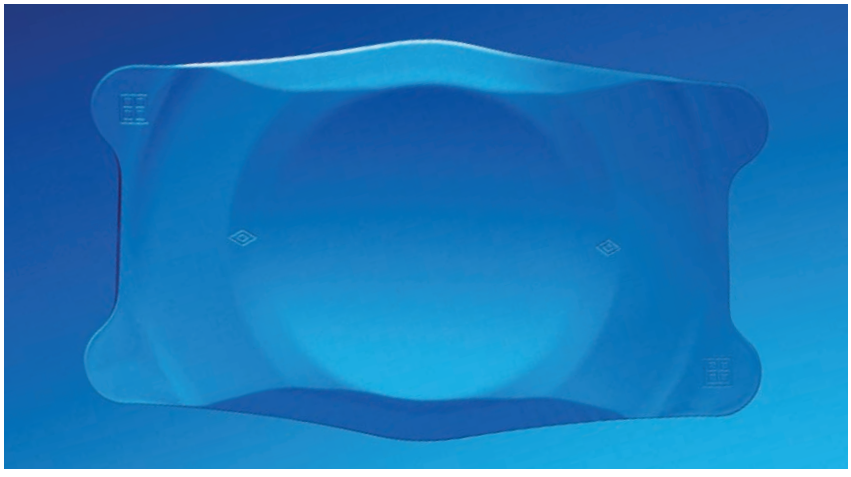
Surgeons discuss how working with this implant compares to working with a standard ICL and in-the-bag toric lenses.

*Christopher Kent, Senior Editor*

**This March, an** independent advisory panel to the Food and Drug Administration finally recommended marketing approval for the Visian Toric ICL. Although the standard Visian ICL has been available in the United States for several years and the toric version has been available outside the United States for more than a decade, American ophthalmologists have not had access to the latter. The advisory panel's recommendation has now raised hopes that FDA approval of the Visian Toric lens will soon follow.

## Track Record

"Overall, about 450,000 ICLs have been implanted globally in the past 17 years," notes Francis W. Price Jr., MD, president of the Price Vision Group in Indianapolis and founder and board president of the Cornea Research Foundation of America. "Where toric lenses are available they represent about 40 percent of the ICLs that are used."



Unlike an in-the-bag toric lens, the Visian Toric ICL is designed to be aligned close to the horizontal axis, with a maximum rotation of 22 degrees in either direction. Multiple versions of each prescription allow astigmatic correction around the clock.

John A. Vukich, MD, an assistant clinical professor at the University of Wisconsin, Madison, medical monitor for Staar Surgical and a principal investigator for the FDA study of the Visian Toric ICL, notes that the Visian Toric has been used extensively outside the United States. "The Visian ICL is currently distributed in 64 countries, and 63 of them already have access to the toric lens," he says. "More than 100,000 of these toric lenses have been placed worldwide."

"All the phakic lens implants give excellent visual results, especially for high myopes," notes Dr. Price. "Nevertheless, I was struck by some of the data I presented to the FDA panel regarding this lens. For example, 77 percent of the eyes in the toric ICL study ended up with uncorrected vision as good or better than their best preop glasses-corrected vision. In addition, 77 percent of the eyes gained one or more lines of BCVA when wearing glasses.

"One area that could be improved on is sizing, to get an ideal amount of vaulting for the ICL lenses," he



*This article has no commercial sponsorship.*

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Effective January 1, 2014

# SYMPTOMATIC VMA
# DON'T WAIT TO TREAT

**JETREA® (ocriplasmin) Intravitreal Injection, 2.5 mg/mL**
**The FIRST AND ONLY pharmacologic treatment for symptomatic VMA**

## Indication

JETREA (ocriplasmin) Intravitreal Injection, 2.5 mg/mL, is a proteolytic enzyme indicated for the treatment of symptomatic vitreomacular adhesion (VMA).

## Important Safety Information

### Warnings and Precautions

- A decrease of ≥ 3 lines of best-corrected visual acuity (BCVA) was experienced by 5.6% of patients treated with JETREA and 3.2% of patients treated with vehicle in the controlled trials. The majority of these decreases in vision were due to progression of the condition with traction and many required surgical intervention. Patients should be monitored appropriately.
- Intravitreal injections are associated with intraocular inflammation/infection, intraocular hemorrhage, and increased intraocular pressure (IOP). Patients should be monitored and instructed to report any symptoms without delay. In the controlled trials, intraocular inflammation occurred in 7.1% of patients injected with JETREA vs 3.7% of patients injected with vehicle. Most of the post-injection intraocular inflammation events were mild and transient. If the contralateral eye requires treatment with JETREA, it is not recommended within 7 days of the initial injection in order to monitor the post-injection course in the injected eye.
- Potential for lens subluxation.
- In the controlled trials, the incidence of retinal detachment was 0.9% in the JETREA group and 1.6% in the vehicle group, while the incidence of retinal tear (without detachment) was 1.1% in the JETREA group and 2.7% in the vehicle group. Most of these events occurred during or after vitrectomy in both groups.
- Dyschromatopsia (generally described as yellowish vision) was reported in 2% of all patients injected with JETREA. In approximately half of these dyschromatopsia cases, there were also electroretinographic (ERG) changes reported (a- and b-wave amplitude decrease).

### Adverse Reactions

- The most commonly reported reactions (≥ 5%) in patients treated with JETREA were vitreous floaters, conjunctival hemorrhage, eye pain, photopsia, blurred vision, macular hole, reduced visual acuity, visual impairment, and retinal edema.

**Please see Brief Summary of full Prescribing Information on adjacent page.**

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ThromboGenics®

JETREA™
(ocriplasmin)
Intravitreal Injection, 2.5 mg/mL

JETREA™
(ocriplasmin)
Intravitreal Injection, 2.5 mg/mL

**BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION**

**Please see the JETREA® package insert for full Prescribing Information.**

## 1 INDICATIONS AND USAGE
JETREA is a proteolytic enzyme indicated for the treatment of symptomatic vitreomacular adhesion.

## 2 DOSAGE AND ADMINISTRATION
### 2.1 General Dosing Information
Must be diluted before use. For single-use ophthalmic intravitreal injection only. JETREA must only be administered by a qualified physician.

### 2.2 Dosing
The recommended dose is 0.125 mg (0.1 mL of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose.

### 2.3 Preparation for Administration
Remove the vial (2.5 mg/mL corresponding to 0.5 mg ocriplasmin) from the freezer and allow to thaw at room temperature (within a few minutes). Once completely thawed, remove the protective polypropylene flip-off cap from the vial. The top of the vial should be disinfected with an alcohol wipe. Using aseptic technique, add 0.2 mL of 0.9% w/v Sodium Chloride Injection, USP (sterile, preservative-free) into the JETREA vial and gently swirl the vial until the solutions are mixed.

Visually inspect the vial for particulate matter. Only a clear, colorless solution without visible particles should be used. Using aseptic technique, withdraw all of the diluted solution using a sterile #19 gauge needle (slightly tilt the vial to ease withdrawal) and discard the needle after withdrawal of the vial contents. Do not use this needle for the intravitreal injection.

Replace the needle with a sterile #30 gauge needle, carefully expel the air bubbles and excess drug from the syringe and adjust the dose to the 0.1 mL mark on the syringe (corresponding to 0.125 mg ocriplasmin). THE SOLUTION SHOULD BE USED IMMEDIATELY AS IT CONTAINS NO PRESERVATIVES. Discard the vial and any unused portion of the diluted solution after single use.

### 2.4 Administration and Monitoring
The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad spectrum microbiocide should be administered according to standard medical practice.

The injection needle should be inserted 3.5 - 4.0 mm posterior to the limbus aiming towards the center of the vitreous cavity, avoiding the horizontal meridian. The injection volume of 0.1 mL is then delivered into the mid-vitreous.

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, blurred or decreased vision) without delay *[see Patient Counseling Information]*.

Each vial should only be used to provide a single injection 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, and injection needles should be changed before JETREA is administered to the other eye, however, treatment with JETREA in the other eye is not recommended within 7 days of the initial injection in order to monitor the post-injection course including the potential for decreased vision in the injected eye.

Repeated administration of JETREA in the same eye is not recommended *[see Nonclinical Toxicology]*.

After injection, any unused product must be discarded.

No special dosage modification is required for any of the populations that have been studied (e.g. gender, elderly).

## 3 DOSAGE FORMS AND STRENGTHS
Single-use glass vial containing JETREA 0.5 mg in 0.2 mL solution for intravitreal injection (2.5 mg/mL).

## 4 CONTRAINDICATIONS
None

## 5 WARNINGS AND PRECAUTIONS
### 5.1 Decreased Vision
A decrease of ≥ 3 line of best corrected visual acuity (BCVA) was experienced by 5.6% of patients treated with JETREA and 3.2% of patients treated with vehicle in the controlled trials *[see Clinical Studies]*.

The majority of these decreases in vision were due to progression of the condition with traction and many required surgical intervention. Patients should be monitored appropriately *[see Dosage and Administration]*.

### 5.2 Intravitreal Injection Procedure Associated Effects
Intravitreal injections are associated with intraocular inflammation / infection, intraocular hemorrhage and increased intraocular pressure (IOP). In the controlled trials, intraocular inflammation occurred in 7.1% of patients injected with JETREA vs. 3.7% of patients injected with vehicle. Most of the post-injection intraocular inflammation events were mild and transient. Intraocular hemorrhage occurred in 2.4% vs. 3.7% of patients injected with JETREA vs. vehicle, respectively. Increased intraocular pressure occurred in 4.1% vs. 5.3% of patients injected with JETREA vs. vehicle, respectively.

### 5.3 Potential for Lens Subluxation
One case of lens subluxation was reported in a patient who received an intravitreal injection of 0.175 mg (1.4 times higher than the recommended dose). Lens subluxation was observed in three animal species (monkey, rabbit, minipig) following a single intravitreal injection that achieved vitreous concentrations of ocriplasmin 1.4 times higher than achieved with the recommended treatment dose. Administration of a second intravitreal dose in monkeys, 28 days apart, produced lens subluxation in 100% of the treated eyes *[see Nonclinical Toxicology]*.

### 5.4 Retinal Breaks
In the controlled trials, the incidence of retinal detachment was 0.9% in the JETREA group and 1.6% in the vehicle group, while the incidence of retinal tear (without detachment) was 1.1% in the JETREA group and 2.7% in the vehicle group. Most of these events occurred during or after vitrectomy in both groups. The incidence of retinal detachment that occurred pre-vitrectomy was 0.4% in the JETREA group and none in the vehicle group, while the incidence of retinal tear (without detachment) that occurred pre-vitrectomy was none in the JETREA group and 0.5% in the vehicle group.

### 5.5 Dyschromatopsia
Dyschromatopsia (generally described as yellowish vision) was reported in 2% of all patients injected with JETREA. In approximately half of these dyschromatopsia cases there were also electroretinographic (ERG) changes reported (a- and b-wave amplitude decrease).

## 6 ADVERSE REACTIONS
The following adverse reactions are described below and elsewhere in the labeling:

- Decreased Vision *[see Warnings and Precautions]*
- Intravitreal Injection Procedure Associated Effects *[see Warnings and Precautions and Dosage and Administration]*
- Potential for Lens Subluxation *[see Warnings and Precautions]*
- Retinal Breaks *[see Warnings and Precautions and Dosage and Administration]*

### 6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

Approximately 800 patients have been treated with an intravitreal injection of JETREA. Of these, 465 patients received an intravitreal injection of ocriplasmin 0.125 mg (187 patients received vehicle) in the 2 vehicle-controlled studies (Study 1 and Study 2).

The most common adverse reactions (incidence 5% - 20%) listed in descending order of frequency) in the vehicle-controlled clinical studies were: vitreous floaters, conjunctival hemorrhage, eye pain, photopsia, blurred vision, macular hole, reduced visual acuity, visual impairment, and retinal edema.

Less common adverse reactions observed in the studies at a frequency of 2% - < 5% in patients treated with JETREA included macular edema, increased intraocular pressure, anterior chamber cell, photophobia, vitreous detachment, ocular discomfort, iritis, cataract, dry eye, metamorphopsia, conjunctival hyperemia, and retinal degeneration.

Dyschromatopsia was reported in 2% of patients injected with JETREA, with the majority of cases reported from two uncontrolled clinical studies. In approximately half of these dyschromatopsia cases there were also electroretinographic (ERG) changes reported (a- and b-wave amplitude decrease).

### 6.2 Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. Immunogenicity for this product has not been evaluated.

## 8 USE IN SPECIFIC POPULATIONS
### 8.1 Pregnancy: Teratogenic Effects
Pregnancy Category C. Animal reproduction studies have not been conducted with ocriplasmin. There are no adequate and well-controlled studies of ocriplasmin in pregnant women. It is not known whether ocriplasmin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The systemic exposure to ocriplasmin is expected to be low after intravitreal injection of a single 0.125 mg dose. Assuming 100% systemic absorption (and a plasma volume of 2700 mL), the estimated plasma concentration is 46 ng/mL. JETREA should be given to a pregnant woman only if clearly needed.

### 8.3 Nursing Mothers
It is not known whether ocriplasmin is excreted in human milk. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when JETREA is administered to a nursing woman.

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

### 8.5 Geriatric Use
In the clinical studies, 384 and 145 patients were ≥ 65 years and of these 192 and 73 patients were ≥ 75 years in the JETREA and vehicle groups respectively. No significant differences in efficacy or safety were seen with increasing age in these studies.

## 10 OVERDOSAGE
The clinical data on the effects of JETREA overdose are limited. One case of accidental overdose of 0.250 mg ocriplasmin (twice the recommended dose) was reported to be associated with inflammation and a decrease in visual acuity.

## 13 NONCLINICAL TOXICOLOGY
### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity, mutagenicity or reproductive and developmental toxicity studies were conducted with ocriplasmin.

### 13.2 Animal Toxicology and/or Pharmacology
The ocular toxicity of ocriplasmin after a single intravitreal dose has been evaluated in rabbits, monkeys and minipigs. Ocriplasmin induced an inflammatory response and transient ERG changes in rabbits and monkeys, which tended to resolve over time. Lens subluxation was observed in the 3 species at ocriplasmin concentrations in the vitreous at or above 41 mcg/mL, a concentration 1.4-fold above the intended clinical concentration in the vitreous of 29 mcg/mL. Intraocular hemorrhage was observed in rabbits and monkeys.

A second intravitreal administration of ocriplasmin (28 days apart) in monkeys at doses of 75 mcg/eye (41 mcg/mL vitreous) or 125 mcg/eye (68 mcg/mL vitreous) was associated with lens subluxation in all ocriplasmin treated eyes. Sustained increases in IOP occurred in two animals with lens subluxation. Microscopic findings in the eye included vitreous liquefaction, degeneration/disruption of the hyaloideo-capsular ligament (with loss of ciliary zonular fibers), lens degeneration, mononuclear cell infiltration of the vitreous, and vacuolation of the retinal inner nuclear cell layer. These doses are 1.4-fold and 2.3-fold the intended clinical concentration in the vitreous of 29 mcg/mL, respectively.

## 14 CLINICAL STUDIES
The efficacy and safety of JETREA was demonstrated in two multicenter, randomized, double masked, vehicle-controlled, 6 month studies in patients with symptomatic vitreomacular adhesion (VMA). A total of 652 patients (JETREA 464, vehicle 188) were randomized in these 2 studies. Randomization was 2:1 (JETREA:vehicle) in Study 1 and 3:1 in Study 2.

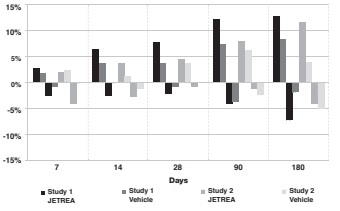
Patients were treated with a single injection of JETREA or vehicle. In both of the studies, the proportion of patients who achieved VMA resolution at Day 28 (i.e., achieved success on the primary endpoint) was significantly higher in the ocriplasmin group compared with the vehicle group through Month 6.

The number of patients with at least 3 lines increase in visual acuity was numerically higher in the ocriplasmin group compared to vehicle in both trials, however, the number of patients with at least a 3 lines decrease in visual acuity was also higher in the ocriplasmin group in one of the studies (Table 1 and Figure 1).

**Table 1: Categorical Change from Baseline in BCVA at Month 6, Irrespective of Vitrectomy (Study 1 and Study 2)**

| **Study 1** | | | |
|---|---|---|---|
| | JETREA | Vehicle | Difference |
| | N=219 | N=107 | (95% CI) |
| **≥ 3 line Improvement in BCVA** | | | |
| Month 6 | 28 (12.8%) | 9 (8.4%) | 4.4 (-2.5, 11.2) |
| **> 3 line Worsening in BCVA** | | | |
| Month 6 | 16 (7.3%) | 2 (1.9%) | 5.4 (1.1, 9.7) |
| **Study 2** | | | |
| | JETREA | Vehicle | Difference |
| | N=245 | N=81 | (95% CI) |
| **≥ 3 line Improvement in BCVA** | | | |
| Month 6 | 29 (11.8%) | 3 (3.8%) | 8.1 (2.3, 13.9) |
| **> 3 line Worsening in BCVA** | | | |
| Month 6 | 10 (4.1%) | 4 (5.0%) | -0.9 (-6.3, 4.5) |

**Figure 1: Percentage of Patients with Gain or Loss of ≥ 3 Lines of BCVA at Protocol-Specified Visits**




## 16 HOW SUPPLIED/STORAGE AND HANDLING
Each vial of JETREA contains 0.5 mg ocriplasmin in 0.2 mL citric-buffered solution (2.5 mg/mL). JETREA is supplied in a 2 mL glass vial with a latex free rubber stopper. Vials are for single use only.

### Storage
Store frozen at or below -4°F ( -20°C). Protect the vials from light by storing in the original package until time of use.

## 17 PATIENT COUNSELING INFORMATION
In the days following JETREA administration, patients are at risk of developing intraocular inflammation/ infection. Advise patients to seek immediate care from an ophthalmologist if the eye becomes red, sensitive to light, painful, or develops a change in vision *[see Warnings and Precautions]*.

Patients may experience temporary visual impairment after receiving an intravitreal injection of JETREA *[see Warnings and Precautions]*. Advise patients to not drive or operate heavy machinery until this visual impairment has resolved. If visual impairment persists or decreases further, advise patients to seek care from an ophthalmologist.

Manufactured for:
ThromboGenics, Inc.
101 Wood Avenue South, 6th Floor
Iselin, NJ 08830

U.S. License Number: 1866

Version 1.0
Initial U.S. Approval: 2012
ThromboGenics U.S. patents: 7,445,775; 7,547,435; 7,914,783 and other pending patents.



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continues. "With that said, data from Staar show that less than 1 percent of lenses are exchanged because of vaulting issues. Data from the five-year study of the myopic ICL and the literature show about a 2-percent rate of cataract formation, with both age and degree of myopia being significant risk factors for development of cataracts. There was a small subset of patients who developed increased cell loss in the first few years after surgery, but the rate of cell loss appears to have leveled off over time. The rate of reported corneal edema with the ICL in the literature and with reporting to Staar appears to be low—0.02 percent—and primarily related to the time of surgery, emphasizing the importance of good technique training prior to implanting ICLs."

## Aligning the Axis in the Eye

In terms of correcting astigmatism, Dr. Vukich notes that the concept here is exactly the same as with an in-the-bag aphakic lens. "However, in a toric in-the-bag IOL the meridian of the axis of astigmatism is not predetermined," he says. "After implantation you simply rotate the lens to whatever meridian is required for astigmatism control. In contrast, the ICL has the axis at a specific meridian. It's designed to be aligned with the 180-degree meridian, with only a minor adjustment of no more than 22 degrees rotation, clockwise or counterclockwise from the 180-degree meridian to correct the astigmatism."

"ICLs are primarily placed horizontally because the sizing of the lens is based on placing the lens in a horizontal meridian," explains Dr. Price. "You don't want to go too far off that meridian. Suppose that Staar has a 10-D sphere lens with 2 D of plus cylinder in stock, with the cylinder at 90 degrees on the lens. You can use that lens in someone with cylinder at 90, 95 or 105 degrees; you would leave the lens horizontal to address 90-degree cylinder, rotate it 5 degrees for cylinder at 95 degrees, and rotate it 15 degrees to treat cylinder at 105 degrees. Staar tells you how much you need to rotate it when you get the lens."

Dr. Vukich notes that allowing this small adjustment eliminates the need for Staar to create a different lens for every possible axis of astigmatism, in addition to different lens sizes, spherical powers in half-diopters from 3 to -20 and astigmatism powers up to 6 D in half-diopter steps (outside the United States—the range of astigmatic correction available in the United States will be determined by the FDA if and when the lens is approved). "Because of this lens design, each lens is matched to what the patient needs," he says. "You go to the online toric ICL calculator; you type in the patient's refractive error. The online calculator gives you a solution and specifies the lens from inventory that you need, along with the instructions for aligning it for that specific patient. The lens is also delivered with a positioning diagram.

"We know that positionally, the Visian Toric ICL is extremely stable," Dr. Vukich adds. "In fact, this was one of the things the FDA has looked at carefully; it meets the standards for rotational stability and refractive correction. It stays where you put it. At the same time, moving it to place it exactly where you want it is not difficult."

## Learning Curve

Dr. Vukich says the learning curve for a surgeon implanting these lenses will be low. "Anyone who is comfortable with ICLs, or even intraocular surgery in general, can very quickly master this," he says. "The Visian Toric looks, feels and handles exactly like the myopic Visian ICL. They insert identically; they go into the exact same meridian—the horizontal meridian. The only difference is that the Visian toric may require a slight adjustment, less than one clock hour, once the lens is in the ciliary sulcus. It's a trivial positioning issue."

Nevertheless, Dr. Vukich says that a surgeon who has never implanted an ICL should undergo a certification course before implanting a Visian Toric. "The skills necessary to implant an ICL are completely within the tool kit of any anterior segment surgeon," he notes. "However, there are nuanced techniques we've learned over the years that will optimize your outcomes—little tips that make things easier for the surgeon. So if you haven't put in an ICL previously you should take a training course."

Dr. Price agrees. "I would recommend taking a course in implanting the Visian if you haven't implanted an ICL before," he says. "You need to take the course for two reasons: to learn the surgical technique, and to learn how to size the lens and how to order it."

Dr. Vukich adds that this type of lens is well-suited to a full range of correction, and the surgery is not "dose-dependent." "By that I mean that the surgical technique and the implant itself aren't any riskier or more challenging whether the patient is -3 D or -20 D," he says. "That's in contrast to LASIK, where the larger the correction is, the more tissue has to be ablated and the greater the impact on the corneal stroma. The ICL uses the same surgery for every correction; it's just a different power of lens.

"I think many U.S. surgeons have eagerly anticipated this lens," he adds. "I believe it will be readily adopted." REVIEW

*Dr. Vukich is a consultant to Staar Surgical Company. Dr. Price has been a paid consultant for Staar, but does not have any financial stake in the company or the ICLs.*


Always fascinating, often promising, ophthalmic research is alive and well worldwide.

This year's Research Report takes a slightly different tack from what you might be used to. The overall number of projects described is far less than has been our custom with traditionally shorter, abstract-based reports, but we hope that the greater depth of description is worth the trade-off. With fewer topics, however, it's worth pointing out that this is by no means intended as an exhaustive report of what ophthalmic researchers are up to. These topics may simply represent intriguing approaches that appealed to the Review staff or our medical advisors. If your favorite topic is not here, there are plenty more pages where these came from.

For their guidance and recommendations, we are very grateful to Drs. Carl Regillo, Kuldev Singh, Louis Probst, Penny Asbell and Natalie Afshari.


# Glaucoma

Research in the field of glaucoma continues to produce promising new approaches to diagnosis and treatment. Here, five scientist/clinicians share the latest findings in three areas: cellular-level imaging; using genetics to diagnose and treat the disease; and long-term drug delivery.

## Imaging at the Cellular Level

One of the most interesting and potentially significant areas of research in glaucoma today is the use of increasingly sophisticated imaging technology to reveal more about the structural changes that accompany glaucoma at the cellular level.

"The technology available to image retinal ganglion cells has advanced enormously over the past few years," says Keith Martin, MA, DM, MRCP, FRCOphth, professor of ophthalmology at the University of Cambridge and Clinical Director for Ophthalmology at Cambridge University Hospitals NHS Foundation Trust. "Some of the work that's going on in the research lab has allowed us to see structural details we've never been able to see before. In fact, there's now some evidence that using advanced imaging techniques to evaluate the retinal ganglion cell complex could be predictive of future functional loss.

"Our lab is using high-resolution imaging techniques to see what happens to retinal ganglion cells, in particular their dendritic trees, when they're injured in glaucoma," he continues. "In animal models we can now fluorescently label ganglion cells using various techniques, and we can observe, *in vivo*, changes that occur longitudinally over time. For example, we've learned from experimental models that one of the things that goes wrong in early glaucoma is axonal transport—the movement of stuff back and forth from the retina to the brain along ganglion cell axons. If we can find a way to image axonal transport in real time in humans—something we can already do in animal models—that might provide a readout of the health of the ganglion cells across the retina.

"Basically, we're interested in identifying markers for cell sickness rather than cell death," he says. "We can identify a cell that is undergoing apoptosis, but that cell is already effectively dead and will disappear shortly. On the other hand, some of the early changes that occur when a cell is put under stress are reversible, and what we're looking for is rescue, not just counting dead bodies."

Dr. Martin notes that this technology could make a big difference in clinical trials of potential neuroprotective drugs. "The neuroprotection trials in glaucoma have been very long and expensive because visual fields are a highly variable outcome measure," he says. "It takes a long time to see a protective effect. What we'd like is something more sensitive, something that will tell us whether our treatments are having a beneficial effect on cells in a more timely and cost-effective manner.

"Unfortunately, right now we don't have any good way to image retinal ganglion cells or their dendrites in humans," he notes. "We don't want to be doing fluorescein injections in human eyes, and some of the best animal models are transgenic animals that express fluorescent proteins, which is not a viable model for humans. However, many researchers are working on ways to use these imaging technologies in human eyes.

> **"We're definitely reaching a point of critical mass in [genomic] research ... now our perseverance is ready to pay off."**
> **—Janey Wiggs, MD, PhD**

"It's an exciting time to be in this field," he concludes. "There's a lot going on and we've got fantastic tools. I can't think of any other area of neuroscience or medicine where we've got the ability to directly observe relevant processes at cellular and subcellular levels in detail, in the living organism."

## Uncovering the Genetics of Glaucoma

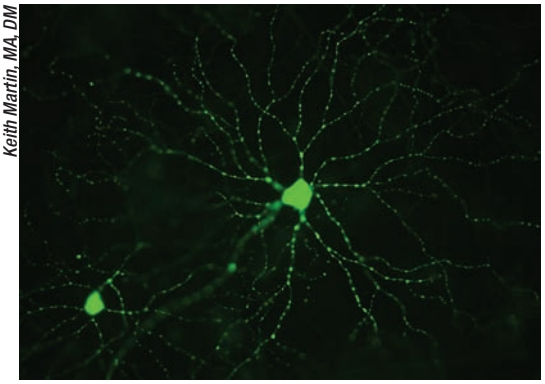
Another area that holds great potential for revolutionizing glaucoma diagnosis and treatment is the study of genetics. Janey Wiggs, MD, PhD, Paul Austin Chandler Associate Professor of Ophthalmology at Harvard Medical School and associate director of the Ocular Genomics Institute in Boston, explains why research in this area started slowly but is now reaching critical mass.

"About 20 years ago people started working with the genetics resources that were available, which meant using genetic linkage analysis with families who had early-onset glaucoma," says Dr. Wiggs. "That was pretty slow going, but this work did identify a handful of genes that cause early-onset types of glaucoma. However, to identify genes influencing adult-onset disease we needed new approaches and larger collections of cases and controls."

Dr. Wiggs lists a number of factors that are now producing much more information at a much faster rate:

• ***Completion of the human genome sequence and map.*** "In 2003 the human genome sequence was completed," she says. "That was very important because it created a map of many markers throughout the human genome. Those markers—specifically, the single nucleotide polymorphisms, or SNPS—made it possible to evaluate regions

of the human genome for genetic associations. This was followed by the completion of the HapMap in 2005, which provided a roadmap for the thousands of SNPs that had already been discovered. With the map in hand, we were able to start doing things like genome-wide association studies, which is what's needed to find genetic risk factors for adult-onset disease."



Keith Martin, MA, DM

New high-resolution imaging techniques are allowing researchers to view cell structures in greater detail than ever before. This may allow the identification of cells in the early stages of glaucoma. Pictured above: retinal ganglion cell dendritic trees.

• ***Larger studies.*** Dr. Wiggs says another restraining factor was an insufficient number of cases and controls. "In the beginning investigators were doing this kind of analysis using really small sample sizes, like 300 cases and 300 controls," she explains. "That just wasn't enough to provide a statistically significant result. It wasn't until 2009 that we were able to get funding for the GLAUGEN project—the first large-scale genome-wide association study for primary opren-angle glaucoma—that included 1,000 cases and 1,000 controls. But the real progress occurred when we were able to conduct the NEIGHBOR study, which added another 2,500 cases and 2,500 controls. This allowed us to do a genome-wide association study that had some statistical significance for both POAG and a normal-tension glaucoma subset.

"Even so, these studies have only found a half-dozen genetic risk factors for POAG, normal-tension glaucoma, pseudoexfoliation glaucoma and angle-closure glaucoma," she says. "These genes are the tip of the proverbial iceberg; to develop a comprehensive picture of the genetic factors that influence susceptibility to adult-onset disease we have to find a lot more genes. To do that, we need even larger sample sizes. That brings us to the NEIGHBORHOOD study, which is going on right now. More than 20 sites are collaborating on one study; as a result we have about 4,000 cases and 30,000 controls. In addition, we're contributing data to international studies that also have very large sample sizes. These large studies should finally allow us to find the majority of genetic risk factors that are contributing to adult-onset disease."

• ***More sophisticated devices in clinics.*** "Another factor contributing to new breakthroughs in this area is the availability of clinical measurement devices like swept-source OCT," notes Dr. Wiggs. "Technologies like this can help define genetically important subgroups of glaucoma patients that have a less-complex genetic underpinning, making the genes in question easier to find.

"For example, in one study we looked at the 10 to 12 percent of glaucoma patients who only have loss of vision in the very center of the visual field, which we believe represents a clinical subtype of glaucoma," she says. "We've already found three genetic risk factors associated with this type of vision loss. The most recent work on this was recently described in the journal *Ophthalmology*."[1]

• ***Rare variant analysis.*** "Rare variant analysis allows researchers to identify specific changes in genes that may be responsible for the biological changes under investigation," says Dr. Wiggs. She notes that the markers that have been studied and used in some screening tests usually do not have a functional, biological effect (although there are exceptions); instead they indicate the presence of a nearby gene or mutation that is having a biological impact. "It wasn't until the development of the rare variant analysis that we've been able to identify the specific changes in the genes that are actually causing the problem," she says. "We're in the midst of doing that kind of analysis as part of the NEIGHBOR project."

## Current Developments

"In addition to the really large studies, several things are happening right now that are really exciting," notes Dr. Wiggs. "One is using modern technologies to identify mutations in families with early-onset glaucoma to help define the diagnosis and inform genetic counseling. Exome-sequencing technology has allowed us to develop test panels that can find the mutations related to early-onset disease in about 90 days; in the past that could have taken a year. So now we can test families with early-onset glaucoma; if they have a mutation in a known gene, we can identify who is at risk and who's not at risk, which can be a very important piece of information for the family. We can also restrict treatment to the family members who carry the mutations."

Dr. Wiggs adds that there has been early progress toward gene-targeted therapies. "For example," she says, "there's some evidence that by using chemical chaperones, we may be able to treat the underlying molecular mechanism of disease caused by mutations in the myocillin gene.

"All of this sounds complicated, but ultimately, we want to do a very simple thing," she says. "In the glaucoma clinic we want to be able to sit down with patients and tell them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what their risk of developing the disease is, based on their genetic background and environmental exposure history. And of course, we'd love to tailor therapy to those factors that are specific to the patient's genetic situation. Eventually, we may be able to use gene-based and gene-directed therapies to mitigate or cure the disease.

"We're definitely reaching a point of critical mass in this research," she concludes. "That's what makes it really exciting right now. Until recently, we were missing the right resources to do the experiments. We needed the human genome to be completed; we needed the haploid map to show us how to look at the relevant markers; and we needed the large sample sizes to conduct the analyses. It took a while to reach that point, but now our perseverance is ready to pay off."

## Long-term Drug Delivery

With patient compliance an ongoing problem in glaucoma, long-term delivery of glaucoma medications has become a high priority for many researchers. Several high-tech delivery methods are now in the pipeline.

One approach being developed at the Singapore National Eye Center involves subconjunctival injection of nanoliposomal latanoprost. A group headed by Tina Wong, MBBS, PhD, FRCOphth, senior consultant ophthalmologist to the Glaucoma Service at Singapore National Eye Centre and head of the Ocular Therapeutics and Drug Delivery Research Group at the Singapore Eye Research Institute, developed the drug formulation, called Lipolat. Nanoparticles in the formulation slowly release the latanoprost over time after injection.

> **"A lot of groups are working on different models [for long-term drug release]. The big challenge is making sure these models work as well in humans as they work in animal models."**
>
> **—Ramesh S. Ayyala, MD**

"The liposomal latanoprost comes in ready-to-use individual vials that you draw up with a 1-mL insulin syringe," says Dr. Wong. "With the patient in the clinic we apply topical anesthesia to the superior bulbar conjunctiva using an orange stick soaked in the drug; then the liposomal latanoprost is delivered subconjunctivally via a 27-g. needle. The advantages of delivering the drug in this way include fast and easy administration in the clinical setting and no learning curve for the ophthalmologist."

The protocol has now been tried in both monkeys and humans, with positive results. In ocular hypertensive monkeys, a single injection lowered IOP for 120 days, with efficacy similar to that of daily drop use. A more recent open-label, pilot study involved six human patients with ocular hypertension or open-angle glaucoma. Unmedicated baseline pressures ranged from 25 to 33 mmHg; each patient received a single injection of 100 µl of Lipolat containing 100 µg of latanoprost.

Patients were followed for three months, including monitoring diurnal IOP in months one and three. All patients had at least a 5-mmHg drop in pressure; three patients (50 percent) had a reduction ≥10 mmHg. Pressure dropped within one hour of receiving the injection and remained reduced throughout the three-month period; no patients showed signs of inflammation or other safety issues. "The data so far show an average IOP lowering of 20 percent from baseline, lasting at least three months," says Dr. Wong. At this writing, the study had just been accepted for publication in the journal *Drug Delivery and Translational Research*.

Dr. Wong says they have tried this approach using other glaucoma drugs. "Some work well, others not as well," she notes. "It depends in part on the structural properties of the drug." She adds that the group is planning a larger multicenter study next. "Eventually, we hope to develop long-term delivery of other medications using the same platform technology," she says. "We hope this system will be available for widespread use within three years."

## A Polymer Drug Depot

Another system for long-term drug delivery currently under investigation is the Topical Ophthalmic Drug Delivery Device, or TODDD, being developed by Amorphex Therapeutics in Andover, Mass. "TODDD is a soft, elastomeric polymer insert designed to provide sustained drug release," explains Robert M. Feldman, MD, Richard S. Ruiz MD Distinguished University Professor, and chairman of the Ruiz Department of Ophthalmology and Visual Science at the University of Texas Medical School in Houston. "The insert, which is smaller than a dime, consists of a drug depot carrier, where the drug or drugs are contained in distinct chambers, and a matrix, throughout which the drug can be dispersed. The insert rests on the sclera under the eyelid; it's shaped so that it will stay in place."

Dr. Feldman says the TODDD insert is currently undergoing human trials. "The trials are designed to demonstrate human comfort and retention, as well as drug delivery effectiveness," he says. "Subjects will wear a timolol-impregnated insert 24/7 for 200-plus days in one eye. At the time of my recent presentation at the annual meeting of the American Glaucoma Society, 10 subjects had passed

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**RESTRICTIONS:**

- Patients must be able to lie flat and motionless in a supine position.
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The physician should base patient selection criteria on professional experience, published literature, and educational courses. Adult patients should be scheduled to undergo cataract extraction.

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- Capsular tear
- Corneal abrasion or defect
- Pain
- Infection
- Bleeding
- Damage to intraocular structures
- Anterior chamber fluid leakage, anterior chamber collapse
- Elevated pressure to the eye

**ATTENTION:** Refer to the LenSx® Laser Operator's Manual for a complete listing of indications, warnings and precautions.

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**INTENDED USES:** The VERION™ Reference Unit is a preoperative measurement device that captures and utilizes a high-resolution reference image of a patient's eye in order to determine the radii and corneal curvature of steep and flat axes, limbal position and diameter, pupil position and diameter, and corneal reflex position. In addition, the VERION™ Reference Unit provides preoperative surgical planning functions that utilize the reference image and preoperative measurements to assist with planning cataract surgical procedures, including the number and location of incisions and the appropriate intraocular lens using existing formulas. The VERION™ Reference Unit also supports the export of the high-resolution reference image, preoperative measurement data, and surgical plans for use with the VERION™ Digital Marker and other compatible devices through the use of a USB memory stick.

The VERION™ Digital Marker links to compatible surgical microscopes to display concurrently the reference and microscope images, allowing the surgeon to account for lateral and rotational eye movements. In addition, the planned capsulorhexis position and radius, IOL positioning, and implantation axis from the VERION™ Reference Unit surgical plan can be overlaid on a computer screen or the physician's microscope view.

**CONTRAINDICATIONS:** The following conditions may affect the accuracy of surgical plans prepared with the VERION™ Reference Unit: a pseudophakic eye, eye fixation problems, a non-intact cornea, or an irregular cornea. In addition, patients should refrain from wearing contact lenses during the reference measurement as this may interfere with the accuracy of the measurements.

Only trained personnel familiar with the process of IOL power calculation and astigmatism correction planning should use the VERION™ Reference Unit. Poor quality or inadequate biometer measurements will affect the accuracy of surgical plans prepared with the VERION™ Reference Unit.

The following contraindications may affect the proper functioning of the VERION™ Digital Marker: changes in a patient's eye between preoperative measurement and surgery, an irregular elliptic limbus (e.g., due to eye fixation during surgery, and bleeding or bloated conjunctiva due to anesthesia). In addition, the use of eye drops that constrict sclera vessels before or during surgery should be avoided.

**WARNINGS:** Only properly trained personnel should operate the VERION™ Reference Unit and VERION™ Digital Marker.

Only use the provided medical power supplies and data communication cable. The power supplies for the VERION™ Reference Unit and the VERION™ Digital Marker must be uninterruptible. Do not use these devices in combination with an extension cord. Do not cover any of the component devices while turned on.

Only use a VERION™ USB stick to transfer data. The VERION™ USB stick should only be connected to the VERION™ Reference Unit, the VERION™ Digital Marker, and other compatible devices. Do not disconnect the VERION™ USB stick from the VERION™ Reference Unit during shutdown of the system.

The VERION™ Reference Unit uses infrared light. Unless necessary, medical personnel and patients should avoid direct eye exposure to the emitted or reflected beam.

**PRECAUTIONS:** To ensure the accuracy of VERION™ Reference Unit measurements, device calibration and the reference measurement should be conducted in dimmed ambient light conditions. Only use the VERION™ Digital Marker in conjunction with compatible surgical microscopes.

**ATTENTION:** Refer to the user manuals for the VERION™ Reference Unit and the VERION™ Digital Marker for a complete description of proper use and maintenance of these devices, as well as a complete list of contraindications, warnings and precautions.

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30 days in the ongoing clinical trial, although one eye in a separate study has been through more than 280 days. All IOP measurements have been below the baseline average, as well as the average IOP in the untreated eye.

"One TODDD can disperse multiple drugs simultaneously," he adds. "Drugs incorporated into the TODDD insert thus far include timolol maleate, prostaglandins, pilocarpine, brimonidine, dexamethasone, prednisolone, ciprofloxacin, ibuprofen and lidocaine, demonstrating that the platform has the ability to potentially deliver many agents and treat many diseases."

Amorphex

The Topical Ophthalmic Drug Delivery Device is a soft elastomeric polymer insert containing a drug depot; it rests on the sclera under the eyelid, gradually dispersing the drug(s) over an extended period of time. The device is currently undergoing human trials.

Dr. Feldman notes that once inserted, the TODDD provides as much as three months of constant drug delivery, depending on the drug and whether it's placed in the matrix or the depot carrier. "Patients using this device wouldn't have to remember to take their drops daily, eliminating daily patient compliance issues," he points out. "Potential disadvantages would include possible patient intolerance and cost, as well as the possibility that the patient may not know if the device falls out." At this point, Dr. Feldman says this technology is at least five years from the marketplace.

## Slow-release Antifibrotics

Another system under development is the glaucoma slow-release drug delivery system, or GLASS. Unlike most of the other slow-release systems under development, GLASS is currently being investigated as a means of providing a slow, ongoing release of antifibrotic agents to minimize the postoperative fibrosis that impacts the function of glaucoma drainage devices. Ramesh S. Ayyala, MD, FRCS, FRCOphth, professor of ophthalmology and director of the glaucoma service at Tulane University School of Medicine in New Orleans, explains.

"Currently, 50 to 60 percent of glaucoma drainage devices fail within five years," he says. "When you place a glaucoma drainage device inside the subconjunctival space, most of the fibrosis happens in the first month. Over the next three months encapsulation sets in, leading to the hypertensive phase. The idea behind the GLASS system is that mitigating that initial burst of inflammation during the first month will translate to longer survival for the drainage device, helping to lower IOP."

Dr. Ayyala explains that his team developed a biodegradable polymer that melts over a period of two to three months in the subconjunctival tissue in the presence of aqueous. "During the process of biodegrading, the drug or drugs are released for up to one month," he says. "This produces an antifibrotic effect after glaucoma drainage device surgery. So far, after trying many combinations and quantities of drugs, the most effective setup seems to be a combination of 0.1 µm of mitomycin-C released in an initial three-day burst, followed by 30 days of sustained release of 0.9 mg of 5-fluorouracil."

Dr. Ayyala's team uses a unique method to cast the polymer so that it can absorb and then elute the drug. "The method is called 'breath technology,' " he says. "Humid air is blown horizontally across the polymer as it's being cast; the polymer traps the water molecules from the humid air. In 24 hours the water molecules evaporate, leaving behind 10- to 20-µm holes in the polymer. These are the holes through which the drug will elute. You can see them in electron microscopy photographs of the polymer."

To use both mitomycin-C and 5-fluorouracil, the drugs are loaded in separate layers. "The 5-fluorouracil is loaded first; then mitomycin-C is loaded on top," he explains. "The result is that the mitomycin gradually comes out in the first 24 to 48 hours to provide the initial burst that kills the fibroblasts that are coming in. The sustained 5-fluorouracil releases slowly over the next 30 days."

To test the effectiveness of this approach, Dr. Ayyala and colleagues recently conducted a study using two different polymer implants containing drugs, as well as a control implant, all attached to the end plate of Ahmed glaucoma valves implanted into rabbit eyes. One device, made of a polyhydroxyethylmethacrylate-based nonbiodegradable polymer, released mitomycin-C for about three weeks. The second device, made of their biodegradable poly (lactic-co-glycolic acid) polymer, released an initial three-day burst of mitomycin-C followed by 30 days of sustained-release 5-fluorouracil. Three months post-surgery the rabbits were sacrificed to evaluate the bleb wall thickness around the end plate.

At three months the bleb roof thickness of the control group was 544 ±170 µm; the nonbiodegradable polymer implant group was 373 ±143 µm ($p$=0.006); and the biodegradable dual-drug implant group was 316 ±55 µm ($p$<0.001). The polymer in the latter eyes had completely disappeared, as expected, and there were no cases of infection or avascular cystic bleb formation in any eyes.

Dr. Ayyala says that their work so far with animal mod-

els suggests that the fibrosis reaction and encapsulation is decreased by more than 50 percent when the GLASS system is employed. "We've seen as much as a 70-percent reduction in fibrosis at the end of three months in the rabbits," he says. "The other important thing about the system is that we're using less than 70 percent of the amount of mitomycin-C that many surgeons currently inject into human eyes at the time of trabeculectomy or Express shunt surgery."

Dr. Ayyala also notes that they haven't seen any side effects at all in the animal model. "We've used GLASS in about 150 rabbits so far," he says. "Not one rabbit has had an eroded conjunctiva or any cystic bleb formation. The blebs are nice and the encapsulation is there, but it's really thin. If this holds true in humans, then we'll have a very useful adjunct to glaucoma shunt surgery."

## Taking It One Step Further

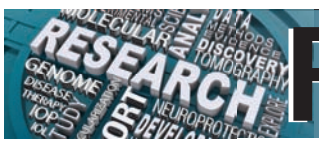
Dr. Ayyala observes that the hypertensive phase usually happens between postop day 30 and 90. "Normally we use an aqueous suppressant like Cosopt to reduce any IOP spike during the hypertensive phase," he says. "Now we're considering the possibility of having a third layer of drug behind the 5-fluorouracil, perhaps an aqueous suppressant such as timolol. The timolol would start to come out at the end of one month, after the 5-fluorouracil is completely released. If this strategy works, it will decrease IOP during the hypertensive phase. However, this possibility is still in the early stages.

"Once the pilot studies of the current device are initiated, we'll also be trying out a variation on the current model that we think will help with Express shunts and trabeculectomies," says Dr. Ayyala. "All you'll need to do is place the device in the area of the operation and close the flap. The polymer will release the drug very slowly over a period of one month. We're getting ready to do animal-model studies on that. In addition, we're in the early stages of developing a polymer device for delivering glaucoma medications that can be applied just like a drop; when applied into the inferior fornix it will latch onto the conjunctiva and release the drug over a period of three months.

"In fact, a lot of groups are working on different models like these," he says. "The big challenge is making sure these models work as well in humans as they work in animal models." *(To read about two more slow-release devices in the works, see Technology Update in the January 2014 issue of Review.)*

*Dr. Ayyala owns a patent on the GLASS system and has formed a company to manufacture the device. Dr. Feldman has no financial ties to the technologies discussed. Dr. Wong is co-owner of the Lipolat patent.*

1. Loomis SJ, Kang JH et al. Association of CAV1/CAV2 genomic variants with primary open-angle glaucoma overall and by gender and pattern of visual field loss. Ophthalmology 2014;121:2:508-16. doi: 10.1016/j.ophtha.2013.09.012. Epub 2013 Oct 25.




# Refractive Surgery

Surgeons and vision researchers have been hard at work on new technologies and techniques that either enhance wavefront-guided LASIK or aspire to replace it as the go-to procedure. Here's a look at several interesting areas of research.

• ***SMILE.*** Small-incision lenticular extraction is a surgical procedure performed with the Carl Zeiss Meditec Visumax femtosecond laser that creates a small lenticule of tissue within the stroma. The surgeon then extracts the lenticule through a corneal incision. The goal is to consolidate the refractive procedure into one surgery with one device and avoid the issues involved with creating a flap. SMILE is currently being studied in a U.S. Food and Drug Administration trial.

"We're just about done with the spherical myopia trial—we're not treating any astigmatism," says John Doane, MD, of St. Louis, a principal investigator for the study. "We can treat from -1 to -10 D and the results look good so far. For my personal data, I've treated 90 patients. One eye of each patient got LASIK and the other SMILE. With the longest postop at over a year, I've yet to enhance either procedure. The effectiveness of the SMILE procedure seems to be as good as anything we've seen with LASIK. The stability is rock-solid, and the results we get at one month stay

> **"We've done cross-linking in more than 1,000 patients over the past six years, and find that most of our patients get very nice changes in corneal shape and an improvement in uncorrected and best-corrected visual acuity." —William Trattler, MD**

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### INDICATIONS AND USAGE

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% or 0.15% is an alpha-adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

### IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

**Neonates and Infants (under the age of 2 years):** ALPHAGAN® P is contraindicated in neonates and infants (under the age of 2 years).

**Hypersensitivity Reactions:** ALPHAGAN® P is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

### WARNINGS AND PRECAUTIONS

**Potentiation of Vascular Insufficiency:** ALPHAGAN® P may potentiate syndromes associated with vascular insufficiency. ALPHAGAN® P should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

**Severe Cardiovascular Disease:** Although brimonidine tartrate ophthalmic solution had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

**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.

### DRUG INTERACTIONS

**Antihypertensives/Cardiac Glycosides:** Because ALPHAGAN® P may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with ALPHAGAN® P is advised.

**CNS Depressants:** Although specific drug interaction studies have not been conducted with ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% or 0.15%, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

**Tricyclic Antidepressants:** Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with ALPHAGAN® P in humans can lead to resulting interference with the IOP-lowering effect. Caution is advised in patients taking tricyclic antidepressants, which can affect the metabolism and uptake of circulating amines.

**Monoamine Oxidase Inhibitors:** Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side effect such as hypotension. Caution is advised in patients taking MAO inhibitors, which can affect the metabolism and uptake of circulating amines.

### ADVERSE REACTIONS

Adverse reactions occurring in approximately 10% to 20% of the subjects receiving brimonidine ophthalmic solution (0.1% to 0.2%) included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus. Adverse reactions occurring in approximately 5% to 9% included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

**Please see the Brief Summary of the full Prescribing Information on the next page.**

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## 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.

Adverse reactions occurring in approximately 10-20% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus. Adverse reactions occurring in approximately 5-9% included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

Adverse reactions occurring in approximately 1-4% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: abnormal taste, allergic reaction, asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, fatigue, flu syndrome, follicular conjunctivitis, foreign body sensation, gastrointestinal disorder, headache, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), insomnia, keratitis, lid disorder, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, somnolence, stinging, superficial punctate keratopathy, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity.

The following reactions were reported in less than 1% of subjects: corneal erosion, hordeolum, nasal dryness, and taste perversion.

**Postmarketing Experience**
The following reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, depression, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), syncope, and tachycardia. Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions.

## DRUG INTERACTIONS

**Antihypertensives/Cardiac Glycosides**
Because **ALPHAGAN® P** may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with **ALPHAGAN® P** is advised.

**CNS Depressants**
Although specific drug interaction studies have not been conducted with **ALPHAGAN® P**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

**Tricyclic Antidepressants**
Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **ALPHAGAN® P** in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

**Monoamine Oxidase Inhibitors**
Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

## USE IN SPECIFIC POPULATIONS

**Pregnancy**
Pregnancy Category B: Teratogenicity studies have been performed in animals.

Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (2.5 mg /kg/day) and rabbits (5.0 mg/kg/day) achieved AUC exposure values 360- and 20-fold higher, or 260- and 15-fold higher, respectively, than similar values estimated in humans treated with **ALPHAGAN® P** 0.1% or 0.15%, 1 drop in both eyes three times daily.

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, **ALPHAGAN® P** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

**Nursing Mothers**
It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from **ALPHAGAN® P** 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**
**ALPHAGAN® P** is contraindicated in children under the age of 2 years (see **CONTRAINDICATIONS**). During postmarketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate have not been studied in children below the age of 2 years.

In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse reactions with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50-83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

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

**Special Populations**
**ALPHAGAN® P** has not been studied in patients with hepatic impairment.

**ALPHAGAN® P** has not been studied in patients with renal impairment. The effect of dialysis on brimonidine pharmacokinetics in patients with renal failure is not known.

## OVERDOSAGE

Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse reaction reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving **ALPHAGAN® P** as part of medical treatment of congenital glaucoma or by accidental oral ingestion (see **USE IN SPECIFIC POPULATIONS**). Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

## NONCLINICAL TOXICOLOGY

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1 mg/kg/day in rats achieved 150 and 120 times or 90 and 80 times, respectively, the plasma $C_{max}$ drug concentration in humans treated with one drop of **ALPHAGAN® P** 0.1% or 0.15% into both eyes 3 times per day, the recommended daily human dose.

Brimonidine tartrate was not mutagenic or clastogenic in a series of in vitro and in vivo studies including the Ames bacterial reversion test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three in vivo studies in CD-1 mice: a host-mediated assay, cytogenetic study, and dominant lethal assay.

Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at doses which achieve up to approximately 125 and 90 times the systemic exposure following the maximum recommended human ophthalmic dose of **ALPHAGAN® P** 0.1% or 0.15%, respectively.

## PATIENT COUNSELING INFORMATION

Patients should 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**). Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

Patients also should 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.

As with other similar medications, **ALPHAGAN® P** may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

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**Revised: 11/2011**



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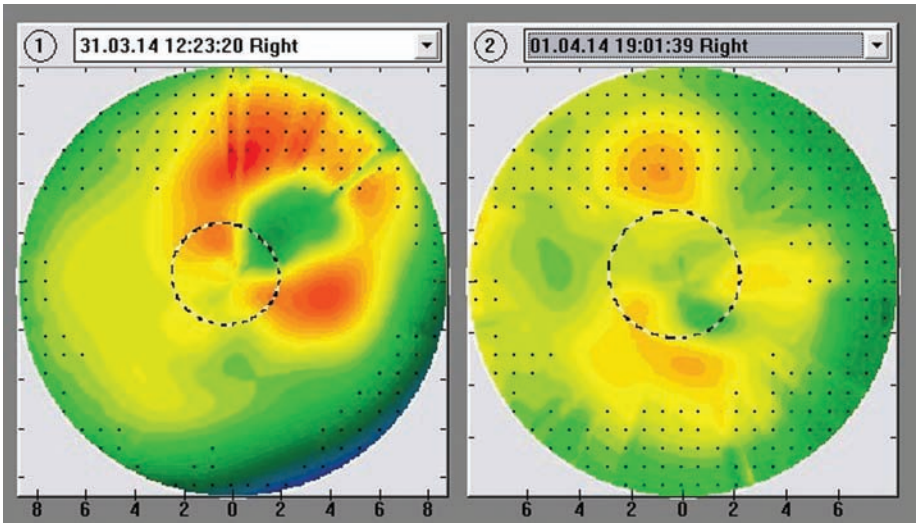
that way. The safety is as good as anything we've done."

One interesting aspect of SMILE that surgeons have commented on is how its predictability remains good even in higher levels of correction. "Looking at the international data, I was pretty sure that, for patients over -6 D, SMILE would be as good as anything we've seen," Dr. Doane says. "And my personal data has borne that out. It also seems to be just as good as LASIK for low myopes. As to why this is, consider what happens when we do excimer laser, either PRK or LASIK. In those procedures, we're opening the corneal stroma to the environment. As such, we're worried about temperature, humidity and barometric pressure—essentially the hydration effects on the stroma or Bowman's layer. But when you do a SMILE procedure, it's being done in a closed system, and all the energy is delivered within the cornea. This is one of the reasons that's being discussed as a possible explanation why SMILE is better predictability-wise with higher myopes; with a high myopic LASIK that lasts 40 seconds or so, the amount of cornea dehydration that occurs may result in more tissue removal per pulse near the end of the procedure than when the procedure first started."

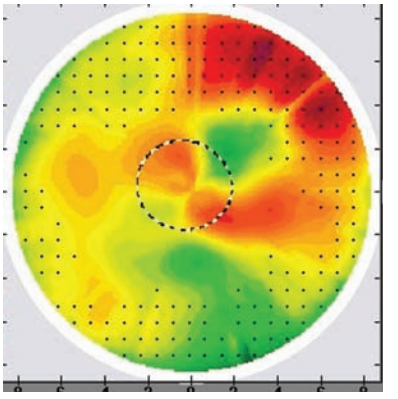



Pre- (left) and postop (right) topography of a patient with significant traumatic irregular astigmatism who underwent topography-guided LASIK. Preop refraction was +3 -4.5 x 55. The targeted refraction postop was +2 -4 x 50 (the axis of topographic astigmatism) with the EX500 WaveLight excimer. The result was 20/10 uncorrected.

The challenges to SMILE are hyperopic treatments—it currently doesn't do them—and enhancements. "The vast bulk—85 percent—of my patients are myopic or compound myopic/astigmatism," says Dr. Doane. "There may also be some mixed astigmatism. I personally don't treat a lot of hyperopia in my practice, however. So, my thinking is if SMILE works for myopia or compound myopic astigmatism, that's the bulk of the patients.

"In terms of enhancement," Dr. Doane continues, "right now the options are PRK or taking the 60-degree SMILE incision and enlarging it to 270 degrees so you can lift the flap and perform an excimer ablation. Will we ever be able to just do an all-femtosecond enhancement? We don't know yet, but there are some thoughts on the table on how that could be done."

• ***Combined refractive surgery/corneal cross-linking.*** Several years ago, surgeons began attempting to fortify the cornea in certain refractive surgery patients with a riboflavin/UV light cross-linking procedure, and have reported stable results. Current bones of contention center on leaving the epithelium on vs. taking it off and whether or not to use a higher fluence and less energy duration.



The difference map, preop to postop, of the patient above. The difference map appears identical to the preop astigmatism image in Figure 1. Athens surgeon John Kanellopoulos says this shows the specificity with which the topography-guided ablation is able to transfer the imaged irregularity as an actual laser intervention.

"We combine collagen cross-linking as a prophylactic measure in routine LASIK cases for high myopes and in hyperopes and have published extensively on this modality, which is now commercially known as LASIK-Xtra," says Athens, Greece, surgeon John Kanellopoulos. "In our practice, where it's been applied for the last eight years, it's a routine procedure. More than half our LASIK cases are now performed in conjunction with very high-fluence collagen cross-linking, specifically 30 mW applied for 80 seconds after pre-soaking the exposed cornea stroma for just 60 seconds. LASIK-Xtra has shown in our clinical practice—and we have reported—a significant advantage in hyperopic LASIK and a significant advantage in very high myopic LASIK, especially in younger patients; we see an

increased stability in these patients and a reduced number of retreatments needed. We've not seen significant risks with the combination."

In cases of progressive keratoconus, Dr. Kanellopoulos says a combination of topography-guided PRK—purely to normalize the corneal shape rather than to try to perfect vision—and collagen cross-linking has been helpful in more than 2,000 patients in his practice. He adds that Avedro (Waltham, Mass.) is currently conducting trials for LASIK-Xtra in the United States.

In addition to high-fluence protocols for cross-linking, another U.S. study, CXL-USA, is using a low-fluence/high duration method similar to the protocol used when cross-linking was introduced. The surgeons in the study leave the epithelium on. The CXL-USA study isn't for FDA approval, but to gather data to learn how to optimize the treatment. Miami surgeon William Trattler is one of the CXL-USA investigators and says the results with his epithelium-on, normal-fluence (4 mW for 30 minutes) treatment has shown good results. "Right now we're using it to treat patients with keratoconus, post-LASIK ectasia, pellucid marginal degeneration and patients with previous RK who have fluctuations in their vision," Dr. Trattler says. "We've done more than 1,000 patients over the past six years, and find that most of our patients get very nice changes in corneal shape and an improvement in uncorrected and best-corrected visual acuity. I've been doing epithelium-on cross-linking for four years and the results are as effective as epi-off without any of the risks or side effects."

In terms of the future, Dr. Kanellopoulos says Avedro is currently developing a cross-linking treatment designed purely to create a refractive change, like LASIK without an excimer. "At our Athens center, we have been able to achieve the correction of small refractive errors—mild myopias, hyperopias and/or astigmatism—with only collagen crosslinking using a very sophisticated device, the KXL II, which has had a CE mark in Europe since 2013," says Dr. Kanellopoulos. "This is very high-fluence collagen crosslinking, achieved through a specific pattern of UV light being produced and applied with a tracker on a cornea that has been pre-soaked with riboflavin, epi-off and epi-on. I think that this will be an area where the next page of refractive surgery may possibly concentrate on thousands, possibly millions, of people with very mild myopic errors."

The CXL-USA surgeons are currently looking for funding for a new study, CXLO, which will look at the effects of conductive keratoplasty combined with corneal cross-linking performed a day later. "We'll be looking at a combination of reshaping the cornea with CK and then locking that in with corneal cross-linking to achieve a better effect," explains Dr. Trattler.

• ***Topography-guided laser vision correction.*** The ability to add topography guidance to a refractive surgery gives surgeons more flexibility in how they can approach refractive cases, especially for patients with corneal irregularities. Two topography-guided systems have been approved in the United States, one by Alcon and the other by Nidek, though they're not yet in clinical use.

Dr. Kanellopoulos has worked with topography-guided systems for several years and thinks U.S. surgeons will appreciate their usefulness. "It is well-known that customized ablations have in the past employed wavefront-guidance," Dr. Kanellopoulos says. "But it is also well-known that wavefront imaging isn't possible in a very high percentage of those cases as the very high irregularity of the cornea creates difficulties in reproducible wavefront measurements. So, topography-guided ablations have found great clinical application over the last decade internationally, outside the United States, in treating difficult cornea problems such as corneal scars, decentered laser ablations, high astigmatism and asymmetric astigmatism, and even to address mild keratoconus to an extent. We have published in numerous publications and book chapters on topography-guided incorporation within the Athens Protocol as a means to not only stabilize keratoconus but to dramatically improve visual function." Dr. Kanellopoulos says the advantages of topography-guided ablations in comparison to wavefront-guided are that the cornea is easier to image and the images are more specific and sensitive. The topography-guided treatments can also flatten steep areas not only by treating the peaks of corneal curvature but by also treating around the troughs, allowing them to use about a third of the tissue that a wavefront-guided approach does. However, they have shortcomings, as well. "Topography-guided ablations only look at and diagnose cornea irregularities," Dr. Kanellopoulos says, "and do not have the ability to incorporate in their planning other biometric data that would also make them very predictable in spherical refractive correction in these corneas, whereas wavefront-guided ablations would treat that as well from the get-go."

> **"Topography-guided ablations have found great clinical application over the last decade internationally, outside the United States, in treating difficult cornea problems such as corneal scars, decentered laser ablations, high astigmatism and asymmetric astigmatism."**
>
> **—John Kanellopoulos, MD**

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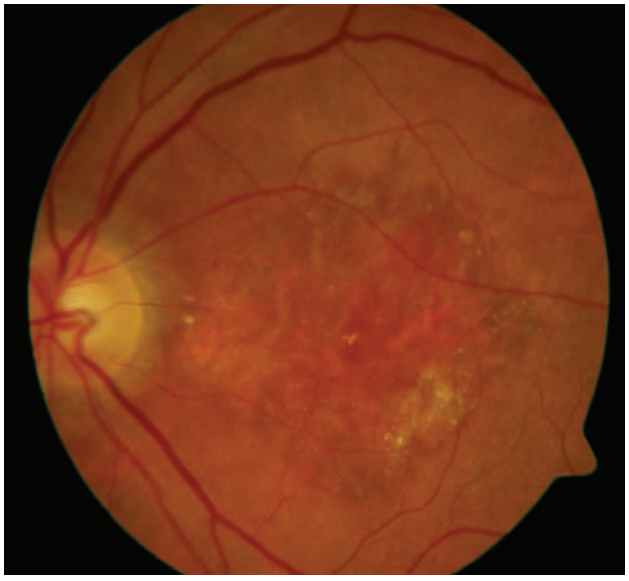
As ophthalmologists and researchers have learned more about the process behind diseases such as dry and wet age-related macular degeneration, they've been able to devise more specific treatments that target certain contributors to those diseases, such as vascular endothelial growth factor and inflammation. In addition, scientists have also been hard at work on entirely new treatment approaches to AMD and other retinal diseases, such as encapsulated cell technology and gene therapy. Here's a look at the latest trends in retinal research.

• ***Dry AMD drugs.*** One avenue of research in dry AMD is the area of complement inhibition. The complement system is part of the immune system that, according to researchers, complements the ability of antibodies and phagocytic cells to eliminate pathogens, and has been implicated in dry AMD. There are many complement factors that are part of the complement cascade, and many of them are the subjects of specific research projects. The most recent data on complement inhibition came out of the Genentech MAHALO study. "It looked at lampalizumab, a complement factor D inhibitor," explains Wills Eye retinal specialist Sunir Garg. "And it showed fairly impressive results: There was roughly a 20-percent reduction in geographic atrophy progression over the study period above and beyond placebo. This was the first trial to show such an impact. The other important finding to come out of that study was that in patients with a specific type of complement factor—complement factor I—the lampalizumab molecule seemed to give a 44-percent reduction in progression."

Phoenix surgeon Pravin Dugel says there are a few caveats with MAHALO, though. "First, it was a post-hoc analysis," he says. "In other words it was an analysis that was done after the study was completed. Second, this was demonstrated with a monthly injection. A legitimate question is: Are patients with geographic atrophy going to be willing to get a monthly injection when the end result may not be obvious to the patient, since you're trying to prevent visual loss rather than show improvement? Third, how many patients will be eligible for this treatment? It turns out this complement factor was present in about 57 percent of the patients in the study. So, it's not a small minority, but instead is a bit more than half. Obviously, all this data will have to be confirmed in a larger, Phase III study, which is currently being organized."

Another approach to dry AMD is visual cycle modulation, which is an attempt to alter the basic way rods and cones operate in an effort to decrease how much metabolic waste they produce, which researchers say represents the drusen that are the hallmark of dry AMD. "One of the strategies to decrease this metabolism is being undertaken by Acucela with its product emixustat in a Phase II/III study," Dr. Dugel says. "This treatment is exciting because the delivery system is a pill that's taken b.i.d. Therefore, the delivery method is very attractive."



Complement inhibition may be an effective strategy in treating patients with geographic atrophy, researchers say.

Dr. Garg says emixustat's Phase II data was "very encouraging in terms of slowing down disease progression." He says some observers will be interested to see the overall effect on the visual cycle. "The attractive thing is it's a pill that patients can take at home," he says. "The potential drawback is if the rods and cones aren't firing as often, perhaps patients won't see very well in dim illumination."

• ***Wet AMD treatment.*** In the clinical trial realm of wet AMD treatments, the agent that most are watching is the anti-pigment-derived growth factor Fovista from Ophthotec. PDGF has become an inviting target for blocking because it's been implicated in vessel remodeling, including the kind that occurs in wet AMD. "Ophthotec completed a large Phase II study of Fovista, the largest Phase II study ever done in retina, and the results were very encouraging," says Dr. Dugel. "It showed that

# LOTEMAX® GEL—UNIQUE FORMULATION DESIGNED TO CONTROL INFLAMMATION

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

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## 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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# LOTEMAX®

loteprednol etabonate
ophthalmic gel 0.5%

***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.**

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Tampa, Florida 33637 USA
US Patent No. 5,800,807

the combination of the drug, when used in conjunction with Lucentis vs. Lucentis alone, resulted in a 62 percent greater improvement in visual acuity. Second, those patients who received the combination had a regression, or shrinkage, of the neovascular membrane. Fluorescein angiography showed that the combination treatment caused regression of the neovascular membrane. On OCT, when we looked at the subretinal hyper-reflective material—which is felt to represent the lesion and lesion components—this also disappeared more commonly in the combination group. Perhaps what's most remarkable is, when we looked at patients who lost vision, those patients who lost vision and had Lucentis monotherapy tended to fibrose and have a large disciform scar, while those patients who lost vision—and there weren't many—and had combination therapy had very little, if any, fibrosis.

"So, I think the combination of Lucentis and Fovista has the potential to address two of the most important components of exudative AMD by having an anti-permeability effect early and an antifibrotic effect over the course of disease," Dr. Dugel adds.

One avenue of AMD treatment that's interesting doesn't involve the drug, but how drugs might get into the eye, and comes from a Rhode Island company called Neurotech.

"It's encapsulated-cell technology that acts as a sustained-delivery device," explains Philip Rosenfeld, MD, professor of ophthalmology at the Bascom Palmer Eye Institute. "The makers transfect RPE cells and place them in a cartridge, which is implanted in the pars plana much like the Retisert was implanted. The cells then produce certain drugs, such as anti-VEGF and anti-PDGF. If you want to stop the production, you take out the cartridge. We did a study in geographic atrophy a couple of years ago in which this device was implanted in the eye, and it sat there for two years cranking out this desired protein, and current clinical trial results from Mexico also look good."

**"Another approach to dry AMD is visual-cycle modulation, which is an attempt to alter the basic way rods and cones operate in an effort to decrease how much metabolic waste they produce, which researchers say represents the drusen that's the hallmark of dry AMD.**

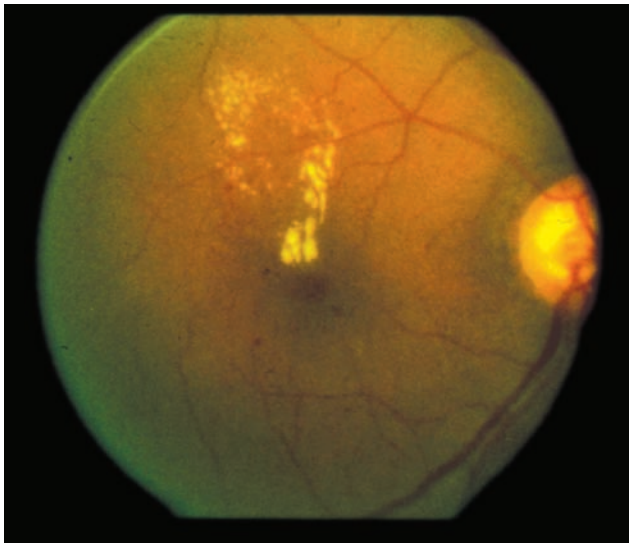
• ***Diabetic macular edema treatment.*** Regeneron's Eylea, which originally entered the ophthalmology world as a treatment for wet AMD, also recently posted results in a trial for the treatment of diabetic macular edema, and surgeons tentatively say it looks like a viable option. "In the Phase III trial of Eylea for DME, roughly 45 percent of the patients got at least two lines of improvement, and around 40 percent got three lines or better," says Dr. Garg. "The results are impressive, and comparable to the Lucentis results for DME. This situation that's now arisen is similar to what happened in AMD: You've got a drug like Lucentis, which is a great drug. Now you have another drug, which is similar, become available. Sometimes, certain drugs seem to work better for certain patients. What's interesting, and what we don't know about Eylea for DME, is we don't know if we can dose it differently than Lucentis or not, or if it will last longer or allow patients to not have to get as many injections. With wet AMD, of course, that's what the VIEW trials were about. In VIEW, patients would get three monthly injections of Eylea initially and then an injection every other month. The researchers found every-other-month injections, on average, worked as well as monthly injections seemed to work with Lucentis. But, in the DME trial of Eylea, we don't know if that's true or not. Any potential advantages to the different drug, though, have yet to be determined."

For patients at a certain stage of diabetic retinopathy, surgeons say an implantable, sustained-release device may be the best treatment option. To this end, Allergan has submitted data from its implantable dexamethasone device Ozurdex for the treatment of DME, and experts believe an FDA ruling is imminent. "The data looks quite good," says Dr. Garg. "The expectation is it will be approved, but what we don't know is if it will be approved for just pseudophakic patients or for both pseudophakic and phakic patients. The issue with steroid trials is that the steroid causes cataracts and, since diabetes patients tend to be younger than AMD patients, a cataract in a 45-year-old is a bit more of a big deal than a cataract in a 70-year-old. We also don't know if Ozurdex will be approved as first-line therapy or if it will be an option to be used only if patients don't respond sufficiently to anti-VEGF."

Dr. Dugel says a sustained-release option might be ideal for certain patients. "We know that anti-VEGF, though effective, when given on monthly basis is difficult to sustain," he says. "We also know that there are some patients in whom inflammation is a factor, as well as some patients in whom anti-VEGF monotherapy isn't sufficient. So, the most exciting thing for DME would be the ability to use sustained-release delivery devices." In addition to Ozurdex, in the future, surgeons believe we may yet see the Iluvien implant (which releases fluocinolone), which was denied FDA approval, return. "I don't think the company is giving up, and I think the FDA is still receptive to the conversation," says Dr. Garg. *(For an update on Iluvien's FDA review, please see*

*Review News, p. 9.)*

Dr. Dugel thinks having both Ozurdex and Iluvien approved would give ophthalmologists the most flexibility in treatment, since they're similar but different. "It's important to understand that these devices aren't the same," Dr. Dugel explains. "The elution rates are different. For instance, with Ozurdex you get a burst pattern in which there's an initial increase of the steroid, dexamethasone, and then a gradual decline in the release. And, afterward, the material is entirely biodegradable. With Iluvien, you get near zero-order kinetics and it lasts for up to three years. Its material isn't biodegradable, though, because it's surrounded by an inert casing, with only the tips exposed."



Depending on the stage of a patient's diabetic macular edema, a course of therapy involving a sustained-release steroid, if and when it's approved, could be the option physicians have been waiting for.

"The reason these devices are exciting is that although we have patients in whom anti-VEGF therapy with or without laser may be sufficient," says Dr. Dugel, "we also have patients who have an unmet need in whom it's not sufficient. In those patients, we may be able to give Ozurdex first, maybe a few times, and that may be sufficient. Yet we also have patients with very severe disease where even that is not sufficient, and in such severe patients we may be able to give Iluvien that will last for three years. Hopefully, these steroid delivery devices will be approved very soon because we desperately need combination treatment options in different phases and severities of DME."

• ***Gene therapy.*** Gene therapy is a broad term that can mean implanting viral vectors that carry genes that code for the release of an anti-VEGF protein to implanting a viral vector that insinuates itself into a faulty part of the eye's genetic code and fundamentally changes the DNA so that it works properly again.

Two companies, Avalanche (Sydney, Australia) and Genzyme (Cambridge, Mass.), are studying the former approach, using a gene to release therapeutic proteins in the eye. Boston retinal specialist Jeffrey Heier, director of the vitreoretinal service at Ophthalmic Consultants of Boston, and a scientific advisor for Genyzme, says, "First, we think gene therapy is very well-suited to the eye because in the eye there are diseases that have been well–studied, tissues that are accessible—either by intravitreal or subretinal delivery—and you have ways of studying the outcomes. In other words, you can monitor the outcome with technology such as fundus photography or OCT. These characteristics make the eye a nice target for gene therapy.

"Next is the concept that so many of the advances we've seen in the past decade require intravitreal injections," Dr. Heier continues. "While the safety and efficacy of these has been quite good, there's still a treatment burden to these injections, especially when the injections, or the monitoring, are required so frequently. Gene therapy offers the potential to be able to achieve this with a single injection that lasts for a prolonged period of time. The concept of treating these eyes that require multiple anti-VEGF injections with gene therapy instead is very enticing."

Dr. Heier says the process is yielding positive results so far. "You take a gene that codes for a protein, such as an anti-VEGF protein (both Genzyme and Avalanche use sFLT01, a soluble VEGF receptor), and combine that with AAV2—adeno-associated virus," Dr. Heier explains. "AAV2 has been studied in numerous trials—around 20 to date, I believe—for many different diseases, and its safety profile is encouraging. You combine the two and inject the gene therapy product, and the gene is expressed in certain cells and these cells, in essence, produce the anti-VEGF protein."

He says that different routes of administration of the gene therapy product offer different benefits. "One approach, which is used by Genzyme, is the intravitreal approach, which has certain advantages," says Dr. Heier. "The other is the subretinal approach, employed by Avalanche, that offers different advantages. The advantage of an intravitreal approach would be ease of administration—it's a technique that we all do multiple times each day. The potential disadvantage is the need to get adequate expression to the tissues you want, and it's been hypothesized that the ILM may prevent adequate uptake or expression from the gene therapy product in areas other than the macula and the peripheral retina.

"The subretinal approach requires a surgical procedure, but is one that many of us do already," Dr. Heier

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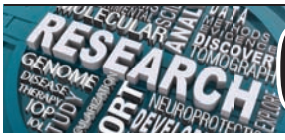
adds. "The procedure is similar to what we use for injecting tPA subretinally in patients with large submacular hemorrhages. So the advantage there is you know you're getting the gene therapy product to the cells that you're interested in having express it. But the disadvantage is you're doing a surgical procedure, albeit one that we use frequently and appears relatively safe."

Avalanche is conducting a Phase I/II study, and Genzyme is doing a Phase I currently. "Avalanche has presented its initial work, and it's encouraging," Dr. Heier says. "They've shown relative safety and nice anatomic outcomes in some patients. Their full data is going to be presented at the meetings in the fall. Genzyme hasn't released their results to date, but is expected to do so in the late fall. Both approaches have had preclinical work in animals that has shown a prolonged effect over time."

For rarer retinal degenerative conditions such as Leber's congenital amaurosis, experts say some of the most exciting work is being done by University of Pennsylvania researcher Jean Bennett, MD, PhD, which also incorporates an adenoviral vector in its mechanism. "The virus, carrying protein complementary DNA, is designed to incorporate itself into the RPE and fundamentally change the RPE's DNA, causing it to express proteins correctly," says Dr. Garg. "This enables the patients to have vision again. It is fixing what is wrong with the gene. In other areas of gene therapy, we know that we can map a genetic defect and, for some diseases, pinpoint it with a high degree of accuracy, but then we run into trouble when we try to do something about it—to replace it, if you will. Dr. Bennett's work is actually taking the virus and incorporating it into the patient's defective DNA, allowing the natural human cells to start making the correct protein."

> **"The reason sustained-delivery steroid devices for diabetic macular edema are exciting is that although we have patients in whom anti-VEGF therapy with or without laser may be sufficient, we also have patients who have an unmet need in whom anti-VEGF therapy is not sufficient."**
>
> **—Pravin Dugel, MD**

Dr. Dugel says one of the most exciting aspects of retinal research is the potential for crossover between diseases. "There's a lot of bio-physiologic commonality between exudative AMD, vein occlusion and DME," he says. "So, if any of these treatments succeed in neovascular AMD, I've no doubt we'll be seeing the same strategy taken up in vein occlusion and DME, as well."




# Contact Lenses

Today, contact lenses are promising to become far more than simply devices for refractive correction. Much of the leading-edge research involving contact lenses is focused on putting them to additional uses: for example, using them to monitor key biological markers in the eye or the body, or to deliver medications to the eye. One of the first products to expand the use of contact lenses was Sensimed's Triggerfish, a disposable silicone contact lens containing a microsensor that monitors intraocular pressure, now being widely used in research. However, the Triggerfish doesn't provide any optical correction, being intended only for brief periods of wear (e.g., 24 hours). Many of the high-tech contact lenses currently under development will take things a step further, also functioning as working refractive lenses intended for continuous wear.

## Monitoring Glucose in Diabetics

One of the most promising new projects has been undertaken by researchers at the University of Washington in partnership with Google. They're developing a contact lens that, if all goes according to plan, will be able to measure glucose levels in a person's tears, thus providing a way to monitoring systemic blood glucose levels. A spokesperson for Google says that their goal is to create a lens that also provides refractive correction, so that the product will help the most people. Obviously, such a lens would be a huge benefit to people with diabetes, many of whom currently have to prick their fingers and draw blood repeatedly to track their glucose levels.

> **"Today, contact lenses are promising to become far more than simply devices for refractive correction.**

In the prototypes, a number of miniaturized electronic components have been embedded in the periphery of the lens, outside the patient's line of vision. The electronics in the lens are powered by radio waves from a mobile device worn by the patient, rather than an internal power supply. The lenses are being made of standard materials such as hydrogels; a pinhole in the lens material will allow tear fluid to directly contact the glucose sensor. Current prototypes can take a glucose level reading once every second; the data will be transmitted to the patient's cellphone (and possibly the doctor's office as well). Dangerously high readings may trigger an alarm, and the developers are also working on the possibility of integrating tiny LED lights into the lenses that would illuminate when glucose levels become too high.

One current concern is whether the glucose level in the tears will provide an accurate measure of blood glucose levels; factors such as an eye infection or even simple irritation may alter the level in the tears, and there may be a lag time between high systemic levels and high levels in the tears. Generally, however, the researchers believe the two are correlated. Extensive monitoring of both is expected to help define what that correlation is, allowing the use of the tear levels as a systemic warning flag.

A new contact lens prototype releases drugs fairly evenly for 30 days or longer, while also correcting refractive error. Human trials of the lens should begin soon.

## Long-term Medication Delivery

Given the fact that contact lenses absorb and release fluids, one of the "holy grails" in contact lens research has been the development of a lens that can elute a drug slowly over a long period of time. Joseph B. Ciolino, MD, a physician-scientist in the Cornea Service at Massachusetts General Hospital in Boston, and Daniel S. Kohane, MD, PhD, from Boston's Children's Hospital, have developed prototypes of just such a lens. Their design incorporates a very thin drug polymer film sandwiched between layers made of standard contact lens hydrogel. Unlike a standard contact lens, which tends to release any drug it's soaked in within two hours or less, their prototype, used in animal models, releases medication fairly evenly over a period of 30 days or more. *(For more on the technology used in this lens, see Long-term Noninvasive Topical Drug Delivery in the January 2014 issue of Review.)*

"Right now we're focusing on delivering latanoprost and anti-inflammatory medications such as dexamethasone," says Dr. Ciolino. "We're also interested in using the lens to deliver antibiotics. If a drug-eluting contact lens were available, patients with uveitis or a corneal ulcer wouldn't have to take drops on an hourly basis. A contact lens like this might even be able to treat dry eye or ocular allergies. It's also possible that it could deliver more than one medication. For example, following cataract surgery the surgeon could place one of these contact lenses on the eye, where it would elute antibiotic and steroid for a week. At the one-week follow-up, the surgeon would simply remove it."

Dr. Ciolino sees a number of advantages to this system. "First, there's decreased frequency of administration," he says. "Second, the lens can provide positive reinforcement for compliance by correcting the patient's myopia or hyperopia. Third, because it doesn't involve drops, there is far less wasted drug. Fourth, we can potentially release medications that are not water-soluble—drugs that are difficult to administer using drops." Dr. Ciolino adds that some other long-term delivery options under development, such as intraocular injections of microparticles, may be less appealing to patients.

Dr. Ciolino says his team hopes to soon begin human trials of the lens. "Contact lenses are something that everyone can relate to," he adds. "They capture the imagination of the public." REVIEW


Much of the coverage of research in cornea in recent years has centered on developing alternatives to penetrating keratoplasty. Despite the success of PK in curing corneal blindness and the widespread adoption of less invasive, partial thickness procedures such as DSEK, DSAEK and DMEK, a major challenge remains—the shortage of donor corneas. Additionally, the success rates of transplant procedures drop off significantly in the developing world. And any donor tissue brings with it attendant challenges of dealing with immunological issues.

An international group of researchers centered in Sweden now has four years of follow-up in its efforts to develop recombinant, human collagen corneas.

Centered at Linköping University in Linköping, Sweden, the group is taking a regenerative medicine approach to repairing diseased corneas. They are testing implants made from Type III recombinant human collagen (RHC), synthesized in yeast and chemically cross-linked, and molded into a biosynthetic cornea. The cell-free implants induce the patient's own epithelial cells to grow over the implant, while stromal cells migrate into the implant and anchor it to the eye. In December, they reported the four-year follow-up of their Phase I study.[1]

> **"This is regeneration or replacement of cells, so it's not a prosthesis. And even after four years, the regeneration is still ongoing."**
>
> **—Professor May Griffith**

Professor May Griffith, of the Integrative Regenerative Medicine Centre, Department of Clinical and Experimental Medicine, at Linköping University is one of the researchers. "This is still a work in progress, but we've found some very interesting things," says Prof. Griffith. "One that was very interesting to us is that we had less inflammation than in donor corneas. We did not have dendritic cells inside the corneas. With donor corneas we found dendritic cells."

The reported data is on 10 patients (eight male, two female; age 18 to 75 at surgery; nine with keratoconus and one with central scarring). The 10 patients were grafted with the biosynthetic implants by anterior lamellar keratoplasty, with the implants being retained by overlying sutures. A second group of nine patients with similar pathologies (six male, three female; age 40 to 79); with keratoconus (five cases), endothelial decompensation (two), a deep central scar (one) and pseudophakic bullous keratopathy (one) were grafted with human donor allograft corneas by full-thickness penetrating keratoplasty, stabilized with peripherally located running sutures.

Key four-year results included:

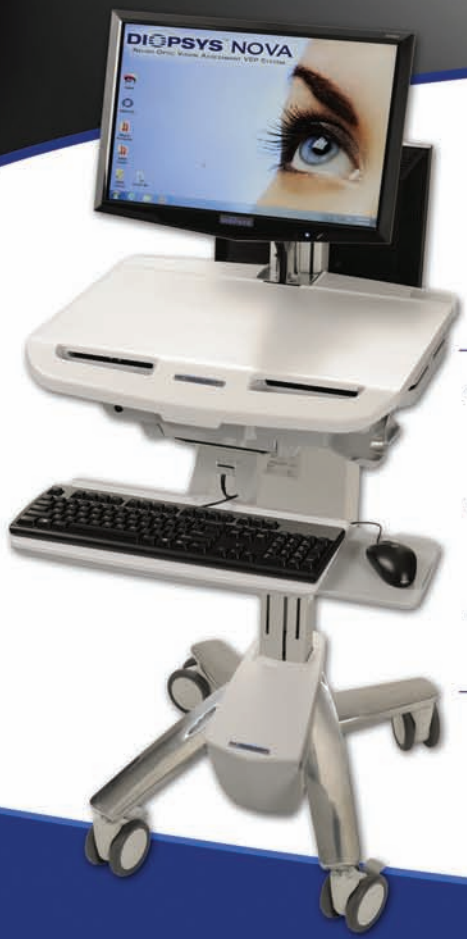
• ***The implants were all well-integrated within the corneas of all 10 patients.*** The mechanical strength of the implants was significantly lower than that of the average human cornea and the implants were softer, resulting in the need for overlying rather than interrupted sutures for retention.

• ***By anterior segment optical coherence tomography, the shape, thickness and border areas of the implanted corneas remained constant from year one to year four.*** Central corneal thickness was not significantly changed from year one to year four in either the biosynthetic implant group or the human cornea transplant group. CCT at four years was 358 ±101 µm in patients with biosynthetic implants; 576 ±50 µm in patients with human donor corneas, and 534 ±30 µm in healthy corneas. The biosynthetic corneas were significantly thinner than healthy corneas, and the human donor corneas were significantly thicker than healthy corneas.

After surgery, a flattening of the cone was sustained to four years in all patients, but with a high degree of surface irregularity. The authors suggest this was due to tight overlying mattress sutures that induced superficial deformation/indentation of the non-rigid implants, as the analyses also confirmed that surface irregularities adopted the hexagonal-shaped paracentral pattern of the tight overlying sutures.

• ***In a key finding, over the four-year postoperative period, no episodes of rejection were observed in the biosynthetic implanted corneas.*** In this group, the sutures were removed at 6.5 weeks (range: four to seven weeks), and prophylactic immunosuppressive steroids were stopped. The nine patients implanted with donor corneas received steroids for 12 months and sutures were removed after a mean of 13 months; one patient in this group had a rejection, which is in keeping with statistical averages in the first year postop.

Dendritic cells, which regulate the immunogenicity of an organ and determine whether a graft is tolerated or rejected,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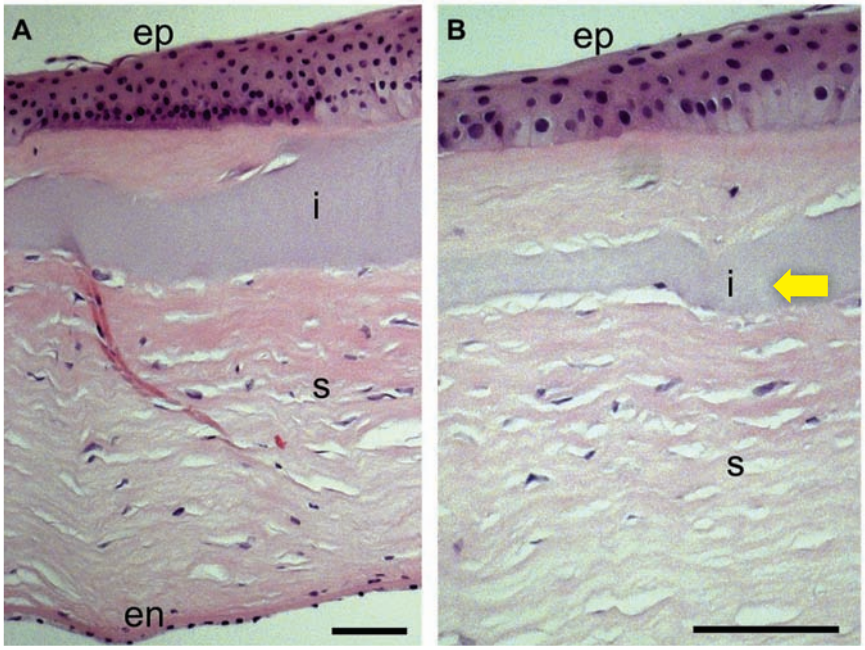


Histology shows a normal corneal morphology with epithelium, stroma and endothelium. Arrow shows the recombinant human collagen implant (i) still present and remodeling after four years.

were present in the center of the human donor corneas but not in the biosynthetic implants, or healthy corneas. Total dendritic cell density in the human donor cornea group was significantly greater than in the biosynthetic group.

• ***Regeneration.*** At four years, the regenerated epithelium remained stratified and displayed cell layers that were similar to human donor corneas and healthy controls. The initially cell-free implants were populated by stromal cells that had grown into the implants, but cell-free areas remained. Human donor corneas had fewer stromal cells than healthy corneas, and additionally had small particulate bodies and linear structures indicative of apoptosis; healthy controls had a dense, even distribution of stromal cells. The nerves from the plexus lying under the epithelium in the human donor cornea group had reached the central corneal region to varying degrees. However, they were generally sparse, highly branched and abnormally tortuous. In corneas that received biosynthetic implants, the regenerated nerves followed straighter, parallel paths as described for healthy corneas, although the nerve fibers in healthy corneas were thicker and more densely packed.

Central corneal touch sensitivity was assessed by contact esthesiometry in the patients' operated eyes and their contralateral unoperated eyes, which served as controls. Touch sensitivity in corneas implanted with human donor and biosynthetic tissue was significantly reduced relative to unoperated eyes, which consistently exhibited normal touch sensitivity. Touch sensitivity in corneas with biosynthetic implants was significantly better than in human donor corneas.

Histology of a regenerated neocornea showed a normal, healthy corneal architecture, with a stratified nonkeratinized epithelium, lamellarly arranged stroma and a layer of endothelium. There was a cell-free region in the center of the stroma, which representsed the part of the implant that had not yet been remodeled. In areas where the remodeling was more advanced, the implant had blended seamlessly into the stroma. The authors say the histology, coupled with the *in vivo* confocal images, supports the contention that active regeneration was still ongoing at four years postop.

Distance-corrected visual acuity was achieved in the biosynthetic group by use of custom-fitted hard contact lenses to regularize an uneven corneal surface. Patients tolerated these lenses after surgery but not before. In the human donor group, distance-corrected VA was measured with spectacles. At four years, distance-corrected VA was 20/54 in the biosynthetic group, and 20/36 in the human donor groups. In terms of vision improvement from the preoperative level, the biosynthetic group had a mean gain of 5.6 Snellen lines, while the human donor group had a mean gain of 9.9 Snellen lines at four years postop.

The next step, says Prof. Griffith, is another trial but with a fortified material. "We have a more robust, reinforced material that we're trying for higher-risk transplants, such as chemical burns. What we had before was just a single network of recombinant human collagen. It's now two networks and that makes it significantly stronger."

It may be some time before this is mainstream, but Prof. Griffith and her coworkers feel its impact could be significant. "This is regeneration or replacement of cells, so it's not a prosthesis. And even after four years, the regeneration is still ongoing."

There are other issues to address as well. "The suturability can be improved," says Prof Griffith. "And we still have the question of whether or not to have an endothelium. Some people have removed the full thickness, some have left Descemet's. So that's a question we have not answered." REVIEW

1. Fagerholm P, Lagali N, Ong J, Merrett K, et al. Stable corneal regeneration four years after implantation of a cell-free recombinant human collagen scaffold. Biomaterials 2014 Mar;35(8):2420-7. doi: 10.1016/j.biomaterials.2013.11.079. Epub 2013 Dec 25.

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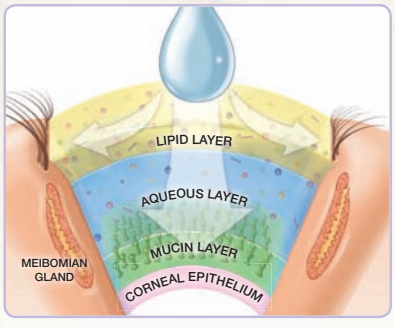


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SYSTANE® Brand products are formulated for the temporary relief of burning and irritation due to dryness of the eye.

**References: 1.** Akpek EK, Smith RA. Overview of age-related ocular conditions. *Am J Manag Care.* 2013;19 (5 suppl):S67-S75. **2.** Korb DR, Blackie CA, Meadows DL, Christensen M, Tudor M. Evaluation of extended tear stability by two emulsion based artificial tears. Poster presented at: 6th International Conference on the Tear Film and Ocular Surface: Basic Science and Clinical Relevance; September 22-25, 2010; Florence, Italy.

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# ASCs Continue to Move Into the Mainstream

*Michelle Stephenson, Contributing Editor*

Multiple factors continue to push ASCs to the forefront as a better alternative to the hospital.

Operating in ambulatory surgery centers rather than hospitals offers benefits to patients, surgeons and payers. It even benefits hospitals. For example, if hospitals can move less-complicated procedures to an ASC, it opens up operating room time for more complex and expensive procedures. This article will look at some ways the ASC scene has evolved in recent years and some of the considerations that are warranted if you're envisioning an ASC in your future.

## Emphasis on Efficiency

"The push to do your work in a surgery center is really just a matter of efficiency," says Jay S. Duker, MD, chairman of the New England Eye Center/Tufts Medical Center in Boston. "In general, outpatient ASCs, whether they are hospital-owned, owned by a group of doctors or owned by a for-profit company, work more efficiently than hospital ORs. Therefore, we can do more surgery in a shorter period of time and have more control over our schedules."

This was demonstrated in a 2009 study that found that outpatient surgery performed in an ASC was superior to procedures performed at a hospital-based facility.[1] The study included 486 cases and performance was measured in five categories: safety; patient-



*This article has no commercial sponsorship.*

# If only you could predict how ocular inflammation will behave.

***DUREZOL® Emulsion has head-to-head data vs prednisolone acetate in patients with endogenous anterior uveitis.[1]***

Scan the QR code with your smartphone or log on to **www.inflammationhappens.com** to see the results for yourself.

**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.**


DUREZOL®
(difluprednate ophthalmic emulsion) 0.05%

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**Reference: 1.** DUREZOL® Emulsion package insert.

# 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 pruritis, 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

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centeredness; timeliness; efficiency; and equitability. In the study, the ASC had no unexpected safety events, compared to nine at the hospital-based facility. Patient satisfaction was similar between the facilities. However, differences in timeliness approached 30 percent. In fact, 77 percent of ASC cases finished within the scheduled time, compared with 38 percent of cases at the hospital-based facility. Additionally, total charges at the ASC were 12 to 23 percent less than those at the hospital-based facility.

Why are ASCs more efficient than hospitals? "Surgery is a team sport," says Stephen C. Sheppard, managing principal of Medical Consulting Group in Springfield, Mo. "When you have a circulating nurse, a surgical technician and a surgeon who are all doing large volumes of cataract surgery, like any team, they get very good at anticipating what the next moves are going to be and who is going to be where when. The process becomes much more efficient, which saves the doctors time and the patients time. It becomes a more relaxed, less stressful environment for not only the staff and the surgeon, but also for the patients."

## Facility Fees

Whether performed in a hospital or in an ASC, there are typically three fees that are charged for each procedure: the surgeon's fee, the facility fee and the anesthesiologist's fee. Medicare is currently paying surgery centers, on average, about 56 percent of what it is paying hospital outpatient departments for the same surgical procedures. "Surgery centers performing cataract surgery right now across the country are getting paid a facility fee of about $975 for Medicare patients," Mr. Sheppard says. "Hospitals are getting a facility fee of $1,760 for the same procedure. This will become more important as society continues to age and feels the increasing cost of health care. We are currently adding 10,000 people a day to the Medicare rolls, and that's going to continue to happen for the next 15 years as the baby boomers age. We are going to have to become more cost-effective, and ASCs are the low-cost providers of surgical services."

Dr. Duker explains that the government has started to wonder what it is getting for its additional money and whether it should be paying hospitals more for the same procedure that an ASC can do as well, if not better. "It is believed that, in the future at some point, the differential payment between hospitals and surgery centers will go away, in which case many of the hospitals won't be able to compete," he says. "They may just drop things like doing retina surgery altogether. If this happens, retina specialists who don't have access to a surgery center could be in trouble. This is an argument for those who don't have access to a surgery center to start to think about it. If they wait, they may not have their choice of centers. They could end up at an ASC 50 miles away and without adequate OR time. It is something to think about, because it is something disruptive that may be coming."

## Should You Consider Ownership?

Some ophthalmologists are choosing not just to affiliate with an ASC, but to become an owner. "It is not unusual for ophthalmologists to be the owners of their ASC," says Mark E. Kropiewnicki, an attorney with Health Care Law Associates in Plymouth Meeting, Pa. "Solo-practicing ophthalmologists rarely own their own ASC, but are typically on the lookout to buy in to either a single-specialty or a multispecialty ASC. Surgeons have to take their cases somewhere, and they would like to affiliate or buy in to an ASC that is in a convenient location and where they can hopefully get a reasonably good and consistent schedule. If you are in a group of four or five doctors, and all of you have a need to use an ASC, the group could build its own ASC that would be just for the practice. Additionally, sometimes, two groups of doctors who could not build an ASC alone will go together to form a jointly owned ASC. Some ASCs are owned by 10, 20 or more doctors, and that's where a solo doctor would look to buy."

Mr. Sheppard notes that owning a portion of an ASC affords the surgeon some economic benefits as well as the quality-of-life benefits. "Without any additional labor hours on their part, they can create a new revenue stream for their professional practice. This is one of the reasons that this has become so popular over the past 20 to 25 years," he adds.

If a surgeon currently owns part of an ASC, selling his share to a hospital can also make sense. "If surgeons are looking to sell their ASC, the best-case scenario would be to sell all of the ASC to a hospital," Mr. Kropiewnicki says. "If a hospital owns an ASC, it can become a hospital outpatient department and qualify for the higher Medicare facility fees. So, the hospital can buy an ASC and convert it into an HOPD, and the reimbursement for Medicare patients is almost double. If the hospital does not buy all of an ASC, the ASC will not qualify as an HOPD. However, if the hospital has any clout whatsoever with the non-Medicare payers, then the hospital may also be able to negotiate better reimbursement rates for the jointly owned ASC for the non-Medicare patients."

He explains that if an ASC is netting $500,000, and a doctor is selling his or her ownership to another doctor, the sale price is typically a two to four multiple of the net income. "A multiple of three is $1.5 million, so that's not an insubstantial amount, but it's not as much money as a surgeon could get by selling it to someone else. Public or private equity firms are typically looking to buy ASCs from doctors, but

keep the doctors involved because they need doctors to continue to operate in it. Public companies may buy it for a five to seven multiple because this will help boost their own profits, because the stock market is selling at more like a 10 to 15 multiple. Hospitals probably can't or won't quite do that. They can probably pay more than a two to three multiple for the purchase of that ASC, but they probably won't go as high as seven, especially nonprofit hospitals," Mr. Kropiewnicki says.

However, owning and operating an ASC is not as simple as it appears at first glance. According to Mr. Sheppard, most ASCs are licensed by the state in which they are located and are certified as enrolled in the federal Medicare program and state Medicaid programs as a separate legal entity. "Of course, you are providing surgical care to individuals, so the ASC as a business entity has professional liability insurance coverage," Mr. Sheppard says. "It is a highly regulated industry, so there's a very detailed policy and procedures manual. You must comply with OSHA and state anti-kickback statutes."

In addition, there are some financial risks to consider. As with any business, there is no guarantee that it will make money. "It must be designed well, structured well and operated efficiently for it to be successful," Mr. Sheppard says. "ASCs are required under the [Center for Medicare & Medicaid Services] Conditions for Coverage to be overseen by a governing body. The governing body typically includes a number of the physicians who are either owners or active participants in the ASC. The Conditions for Coverage lay out in great detail the responsibilities of the governing body for oversight and for management of the facility. The governing body is responsible for a quality assurance program, for an infection control program, for credentialing the surgeons and for peer review. It's a miniature hospital, and it is regulated, justifiably, like a miniature hospital."

Before investing in an ASC, Dr. Duker recommends performing an assessment of the return on your investment. Try to determine the likelihood that the surgery center is going to continue to make money in the term long enough for the surgeon to make his money back. "These are business decisions that have to be made on an individual basis," he says. "Fifty percent of all surgery centers in the United States in recent years have failed. Maybe you are going to make money, and maybe you're not going to make money. Maybe it's a good investment, and maybe it's not. That's something that has to be evaluated on a case-by-case basis. However, whether you own part of a surgery center or whether you have access to a surgery center, physician happiness with surgery centers is high.

"If you are asked to buy in to an existing surgery center that is profitable already, the buy-in price is apt to be high because you are buying into an already profitable business. In general, being a partner in a well-run surgery center is a good thing. In general, having some control and say over the direction that the surgery center goes is a good thing, even above any profitability. If your principles as a physician are that you want to have the best facility for your patients, if you don't own that surgery center, you don't make the decisions about things like what equipment is being bought in the surgery center. As a retina specialist, if there are certain things that you feel you need to do your surgery, you want to try to be an owner so that you can have a say in that."

## The Future

The future of ASCs looks bright. There are currently more licensed, certified ASCs than there are licensed, certified hospitals, and with less-invasive procedures becoming the norm, their use will continue to increase. "Back in the 80s, this movement started with ophthalmology," says Mr. Sheppard. "In the early 90s, gastroenterology became very feasible and very reasonable to do in an ambulatory surgical environment. As the technology has continued to improve and as more and more surgery is done endoscopically, it makes more and more sense to move those surgeries into a less-intense, lower-cost environment."

Recently, even some retina procedures have moved to ASCs. Dr. Duker notes that there have traditionally been two arguments for not performing retina surgery in an ASC: Retina patients are sicker and the cases are longer, and there is the potential for emergencies.

"That's generally not as true anymore with smaller-incision vitrectomy, fewer buckles and fewer re-operations," he says. "In general, retina surgery is more amenable to an outpatient setting than it used to be. As far as emergencies, people will argue that they need access to a hospital OR. However, recent numbers suggest that the true number of retinal emergencies is very low. Retinal detachments, even macula-threatening retinal detachments, are not considered true emergencies anymore. Even metallic intraocular foreign bodies, which we used to do in the middle of the night because we thought they were emergencies, are not emergencies. There is evidence now out of the Middle Eastern wars that foreign bodies can be left in for weeks with excellent results."

The move to ASCs really benefits all parties involved. Mr. Sheppard notes that, by partnering with the ASC, hospitals can keep a part of the revenue stream. "Then, they have a symbiotic relationship between the doctors and the hospital at that point. It benefits the patients and society as a whole," he adds. REVIEW

1. Grisel J, Arjmand E. Comparing quality at an ambulatory surgery center and a hospital-based facility: Preliminary findings. Otolaryngol Head Neck Surg 2009;141:701-709.

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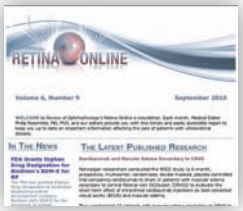


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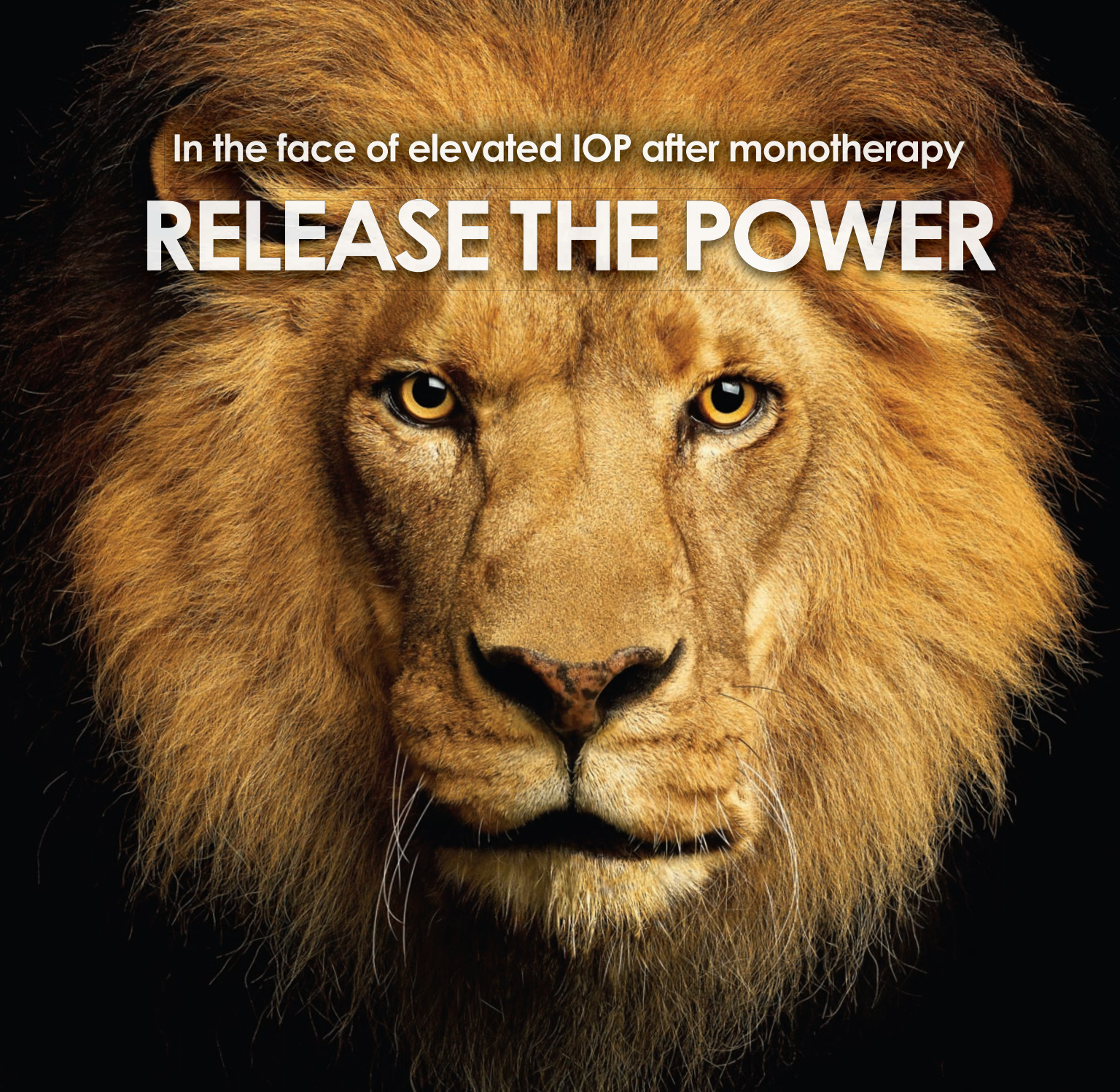


**INDICATIONS AND USAGE:** COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is an alpha-adrenergic receptor agonist with a beta-adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP-lowering of COMBIGAN® dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution dosed twice a day and 0.2% brimonidine tartrate ophthalmic solution dosed three times per day.

**IMPORTANT SAFETY INFORMATION**
**CONTRAINDICATIONS:** COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; in neonates and infants (under the age of 2 years); in patients with a hypersensitivity reaction to any component of COMBIGAN® in the past.

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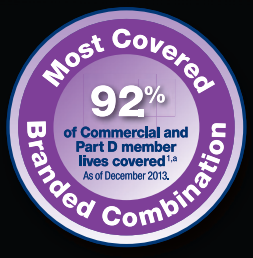


**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS:** COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% contains timolol maleate; while administered topically, it can be absorbed systemically and systemic adverse reactions to beta-blockers may occur (eg, severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported).

Sympathetic stimulation may be essential to support the circulation in patients with diminished myocardial contractility and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. In patients with no history of cardiac failure, continued depression of the myocardium with beta-blocking agents over time can lead to cardiac failure. Discontinue COMBIGAN® at the first sign or symptom of cardiac failure.

Patients with chronic obstructive pulmonary disease (eg, chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease should not receive COMBIGAN®.

COMBIGAN® may potentiate syndromes associated with vascular insufficiency. Use caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

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

Although rare, timolol can increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS: (continued)**

Beta-blockers may mask the signs and symptoms of acute hypoglycemia and clinical signs (eg, tachycardia) of hyperthyroidism. Use caution in patients subject to spontaneous hypoglycemia or diabetics (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Carefully manage patients who may develop thyrotoxicosis to avoid abrupt withdrawal of beta-blockers that might precipitate a thyroid storm.

Ocular hypersensitivity has occurred with brimonidine tartrate ophthalmic solutions 0.2% (eg, increase in IOP).

Some authorities recommend gradual withdrawal of beta-blockers due to impairment of beta-adrenergically mediated reflexes during surgery. If necessary during surgery, the effects of beta-blockers may be reversed by sufficient doses of adrenergic agonists.

**ADVERSE REACTIONS:** The most frequent reactions with COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% in about 5% to 15% of patients included: allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging.

**DRUG INTERACTIONS:** Use caution in the co-administration of COMBIGAN® with: antihypertensives or cardiac glycosides; beta-blockers (concomitant use of two topical beta-blockers is not recommended); calcium antagonists (avoid co-administration in patients with impaired cardiac function); catecholamine-depleting drugs; CNS depressants/anesthetics; digitalis and calcium antagonists; CYP2D6 inhibitors; tricyclic antidepressants; and monoamine oxidase inhibitors.

**Please see the Brief Summary of the full Prescribing Information on the next page.**

[a]Includes preferred, approved, and tiers 1-4, with and without step-edits, and also includes prior authorization, based on 203,671,234 total lives.

**1.** Managed Markets Insight & Technology, LLC, database as of December 2013.

Combigan®

(brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%

# COMBIGAN®

(brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%

**BRIEF SUMMARY**

Please see the **COMBIGAN®** package insert for full prescribing information.

**INDICATIONS AND USAGE**

**COMBIGAN®** (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is an alpha adrenergic receptor agonist with a beta adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP-lowering of **COMBIGAN®** dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution dosed twice a day and 0.2% brimonidine tartrate ophthalmic solution dosed three times per day.

**CONTRAINDICATIONS**

**Asthma, COPD: COMBIGAN®** is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease.

**Sinus bradycardia, AV block, Cardiac failure, Cardiogenic shock: COMBIGAN®** is contraindicated in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock.

**Neonates and Infants (Under the Age of 2 Years): COMBIGAN®** is contraindicated in neonates and infants (under the age of 2 years).

**Hypersensitivity reactions:** Local hypersensitivity reactions have occurred following the use of different components of **COMBIGAN®**. **COMBIGAN®** is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

**WARNINGS AND PRECAUTIONS**

**Potentiation of respiratory reactions including asthma: COMBIGAN®** contains timolol maleate; and although administered topically can be absorbed systemically. Therefore, the same types of adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported following systemic or ophthalmic administration of timolol maleate.

**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, **COMBIGAN®** 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 **COMBIGAN®** is contraindicated] should, in general, not receive beta-blocking agents, including **COMBIGAN®**.

**Potentiation of vascular insufficiency: COMBIGAN®** may potentiate syndromes associated with vascular insufficiency. **COMBIGAN®** should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

**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.

**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.

**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.

**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.

**Ocular Hypersensitivity:** Ocular hypersensitivity reactions have been reported with brimonidine tartrate ophthalmic solutions 0.2%, with some reported to be associated with an increase in intraocular pressure.

**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.

**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.

**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. **COMBIGAN®:** In clinical trials of 12 months duration with **COMBIGAN®**, the most frequent reactions associated with its use occurring in approximately 5% to 15% of the patients included: allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging. The following adverse reactions were reported in 1% to 5% of patients: asthenia, blepharitis, corneal erosion, depression, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, eyelid pruritus, foreign body sensation, headache, hypertension, oral dryness, somnolence, superficial punctate keratitis, and visual disturbance.

Other adverse reactions that have been reported with the individual components are listed below.

**Brimonidine Tartrate (0.1%-0.2%):** Abnormal taste, allergic reaction, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, fatigue, flu syndrome, follicular conjunctivitis, gastrointestinal disorder, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), hordeolum, insomnia, keratitis, lid disorder, nasal dryness, ocular allergic reaction, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, taste perversion, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity. **Timolol (Ocular Administration):** *Body as a whole:* chest pain; *Cardiovascular:* Arrhythmia, bradycardia, cardiac arrest, cardiac failure, cerebral ischemia, cerebral vascular accident, claudication, cold hands and feet, edema, heart block, palpitation, pulmonary edema, Raynaud's phenomenon, syncope, and worsening of angina pectoris; *Digestive:* Anorexia, diarrhea, nausea; *Immunologic:* Systemic lupus erythematosus; *Nervous System/Psychiatric:* Increase in signs and symptoms of myasthenia gravis, insomnia, nightmares, paresthesia, behavioral changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss; *Skin:* Alopecia, psoriasiform rash or exacerbation of psoriasis; *Hypersensitivity:* Signs and symptoms of systemic allergic reactions, including anaphylaxis, angioedema, urticaria, and generalized and localized rash; *Respiratory:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnea, nasal congestion, respiratory failure; *Endocrine:* Masked symptoms of hypoglycemia in diabetes patients; *Special Senses:* diplopia, choroidal detachment following filtration surgery, cystoid macular edema, decreased corneal sensitivity, pseudopemphigoid, ptosis, refractive changes, tinnitus; *Urogenital:* Decreased libido, impotence, Peyronie's disease, retroperitoneal fibrosis.

**Postmarketing Experience: Brimonidine:** The following reactions have been identified during post-marketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, depression, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions. **Oral Timolol/Oral Beta-blockers:** The following additional adverse reactions 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:* Decreased exercise tolerance, extremity pain, weight loss; *Cardiovascular:* Vasodilatation, worsening of arterial insufficiency; *Digestive:* Gastrointestinal pain, hepatomegaly, ischemic colitis, mesenteric arterial thrombosis, vomiting; *Hematologic:* Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Increased pigmentation, pruritus, skin irritation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* An acute reversible syndrome characterized by disorientation for time and place, decreased performance on neuropsychometrics, diminished concentration, emotional lability, local weakness, reversible mental depression progressing to catatonia, slightly clouded sensorium, vertigo; *Respiratory:* Bronchial obstruction, rales; *Urogenital:* Urination difficulties.

**DRUG INTERACTIONS**

**Antihypertensives/Cardiac Glycosides:** Because **COMBIGAN®** may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with **COMBIGAN®** is advised. **Beta-adrenergic Blocking Agents:** Patients who are receiving a beta-adrenergic blocking agent orally and **COMBIGAN®** 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 co-administration of beta-adrenergic blocking agents, such as **COMBIGAN®**, 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. **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. **CNS Depressants:** Although specific drug interaction studies have not been conducted with **COMBIGAN®**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. **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. **Tricyclic Antidepressants:** Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **COMBIGAN®** in humans can lead to resulting interference with the IOP-lowering effect. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines. **Monoamine oxidase inhibitors:** Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** Pregnancy Category C: Teratogenicity studies have been performed in animals.

Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (1.65 mg/kg/day) and rabbits (3.33 mg/kg/day) achieved AUC exposure values 580 and 37-fold higher, respectively, than similar values estimated in humans treated with **COMBIGAN®**, 1 drop in both eyes twice daily.

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day [4,200 times the maximum recommended human ocular dose of 0.012 mg/kg/day on a mg/kg basis (MRHOD)] 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 1,000 mg/kg/day (83,000 times the MRHOD) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses 8,300 times the MRHOD without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, **COMBIGAN®** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

**Nursing Mothers:** Timolol has been detected in human milk following oral and ophthalmic drug administration. It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from **COMBIGAN®** 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: COMBIGAN®** is not recommended for use in children under the age of 2 years. During post-marketing surveillance, apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate and timolol maleate have not been studied in children below the age of two years.

The safety and effectiveness of **COMBIGAN®** have been established in the age group 2-16 years of age. Use of **COMBIGAN®** in this age group is supported by evidence from adequate and well-controlled studies of **COMBIGAN®** in adults with additional data from a study of the concomitant use of brimonidine tartrate ophthalmic solution 0.2% and timolol maleate ophthalmic solution in pediatric glaucoma patients (ages 2 to 7 years). In this study, brimonidine tartrate ophthalmic solution 0.2% was dosed three times a day as adjunctive therapy to beta-blockers. The most commonly observed adverse reactions were somnolence (50%-83% in patients 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

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

**OVERDOSAGE**

No information is available on overdosage with **COMBIGAN®** in humans. There have been reports of inadvertent overdosage with timolol 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. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

Rx Only



Based on package insert 72060US13 revised 10/2012.



APC33KM13

ALLERGAN

# Should You Scratch The Itch to Sell Out?

*Frank Celia, Contributing Editor*

How to assess the landscape if you're approached or are considering selling your practice.

Medico-legal doctrine has long been ambivalent regarding the employment of physicians by anyone else besides other physicians. For most of the last century, it was considered unethical. Critics, led by doctors themselves, claimed it lent medicine a dubious profit motive, divided physician loyalty between employer and patient, and gave unqualified laypersons excessive control over physician behavior. To this day prohibitions that ban doctors from employment except under special circumstances—certain charities, for example—exist in the form of state laws, medical licensing statutes and case-law precedent in almost every state. It's known as the ban against the "corporate practice of medicine," or CPM.

Not until the rise of managed care did policymakers reconsider this barrier. Trying to stem the rising tide of health-care costs, legislatures waived the ban on CPM for HMOs, allowing them to hire physicians. Soon exemptions were everywhere: teaching hospitals; community clinics; narcotic treatment programs; non-profit hospitals; etc. Consolidation became all the rage. And where exemptions did not exist, doctors developed such a complex web of financial relationships with business-like enterprises that medical fraud and abuse laws became

necessary (e.g., the Stark law).

By now the pendulum has swung all the way back. Few lawmakers today raise an eyebrow as hospitals, physicians management firms, even insurance companies, splurge on epic practice-buying sprees. The CPM bans still extant often go unenforced. Even the AMA no longer views physician employment per se as an ethics violation. Indeed, employing physicians has emerged as one of the central strategies for achieving the goals set forth by the Affordable Care Act.

Where does this leave ophthalmology? Mostly sidelined, it turns out. Hospitals, the main force behind the employment boom, have little interest in eye care. Nevertheless, many ophthalmologists, particularly younger ones, are taking matters into their own hands. Increasingly concerned about the viability of small solo practices, seeking a more stable work environment and eager to avoid ever-multiplying office-work hassles, these practitioners are banding together in group practices that pay physicians a salary.

## Now and Then

Health care has been down this road before, with disastrous results. In anticipation of Clinton-era health-care reforms in the 1990s, hospitals, physician practice management companies and various other for-profit entities, often fueled by venture capital, went on a physician employment binge, favoring primary-care practices over specialists. At the peak of the frenzy, some primary-care practices were being bought for as much as 10 times their market value, while practitioners received lavish, guaranteed salaries.

When reforms failed to materialize and managed-care capitation plans gave way to preferred-provider type products, buyers were left holding catastrophic losses. PPMs alone took an estimated red-ink bath of $12 billion in market capitalization.[1]

As industry sifted through the wreckage of these failures, one of the things it soon discovered was salaried physicians were grossly less productive than their practice-owning colleagues. According to one white paper, despite lower expenses among hospital-owned practices, they still performed much worse: "[P]hysician productivity in hospital employment was far lower. Net collected revenues for hospital-owned practices were more than $100,000 per FTE physician lower than revenues for physician owned practices and an impressive 35 percent lower than better-performing practices—a result of dismal billing and collection practices and markedly lower physician productivity."[2]

Hard-knock lessons learned, this time round is proving more a buyer's market—and for other reasons as well. Hospitals and employers hold stronger cards as physicians flee from the mandated rigors of the ACA, meaningful use EHR cuts, pending shifts away from the fee-for-service model, the looming implementation of ICD-10, and much more. Gone are the days of overpaying for practices, and negotiations are tight. Less-tangible assets like "goodwill" and "brand recognition" hold far less sway. Instead of a lump sum, buyers might spread payment for a practice over several years to maintain employee incentive. Flat salaries, essentially a thing of the past, have been largely replaced by productivity-based compensation, usually some scheme involving relative value units.

## Culture Clash

Perhaps the first question a private practitioner should consider before selling is this: Should it even be considered at all?

One school of thought suggests not all physicians are well-suited for the essentially subservient role of employment. "It depends on their specialty a bit, but most surgeons—and I'll include ophthalmologists on this—do not respond well to being told what to do," observes Jeffrey J. Denning, a partner in the consulting firm, Practice Performance Group, in La Jolla, Calif. Among the smartest and most accomplished members of society, surgeons, who spent many years learning to perform the most complicated, difficult, stress-inducing work the world has to offer, are seldom inclined to snap to attention over fussy pieces of minutiae like the proper way to fill out medical records.

"Most doctors, once they pull the plug and sell their practice, they hate it," notes Mr. Denning. "The doctors who like working at the VA and places like that go there right out of training and stay because they like that environment and can adapt to that. But I see a lot of doctors get out of training, join a big group practice, and hate it. Two years later they quit and go into a more traditional-style practice." Mr. Denning says his firm spends a lot of time extricating physicians from employment-type contracts. Indeed, many of the discontented physicians who sold their practices in the first wave of hospital buyouts over the past few years end up on his doorstep, he says.

And physicians who hope an employer will be better equipped to handle the management side of the business are often disappointed. Hospitals, for example, are notoriously inept at accounts receivable. "There is a close relationship between the billing people and the front desk staff," he says. "When you take the billing people and move them off-site, to a hospital, the accountability and communication between those groups suffers."

## Potential Suitors

Hospital administrators seldom approach ophthalmic practices offering buyouts. Eye care accounts for

only 3 percent of hospital revenue, and large employers are more interested in locking down access to bigger earners. However, ophthalmologists do occasionally find homes at hospitals. For example, Mercy Clinic Eye Specialists, an eight-member eye-care practice in Springfield, Mo., is owned by Mercy, a multi-site hospital system.

Specialists such as cardiologists, orthopedists and gastro-intestinal surgeons field more employment offers from hospitals. These physicians tend to command high salaries, and hospitals have made no secret about losing money on every physician they employ—somewhere around $150,000 to $250,000 per year, per full-time physician in the first three years of employment.[3] However, it is important to note that these figures do not include the enormous technical and facility fees such high-volume surgeons generate for hospitals.

For certain specialties, it is estimated that hospitals receive five to 10 times more in fee revenues than they pay toward the surgeon's salary. For example, an average orthopedic surgeon making $400,000 a year can easily rack up $2.1 million in surgery fees for the hospital where he performs hip and knee replacements. Yes, it could be argued that the hospital could still receive those fees without necessarily employing the surgeon, but by putting such professionals on staff, hospitals guarantee that revenue year after year, and minimize the threat of it going to competitors.

The much higher technical and facility fees charged in a hospital setting compared to those that can be charged in a doctor's office account for the one area of interest hospitals do seem to have for vision care—ambulatory surgery centers. Eye surgeons pioneered the use of ASCs. At one point in the 1990s, ophthalmologists owned more than half of ASCs, and the specialty continues to maintain a dominant presence in the field. Hospitals have purchased ASCs and continue to investigate the possibility of purchasing more. A popular strategy is to repurpose eye-care ASCs to include additional surgeries such as orthopedic and GI ones. Depending on state law and various insurance regulations, in some cases these centers can produce exponentially more revenue simply by having their titles of ownership changed over to a hospital.

*Buyers want strong, vital practices, not fixer-uppers. ... The maxim "Sell your horse before it dies" applies here.*

Accountable care organizations, an important creation of the Affordable Care Act, have also emerged as a physician employer, but they too have shown minimal interest in wooing ophthalmic practices. However, there could be an exception here as well. In absolute dollars, vision care ranks as the third largest expenditure for Medicare, and ophthalmologists make the largest part of their revenue from Medicare. Hence, at least theoretically, an ACO that specializes in Medicare patients may have more use for ophthalmologists, since ACOs offer greater opportunity to take advantage of shared savings rebates via ACA provisions.

Some of the larger commercial insurers have joined the trend as well. A few years ago, Humana purchased Concentra, a national chain of worksite health- and urgent-care providers, and Senior Bridge, which specializes in home care for Medicare patients. OptumHealth has acquired risk-bearing physician groups, and is said to control more than 800,000 lives in Texas, Florida and California. WellPoint owns CareMore, a Los Angeles-based special needs plan/Medicare Advantage provider with a network of 26 primary-care clinic sites.[2]

## Trust Issues

For physicians keen to sell and become an employee, here are a few factors to consider before walking, so to speak, down that aisle:

- Generally speaking, the more money an employer offers you and the more of it that is guaranteed, the more that employer will expect autocratic control of your actions. On the other hand, when your compensation is based more on production factors, such employers will tend to offer more leeway, control-wise.
- Paper charts are generally seen as a liability and will usually lower the value of your practice's hard assets.
- Buyers want strong, vital practices, not fixer-uppers. Selling is usually not a viable bailout strategy. If you are thinking about selling as a transitional phase prior to retirement, do not reduce work hours before doing so. The maxim "Sell your horse before it dies" applies here.
- Leave an exit strategy. Consultants will tell you to avoid signing a non-compete contract, but given the current market, and ophthalmology's low standing within it, a non-compete contract is almost a foregone conclusion. However, that does not mean you have to sign whatever is put before you. Have your lawyer parse it carefully. Negotiate wiggle room if possible.
- Scrutinize your potential partner. What are its short-term and long-term goals? Are they congruent with yours? Ask other physicians employed by the organization their opinions. If it is a hospital, look to its mid-level managers. If they have been there eight or

nine years, that is a positive sign.

Among the most significant questions facing large entities buying up practices—ACOs, hospitals, insurers, PPMs, group practices, etc.—is how all these much-hoped-for economies of scale will coexist with anti-trust laws. In public statements, the department of Health and Human Services, the Federal Trade Commission and the Department of Justice have all vowed to create "safe harbors"—in other words, make exemptions in the law—for large integrated health-care systems, but how this will play out in real-world scenarios is still very much an open question. Moreover, consider the fact that anti-trust actions can be initiated by non-government entities. Rival health-care systems can file suits, for example. And it is difficult to imagine powerful organizations like the National Association of Manufacturers, AdvaMed and PhRMA standing around idly while some of their largest customers engage in what will almost certainly be perceived as price fixing.

## Hanging Together

A strategy often espoused by consultants and industry watchers who specialize in ophthalmology holds that eye-care practitioners should hang back and decline to join large integrated, multi-specialty organizations such as hospitals and ACOs. Health-care is so tumultuous right now, the future so uncertain, that to join these organizations, when they clearly have so little interest in vision care anyway, would be premature. Advisors tell ophthalmic practices instead to join forces among themselves, form large group practices, become a more unified profession. That way, if these giant multi-specialty consolidations turn out to be successful, the ophthalmic world will be in a position of strong bargaining power. After all, sooner or later patients are going to require eye care. On the other hand, if these large colossi turn into colossal disasters—a genuine possibility, given all the challenges noted above—ophthalmology will have avoided going down on a sinking ship.

Broadly speaking, for practitioners eager to avoid the ever-increasing hassles of practice ownership, large group ophthalmic practices have been among the most popular and welcoming employment options. Organizations like Minnesota Eye Consultants, in Minneapolis, with a mix of 25 practitioners (MDs, ODs and PAs), founded by Richard L. Lindstrom, MD; Ophthalmic Consultants of Long Island, based in Westbury, N.Y., six surgeons including outgoing ASCRS President Eric D. Donnenfeld, MD, with 30 MDs and four ODs at 11 locations throughout Long Island; and Barnet, Dulaney, Perkins Eye Center, in Phoenix, founded by the late David Dulaney, MD, a pioneer of refractive surgery, with 15 MDs and 22 ODs, are always on the lookout to expand.

"You kind of want to be a size where you are too big to ignore," says Candace S. Simerson, president of Minnesota Eye Consultants, citing the cautionary tale of several solo ophthalmologists who were excluded from a new, so-called "narrow network" plan initiated on the East Coast by the commercial insurer United Healthcare. "Physicians are feeling more comfortable being part of a larger organization that maybe has the talent and the strength and the size that will enable it survive."

According to Tom Burke, CEO of Ophthalmic Consultants of Long Island, a big misconception among physicians considering merging with his company is their fear they will lack control of their geographic office location and of hiring and firing decisions. In fact, Mr. Burke stresses, it is in his best interest to give physicians as much autonomy as possible. "We don't want to do anything so drastic that it changes the culture of the practice," he says. "They have patients who are loyal to them and are used to a certain style, and we do our best to maintain that."

## Doomed to Repeat It?

With so much rapid change occurring right now, it is impossible even to guess at the long-range effects of increased physician employment. But when reflecting on the secure future offered by vast, equity capitalized, umbrella conglomerates, it never hurts to turn an eye toward past events.

In the 1990s, when the PPMs and their ilk went belly up, after the corporate officers had resigned in disgrace, and untold billions had been lost, the inevitable flock of lawyers swooped in to clean up the mess. These attorneys were shocked—shocked!—to discover the physician employment contracts at issue represented textbook violations of the sacrosanct and time-honored ban on the corporate practice of medicine. Because of this, they argued in court case after court case, such agreements had been illegal from the outset and were therefore null and void.

In many cases, they were successful.[4] REVIEW

*Mr. Celia is a freelance health-care writer based in the Philadelphia area.*

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# When Glaucoma Patients Have Cataract Surgery

These individuals should not be treated as standard cataract patients; extra attention is required.

*James D. Brandt, MD, Sacramento, Calif.*

**Sooner or later,** most people need cataract surgery. That includes glaucoma patients, but their disease complicates matters; these patients need extra care both before, during and after surgery. In addition, some positive side effects of cataract surgery usually seen in healthy eyes, such as a drop in intraocular pressure, may not always appear when a patient is being treated for glaucoma.

Here, I'd like to discuss some of what we've learned about performing cataract surgery on patients with glaucoma, including what kind of pressure change you might expect the cataract surgery to produce, and the steps a clinician should take to ensure the best outcome in this situation.

## Is a Pressure Drop Likely?

Although the evidence suggests that cataract surgery is likely to reduce IOP somewhat in a healthy eye, the evidence is far less clear for glaucoma patients. A few studies that have looked at this question have indeed found a reduction in the number of medications needed by glaucoma patients following cataract surgery.[1-3] The problem is that this data is of varying quality—especially the baseline IOP data—and all of the studies are retrospective in nature. Most used a single IOP measurement before surgery to define the baseline, which subjects all subsequent analyses to regression to the mean, and postop measurements were not masked. Furthermore, in most of these studies the use of medications was not controlled. That means the data is subject to significant potential bias.

The highest-quality data we have regarding the isolated effect of phaco on lowering IOP in patients with higher-than-normal IOPs comes from the Ocular Hypertension Treatment Study. Half of the patients in the OHTS were being treated with glaucoma medications; however, the published analysis relating to the effect of phaco on IOP didn't include those patients. In order to look at the isolated influence of phaco, Steven L. Mansberger, MD, and colleagues at Devers Eye Institute in Portland, Ore., only evaluated the patients who were not on medications.[4] (Those patients were not being treated because they showed no evidence of visual field or optic nerve damage at the time, despite their elevated pressures.)

The OHTS investigators have years of high-quality IOP data for the untreated subjects, both before and after cataract surgery, and there were many matched control subjects who did not have cataract surgery. The IOPs of the untreated OHTS subjects hovered around 24 mmHg before surgery; the group that underwent phaco had a pressure drop of about 4 mmHg, which persisted for several years. *(See chart, p. 62)*

Also of note, the data from the OHTS study, as well as the others already mentioned, showed that the strongest predictor of a significant IOP drop after cataract surgery was a higher starting IOP. One study, for example, found that patients with starting IOPs in the upper 20s experienced a six-point drop in IOP, on average; patients with a starting IOP in the upper teens only showed a 2.7-mmHg drop in pressure.[3] Other published papers have confirmed this finding.[5]

Of course, most patients coming into cataract surgery with a known diag-

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nosis of glaucoma are already on treatment, so using that data to guide clinical practice with a glaucoma patient is fraught with peril. However, I did have personal experience with many of the other OHTS patients—the patients using glaucoma medications who underwent cataract surgery. After we did phaco, I gave them a drug holiday before reintroducing their glaucoma medications to see how much pressure-lowering the phaco provided.

My purely anecdotal experience was that their pressures did tend to drop a little; the majority of ocular hypertensive patients on treatment were able to stay off medications and still achieve the OHTS-specified 20-percent IOP lowering for about a year. But after a year, most of them had to go back on medication to reach the OHTS-defined target. This supports the conclusion that pressure-lowering after cataract surgery is not a long-term effect in glaucoma patients on medications. (Again, this is anecdotal; there is no solid clinical data to confirm my experience.)

Assuming a pressure drop does occur in a glaucoma patient following cataract surgery, what kind of pressure drop should you expect? In addition to the finding that a larger preop pressure correlates with a larger drop in pressure, the retrospective studies found that any drop that occurs will likely be much smaller in a patient who is on a lot of glaucoma medications than in a patient who's on a single medicine.

## Consider a Drug Holiday

Of course, a glaucoma patient could simply be returned to his preoperative medication regimen after cataract surgery. However, if the surgery does produce a decrease in IOP, it may be possible to reduce the patient's medication load postop.

If a patient is an ocular hypertensive, I'll often give him a drug holiday to see how much the pressure is lowered by the cataract surgery. I'm less inclined to try this in a patient with known glaucoma, although if the patient has relatively mild disease, I will sometimes do a drug holiday after simple cataract surgery based on what her pressure is shortly after surgery. I see this as an acceptable risk because taking out a cataract using a clear cornea approach doesn't paint you into any corners in terms of later options. It doesn't eliminate the possibility of performing subsequent glaucoma surgery, if needed.

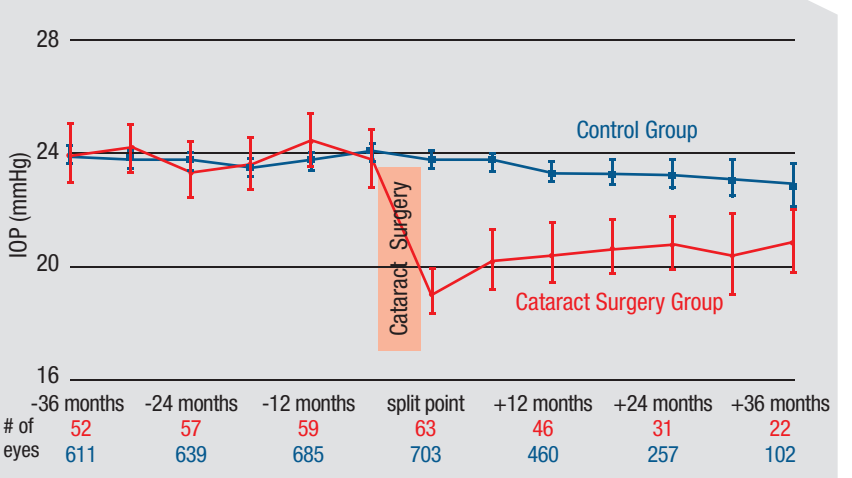
If the patient's pressure is in a reasonably safe range after cataract surgery, I'll keep her off medications until she's done with the steroids so I can get a sense of where the pressure is going to settle, then I'll reintroduce medications as needed. How quickly I restart medications depends on the severity of the disease; in some cases the patient may go back on drugs relatively quickly. Generally, pressure spikes and other concerns are relatively manageable in the early postoperative period in this type of patient.

If a patient is on multiple glaucoma medications before cataract surgery, my decision regarding whether or not to give the patient a drug holiday would be based on the indication for the multiple medications. If the indication was advanced disease, that's probably a patient who should have a combined procedure rather than cataract surgery alone. If the patient is on three or four medications because he started at a really high pressure but he still has relatively mild damage, it may be reasonable to do cataract surgery alone, although it's unlikely that the patient will end up off of all of his medications. Whether I'll consider a drug holiday in that situation depends on how the patient looks right after surgery.

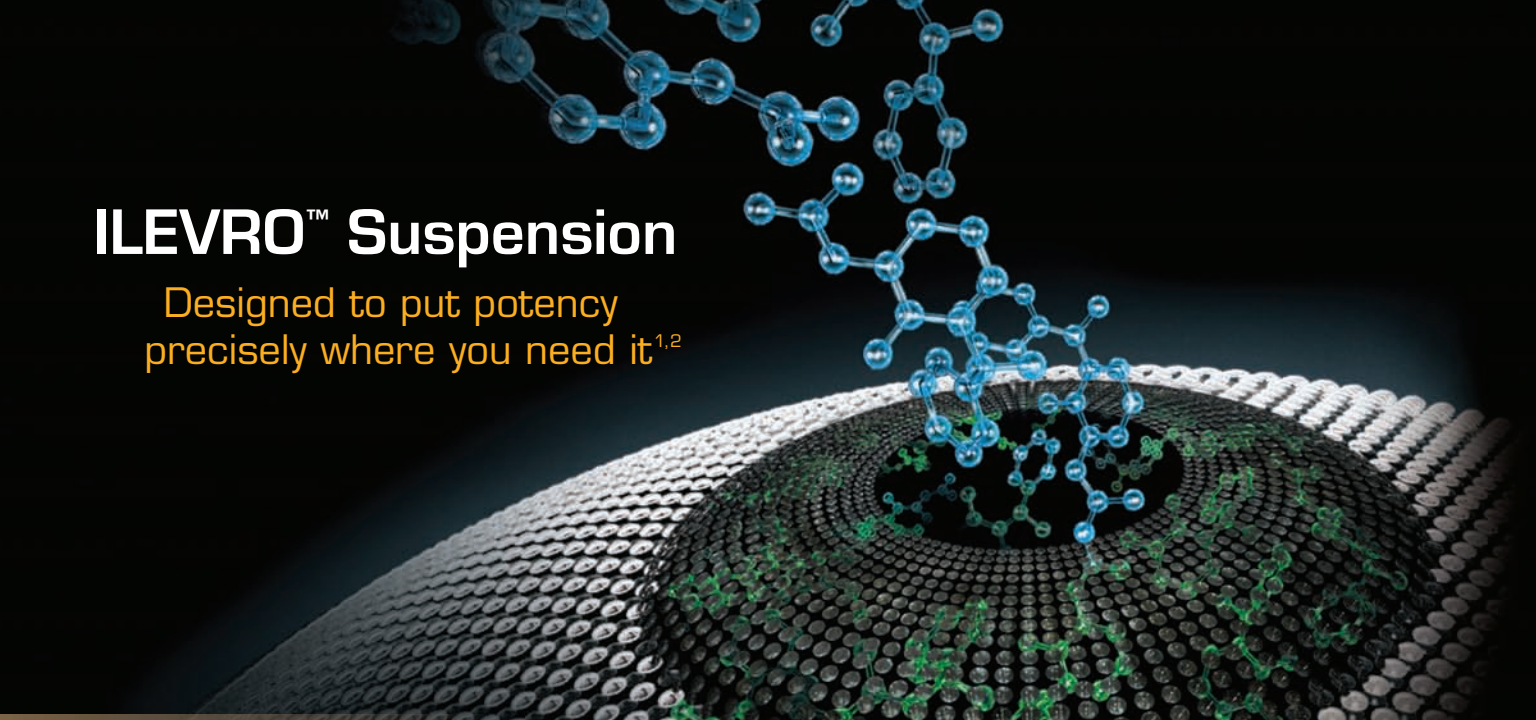
## Trabeculectomy or Tube Shunt

A cataract surgery patient who already has a trabeculectomy or a tube shunt in place raises totally different concerns. If someone has a function-

**IOP Reduction in Hypertensives After Cataract Surgery Alone**




Intraocular pressure was very carefully monitored in the Ocular Hypertension Treatment Study, making it a reliable source for data. Sixty-three patients in the medically untreated hypertensive group underwent cataract surgery during the study; this chart compares their IOPs to control subjects who did not undergo cataract surgery. Following cataract surgery IOPs dropped about 4 mmHg, and the effect persisted for several years. (Adapted from Mansberger, et al.[4])



# ILEVRO™ Suspension

## Designed to put potency precisely where you need it[1,2]

## ONCE-DAILY POST-OP

One drop should be applied once daily beginning 1 day prior to surgery through 14 days post-surgery, with an additional drop administered 30 to 120 minutes prior to surgery[3]

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[3]

### INDICATIONS AND USAGE

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

**Dosage and Administration**

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.

### 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.**

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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 post-implantation 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**
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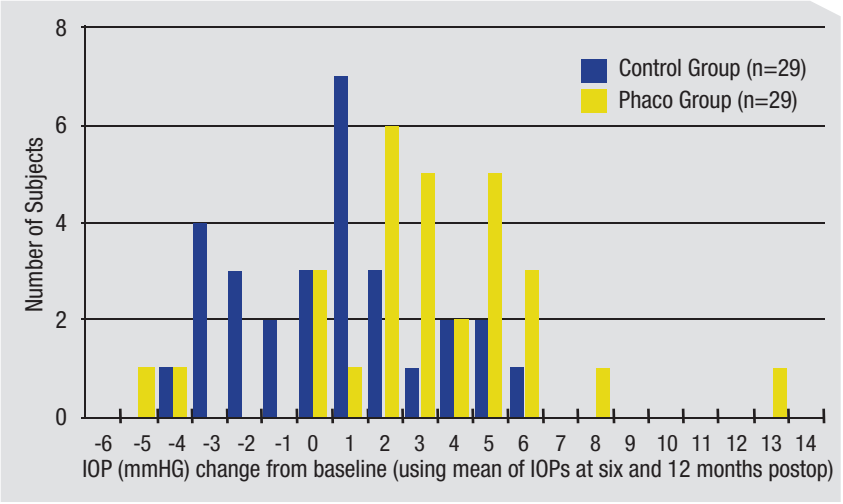
## Phacoemulsification's Effect on Trabeculectomies




Although phaco-based cataract surgery doesn't have the destructive impact on trabeculectomies that earlier forms of cataract surgery did, it still may have a negative effect. In this study, mean intraocular pressure rose by 0.4 mmHg in control eyes following cataract surgery, but rose 3.1 mmHg in eyes with trabeculectomies ($p<0.003$). (Adapted from Figure 1 in Swamynathan, et al.[6])

ing trabeculectomy and you perform phacoemulsification, one of the biggest risks is that you're going to cause the trabeculectomy to fail because of inflammation, scarring or related problems. Although clear cornea cataract surgery doesn't directly alter the bleb (unlike earlier forms of cataract surgery) one study found that IOP rose about 3 mmHg in patients with functioning trabeculectomies after uncomplicated phacoemulsification.[6] *(See chart, above.)* Clearly the surgery does impact the efficacy of the bleb, even if it doesn't destroy it.

There's remarkably little data regarding how phaco influences the efficacy of an existing drainage device. My perception, at least, is that a glaucoma drainage device is less likely to fail because of subsequent surgery than is a trabeculectomy. For that reason, when I have a glaucoma patient who needs IOP-lowering surgery and is likely to need other ocular surgery in the next few years—whether it's cataract surgery, vitrectomy or something else—I generally prefer to put in a glaucoma drainage device rather than perform a trabeculectomy. It's great if a trabeculectomy works well, but trabeculectomies are fragile and subject to late failures because of subsequent surgery, more so (in my opinion) than glaucoma drainage devices.

Unfortunately, there are only a few retrospective studies that have considered this issue, so there's not much solid data to back up my conclusion. The American Academy of Ophthalmology's newly launched IRIS Registry should eventually provide the kind of national, large-scale data that could help us answer this question.

When performing phacoemulsification on a glaucoma patient with a tube or trabeculectomy, the following strategies can help ensure a good outcome:

• ***If a patient has had prior glaucoma surgery, include the risks of failure in the consent discussion.*** When I see a patient in need of cataract surgery who has had prior glaucoma surgery, I explicitly include in my consent discussion—and document in the chart—that one of the biggest risks of doing cataract surgery in this situation is that the previous glaucoma surgery will fail and we'll have to go back and do more glaucoma surgery.

• ***Schedule the surgery based on the patient's visual needs and logistical considerations.*** If a patient has a trabeculectomy or a tube, I'd base the timing of cataract surgery primarily on two things: the patient's visual needs, and the logistics of how the surgery will impact the patient's life. In terms of the patient's visual needs, the fellow eye becomes part of the discussion. Is it a priority to have visual rehabilitation as quickly as possible? Or does the patient have a fellow eye that he can get along with just fine?

In terms of logistics, you have to consider what the patient wants and what he can manage. I'd explain to the patient that he may need a lot more follow-up than that needed by a routine cataract surgery patient. In my practice a significant number of patients live two or three hours away, so the more involved follow-up may entail some significant logistic challenges for the patient and/or the patient's family. In that situation I may time the surgery based on when it's practical for the family.

• ***Keep a close eye on a patient with a trabeculectomy after cataract surgery.*** If your cataract patient has a functioning trabeculectomy, you don't want to follow a standard postop routine in which you see the patient one day after surgery, a week to 10 days after that, and then a month later. Suppose you see the patient at one week and there's a lot of inflammation. When there's inflammation and the conjunctiva around the bleb is injected during the first week or two, if you fail to intervene with increased steroids or 5-fluorouracil injections or other maneuvers to prevent scar-

ring you will have lost your opportunity to intervene and save the trabeculectomy. The postoperative care of such patients should not be delegated to others.

## Checklist for Success

I find it helpful to use the following preoperative checklist when making a decision about how to proceed with a glaucoma patient who needs cataract surgery:

• ***Stage the glaucoma in both eyes.*** Before proceeding with the cataract surgery, you need to know how bad the glaucoma is. Knowing the pressure is not sufficient; you need to evaluate the optic nerve and visual fields.

• ***Perform gonioscopy.*** It's important to determine the condition of the angle prior to cataract surgery. Perhaps gonioscopy has never been done on a patient; sometimes it was done years ago, and you need to reevaluate the condition of the angle.

Some literature suggests that the patient who has a narrow angle before cataract surgery is more likely to experience a drop in IOP after cataract surgery as a result of the opening of the angle; but if the patient has lots of peripheral anterior synechiae, you may be dealing with chronic angle closure that wasn't previously recognized. The presence of PAS might indicate that the pressure will not decrease following the cataract surgery, and you might need to perform goniosynechialysis or another type of procedure to deal with the angle closure.

In any case, it's always a good idea to also do gonioscopy after the cataract surgery to find out what happened to the angle.

• ***Review the medications.*** Not every patient who is on one medication is the same. A patient may have significant disease but be on only one medication because he's allergic or intolerant to the others. You want to know that ahead of time, so if the patient has a pressure spike you'll know what options you have for treating him. (In most situations like this you'll want to consider combining a glaucoma surgery with the cataract surgery.)

*It seems reasonable to consider using phaco alone as a means to reduce IOP in some glaucoma patients with mild disease; it may delay or avoid the need for a future trabeculectomy.*

• ***Review patient-related factors.*** As noted earlier, factors such as how easy it is for the patient to come in for follow-up and the condition of the fellow eye must be considered when you decide how and when to proceed with the cataract surgery.

• ***Talk to the patient.*** Make sure everyone is on the same page in terms of expectations. Given the very high expectations for cataract surgery vision outcomes that people have today, it's always best to underpromise and over-deliver. (Note that visual recovery is known to be slower after a glaucoma patient undergoes combined surgery, although the final outcomes are similar to those with cataract surgery alone.) A glaucoma patient needs to understand that because of the disease he won't be playing tennis and seeing 20/20 the day after surgery; he should not expect to have the same fabulous result that his neighbor may have had. And, make sure you document this conversation in the chart.

## Proceed With Caution

Given the relative safety of today's phaco-based clear cornea cataract surgery and its lack of impact on future glaucoma surgery options, it seems reasonable to consider using phaco alone as a means to reduce IOP in some glaucoma patients with mild disease; it may delay or avoid the need for a future trabeculectomy. Of course, minimally invasive glaucoma surgery can also be combined with cataract surgery in patients with mild disease.

A few other things to keep in mind in this situation:

• ***Keep the surgery simple.*** If you're doing cataract surgery on a patient currently being treated for glaucoma, do the simplest and cleanest surgery you can, doing everything possible to avoid stirring up inflammation. I would use more steroids with this type of patient, rather than less.

• ***Don't remove an asymptomatic cataract in a glaucoma patient just to reduce pressure.*** Some surgeons might consider removing an early, asymptomatic cataract as a way of lowering pressure. However, this option is probably unwise when an individual is being treated for glaucoma. I believe you should only take out a cataract based on a glaucoma patient's visual needs, for two reasons: First, the IOP-lowering effect is not that predictable on an individual basis. Second, cataract surgery is not without risk; you can have complications. I certainly don't think that cataract surgery as an IOP-lowering procedure (in the absence of vision-based indications) is the standard of care.

• ***Be prepared in case IOP increases instead of decreasing.*** The

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predictability of a pressure decrease in an individual patient is relatively poor. A recently published study by Mark A. Slabaugh, MD, and colleagues at the University of Washington in Seattle found that out of 157 open-angle glaucoma patient eyes undergoing cataract surgery, 60 eyes needed additional medications or laser treatment to control IOP during the first year postoperatively, or were found to have a higher IOP one year after surgery on the unchanged preoperative medication regimen.[5] (In the latter group, higher preoperative IOP [$p<0.001$], older age [$p=0.006$], and deeper anterior chamber depth [$p=0.015$] were associated with lower postoperative pressure.) Enough patients will have an unexpected rise in pressure that you need to have a game plan ahead of time for dealing with such a possibility. It's a good reminder that cataract surgery is not totally benign, especially when dealing with a glaucoma patient.

The main thing to remember is that a cataract patient who also has glaucoma should not be treated like a simple cataract patient. It's easy to get burned if you don't take stock of the patient's disease, both in terms of what might need to be done during and after the cataract surgery, and in terms of how cataract surgery will influence the subsequent management of the glaucoma. If you evaluate the patient's disease carefully, set appropriate expectations, do meticulous surgery and follow-up diligently, your glaucoma patient should end up with good vision, and you should end up with a happy patient. REVIEW

*Dr. Brandt is director of the glaucoma service and a professor in the department of ophthalmology at the University of California Davis School of Medicine; he is also a principal investigator in the Ocular Hypertension Treatment Study.*

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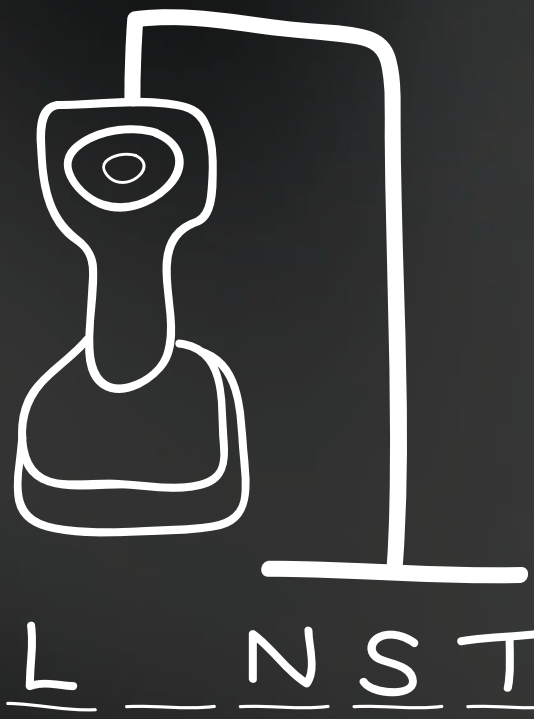


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# Innate Immunity: A Question of Balance

A look at the processes of immunity and ocular inflammation, and new avenues for disease therapy.

*Mark B. Abelson, MD, CM, FRCSC, FARVO, Daniel Gamache, PhD, and James McLaughlin, PhD, Andover, Mass.*

**Inflammation is one** of the oldest of medical terms. In fact Celsus, approximately 2,000 years ago, gave us the cardinal signs of inflammation: *rubor*; *tumor*; *calor*; *dolor* and *functio laesa*. After two millennia of research (How often do we get to say that?), our understanding of inflammatory mechanisms continues to evolve. Inflammatory processes encompass a broad spectrum of responses designed for protection and preservation of healthy, optimally functioning tissue. Physiological inflammation is intimately linked to innate immunity, the body's primordial defense system of macrophages and other phagocytic cells that are the specialized first responders to invading pathogens and tissue injury. In contrast, pathological inflammation occurs when regulatory mechanisms fail and the cellular defense system morphs into a suicide machine that attacks and degrades otherwise healthy tissue. The professional cells of innate immunity are often some of the major culprits in pathological inflammation, so it's clear that in devising therapies for conditions with an underlying inflammatory component it's critical to strike a balance between suppressing the aberrant actions of immune cells and signals and preserving proper protective functions.

In past columns we've discussed chronic inflammation of the type associated with allergy and dry eye, and we've also looked at new potential treatments for these conditions. Inflammation is central to so much of what we deal with on a daily basis—keratitis, uveitis, conjunctivitis and dry eye—all of which involve pathological inflammatory responses. This month, we dig a little deeper into some of the fundamental pathways that shape the inflammatory process. In particular, we'll look at the basic signal transduction events involved in innate immunity, and examine how both professional immune cells and the resident cells of inflamed ocular structures contribute to the overall orchestration of inflammation. Not surprisingly, these efforts will uncover a number of potential targets for therapeutic intervention.

## Detecting Pathogen Patterns

The innate immune system is that part of our overall response to foreign invasion or traumatic insult that occurs without provoking an antibody-mediated response. Phagocytic cells such as macrophages, neutrophils or other white blood cells engulf and degrade intruding debris, bacteria and other foreign flotsam. Historically, innate immunity was considered a nonspecific response to any invaders, but research from disparate fields came together in the late 1980s to demonstrate that the immune system used a collection of pattern recognition receptors that orchestrate both innate immune responses and the complex interactions between the innate and adaptive immune systems.[1]

As in all tissues, specialization in the professional ranks of the immune system is conferred by expression of a repertoire of receptors, signaling molecules and mediators that function to neutralize the insult and restore homeostasis. Included among these molecules are the PRRs that bind to conserved PAMPs, or pathogen-associated molecular patterns, presented by bacteria, fungi, viruses and parasites.[2,3] Other studies have expanded this category to include DAMPs, danger-associated molecular patterns, de-



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rived from endogenous molecules released by tissue trauma.[4] The PAMPs and DAMPs are fragments of protein, nucleic acid or polysaccharide that have, over the course of evolution, become uniquely associated with a specific source, and so can be used by immune cell receptors as indicators of the presence of intruders, either foreign or domestic.

Recognition of PAMPs or DAMPs leads to activation of PRRs and subsequent triggering of gene transcription factors including NFκB. These direct the production of pro-inflammatory cytokines, chemokines, type-1 interferons, antimicrobial proteins and tissue repair proteins. Pivotal cytokines that initiate and mediate the acute innate response include established therapeutic targets such as TNF alpha, interleukin-1 (IL-1) and IL-6.

Four different families of PRRs have been identified *(See Table 1, above)*, and each of these receptors acts as a molecular sentry, recognizing molecular patterns displayed by proteins, lipids or nucleic acids derived from potentially harmful sources. The largest and best characterized family of PRRs is the plasma-membrane-associated Toll-like receptors initially discovered in *Drosophila*.[5] To date, 10 human TLRs have been described. A second class of membrane PRRs are the C-type lectin receptors,[6] proteins with high affinity for certain complex carbohydrates. The two other families are intracellular proteins: the NOD-like receptors and the retinoic acid gene-like receptors.[7] These detect molecular patterns from the products of endosomal processing.

Despite the diversity of the primary signals, the majority of the PRRs act via a small subset of signaling molecules.[2,3,8,9] With the exception of TLR3, ligand binding to all of the TLRs leads to recruitment of a common adaptor molecule called MyD88 *(See Table 2, p. 75)* to the membrane, and subsequent activation of a cascade of intracellular signaling intermediates. These events culminate in transcriptional activation by NFκB or other transcription factors. The net effect is enhanced expression of a variety of target pro-inflammatory genes. TLRs, MyD88 and NFκB therefore represent potential sites for therapeutic intervention in the innate immune response. Of note, TLRs also represent a critical link between innate and adaptive immunity. For example, dendritic cell TLR activation is thought to play a key role in the physiological balance between sensitization and tolerance.[10]

**Table 1. Properties of Pattern Recognition Receptors**

| PRR | Localization | Ligands | Ligand Sources |
|---|---|---|---|
| TLR<br>Toll-like receptors | Plasma membrane | lipoproteins, DNA, RNA, endotoxin, endogenous danger signals | bacteria, viruses, parasites, self |
| NLR<br>NOD-like receptors | Cytoplasm | endogenous danger signals, muramyl dipeptides | self, bacteria |
| CLR<br>C-type lectin receptors | Plasma membrane | beta-glucans | fungi |
| RLR<br>Retinoic acid-inducible gene-1-like receptors | Cytoplasm | double-stranded RNAs | RNA viruses |

## A Nod's as Good as a Toll

Another family of PRRs expressed by professional innate immune cells, and also by other cells, is the NOD-like receptors. NLRs are part of cytoplasmic multi-protein complexes called inflammasomes that act as sensors of cellular stress.[7,11] Activation of inflammasomes (by stress or by other signals) stimulates a transcriptional pathway similar to that which is activated by TLRs, and includes induction of pro-inflammatory cytokines. Upon activation, changes in NLR conformation lead to recruitment of the enzyme caspase-1 to the inflammasome. Caspase-1 then converts cytosolic pro-IL-1 to the active cytokine, IL-1β. Receptors for IL-1β are widely expressed in immune and non-immune cells and, consequently, IL-1β exerts both autocrine and paracrine pro-inflammatory effects. As with TLRs, IL-1R signals through MyD88 and NFκB to increase pro-inflammatory cytokine levels, including pro-IL-1. Approved biologicals that target IL-1 include the receptor antagonist Anakinra (Kineret, Biovitrum AB) and the soluble IL-1R mimetic Rilonacept (Arcalyst, Regeneron).[12]

Mutations in NLRs lead to spontaneous activation of caspase-1, elevated production of IL-1β and to a variety of diseases that have been labeled "auto-inflammatory."[11] Auto-inflammatory diseases are non-infectious conditions with no evidence of involvement of an adaptive immune response. An example is Blau syndrome, which is characterized by the triad of uveitis, arthritis and dermatitis and results from a mutation in the inflammasome NLR, NOD.[2,13] The mutated NOD2 spontaneously activates NFκB for production of pro-inflammatory cytokines, including IL-1. In addition to NLR mutations, various other triggers of innate immunity contribute to the growing list of diseases that can be described as auto-inflammatory. These include type 2 diabetes mellitus, Crohn's disease and various ocular diseases that are associated with



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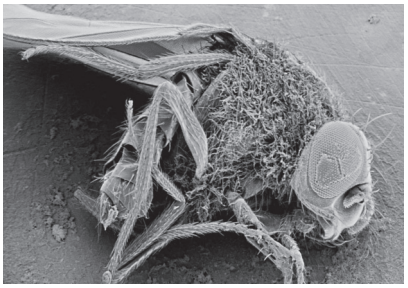
sight-threatening, degenerative conditions.[11-14]

## Innate Signaling in the Eye

In addition to innate immune cells, non-professional resident tissue cells also actively engage in immune responses through their own repertoire of receptors, signaling molecules and mediators. This resident tissue cell repertoire includes PRRs, activation of which provides mediators that recruit professional innate immune cells to the affected site. Human ocular surface epithelial cells and conjunctival fibroblasts express TLR receptors and respond to activation by TLR ligands.[15] Similar to professional innate immune cells, corneal epithelial cells, mast cells and fibroblasts secrete pro-inflammatory cytokines upon activation of TLRs through MyD88 and NFκB signaling. As with dendritic cells, TLR activation of these residents of the conjunctiva participates in local innate responses in addition to more far-reaching, adaptive processes. Beyond the ocular surface, TLRs can be found in a variety of resident tissue cells of the retina, the uvea and in the lacrimal glands.[9,15]

The endogenous, non-microbial DAMPs are products released from stressed or necrotic cells and damaged tissue. DAMPs include intracellular proteins such as heat shock proteins, extracellular matrix fragments, nucleic acids (DNA, RNA) and purine metabolites including ATP and uric acid.[16-18] Recognition of signals of cell stress and death evolved as mechanisms to more effectively fight against pathogens. Tissue injury therefore provides endogenous amplifiers of the inflammatory response. Danger signals may be produced during inflammation caused by infection and by environmental triggers such as pollutants or chemicals, and by mechanical trauma. Reactive oxygen species produced during cell stress are critical danger signals that stimulate the innate immune response. Endogenous danger signal production is a key mechanism by which non-professional tissue resident cells actively participate in the innate immune response.



The Toll-like receptors were first identified in a *Drosophila* mutant termed Toll, a German word for "strange" or "weird." Flies with this mutation underwent abnormal development and, as shown here, were highly susceptible to *Aspergillus* and other fungal infections due to the mutation in the Toll PRR gene.

The innate immune system is implicated in a number of ophthalmic disorders. Uveitis was traditionally considered to be due to loss of immune tolerance to retinal proteins and, therefore, an autoimmune disease. Accordingly, a large body of evidence supports critical roles for Th1 and Th17 cells in mediating pathology in uveitis. However, selective therapeutic targeting of T-lymphocytes has not been as effective a strategy as broadly acting corticosteroids.

The role of innate immunity in uveitis has remained underappreciated despite the fact that it is well known that activation of the innate immune system using microbial adjuvants is required to produce the disease in animals.[18] For example, the uveitis seen in Blau syndrome is caused by a specific mutation that activates NLRs.[13]

Alternatively, activation of innate immunity by prior infection is strongly implicated in Fuchs heterochromic cyclitis. Systemic diseases associated with uveitis in which innate mechanisms are suspected to play critical roles include Behçet's, Crohn's and sarcoidosis.

There is also a growing body of evidence that supports a role of inflammation in the pathogenesis of degenerative diseases including Parkinson's and Alzheimer's. A similar pattern is seen in diseases of the retina, where evidence demonstrates ongoing inflammation involving innate mechanisms.[16] In diabetic retinopathy, one underlying mechanism for tissue damage seems to be a chronic inflammation leading to blockage of retinal capillaries by recruited leukocytes. In animal models, activated circulating bone marrow-derived monocytes have been identified as the primary ischemia-inducing culprit.[19] This suggests that innate immune system cells may be part of the trigger for neovascularization and associated visual complications in diabetic patients.

In age-related macular degeneration, the attention of researchers has focused on the role of complement factor gene polymorphisms in individual susceptibility, and the possible associated defects in complement inactivation.[20] However, evidence for critical roles by other components of the innate immune system is increasing. Drusen accumulation is associated with increased macrophage and dendritic cell activity[21] and the severity of disease is correlated with the presence of macrophages that express a more pro-inflammatory phenotype.[22] Cell death, including death of RPE cells, is associated with production of danger signals recognized by membrane-bound and intracellular PRRs, providing a stimulus for inflammatory cytokine production and further macrophage recruitment.

## Balancing Immune Signals

Environmental exposure of the ocular surface renders it susceptible to a host of innate immune system triggers. As the first line of defense, the barrier to infiltration imposed by the epithelial cells of the cornea and

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sclera presents both a physical impediment and a set of physiological sensors that include TLRs. As in other tissues, activation of TLR signaling on the ocular surface initiates a cascade of signaling events that activate innate defenses and set the stage for adaptive immune system intervention.

Activation of innate immune system signaling is a critical aspect of a number of ocular surface disorders. For example, under normal conditions basal tear secretion is regulated by corneal sensory receptors (cold thermoceptors of the transient receptor potential family, TRPM8) that are exquisitely sensitive to the reduction in surface temperature that occurs when tears evaporate.[23] These sensory neurons may drop out over time, which may explain why age is such a major risk factor for dry eye. Consistent with hydration as a key to ocular surface homeostasis, exposure to desiccating environmental conditions is one of the most frequently employed clinical and preclinical models of dry eye. Tear-film dysregulation such as desiccation has been shown to impact corneal epithelial expression of TLRs.[24] A role of PRRs and DAMPs in dry eye is further supported by reports on the role of IL-1β in this disease.[25] Dry eye represents a clear example of the active participation of non-professional resident tissue cells in the immune response.

Links between innate and adaptive immunity can also be found in features of allergic conjunctivitis. Activation of corneal fibroblast and epithelial cell TLRs induces the production of the cytokine thymic stromal lymphoprotein that promotes a pro-allergy, Th2-mediated immune response.[26] TSLP promotes Th2 differentiation and proliferation, and enhances other adaptive immune functions of Th2 cells, including activation and recruitment of mast cells and eosinophils.[27] In addition, mast cells have been found to express TLRs that, when activated, can synergize with antigen activation of the high-affinity IgE receptor.[28]

**Table 2. ABCs of Innate Immunity**

| | |
|---|---|
| PRR | pattern recognition receptors |
| PAMP | pathogen-associated molecular pattern |
| DAMP | danger-associated molecular pattern |
| MyD88 | product of Myeloid Differentiation gene 88 |
| NFκB | nuclear factor κ-B, a transcription regulator |
| TLR | toll-like receptor, a PRR similar to the *Drosophila* toll gene product |
| NLR | nod-like receptor, a PRR similar to the nucleotide oligomerization domain proteins |
| CLR | C-type lectin receptor, a PRR with high affinity for some carbohydrates |
| RLR | PRRs induced by retinoids that act as receptors for RNA viruses |

Disruption of homeostasis and compromised ocular surface health in dry eye may be a key determinant in a patient's susceptibility to further disease. An example of this is the comorbidity of allergic conjunctivitis and dry eye, and it's of particular interest to us. Patients with chronic allergic disease experience elevated levels of immune cells and pro-inflammatory mediators, setting the stage for a protracted state of allergic inflammation that shares many of the features of dry eye.

Conversely, ocular surface abnormalities in dry eye may predispose to ocular allergy since barriers to allergen entry into conjunctival tissue are compromised. In a recent clinical study,[29] experimentally induced dry eye predisposed patients to more severe responses to antigen, demonstrating the role of innate immunity in the regulation of adaptive immune responses in the eye.

It has been suggested that PRR activation and crosstalk in tissues such as the cornea may be a key in the balance between Th1 and Th2 adaptive immune responses,[30] and so could represent a uniquely positioned target for therapeutic intervention. Increased understanding and appreciation of innate immunity has solidified the notion that a balanced ebb and flow of inflammatory responses to environmental stimuli is a key part of healthy tissue homeostasis. Yale researcher Ruslan Medzhitov, PhD, has proposed the term "para-inflammation" to describe a controlled physiological response that is beneficial in terms of protection from infection and maintenance of tissue and organ function.[31] The broad spectrum that inflammatory mechanisms encompass is brought into perspective when considering these concepts. Maintenance of health and tissue homeostasis is a delicate balance to maintain, since organisms are constantly exposed to exogenous and endogenous stress and consequent danger signals.

Recent efforts to target the function of PRRs as a therapeutic intervention strategy have focused on TLRs (especially TLR-4, -7 and -9), and although the results from these studies have been equivocal, a number of new trials are either under way or in the planning stages. NLRs have also been the subject of great interest, both because of their importance in

*(continued on page 90)*

# How to Stay on Track with Intacs

You can get a good visual and anatomic result, and avoid complications, by following these steps.

*Walter Bethke, Managing Editor*

**Intacs intracorneal ring** segments can help stabilize a keratoconus patient's cone and improve his vision, as long as the surgeon plans the procedure properly and understands the nuances of the technique. A breakdown at any stage of the process can lead to decentered segments, segments outside of the proper channels or even a corneal perforation. Here, corneal surgeons share their tips for the best results for each step of the process.

## Preop Planning

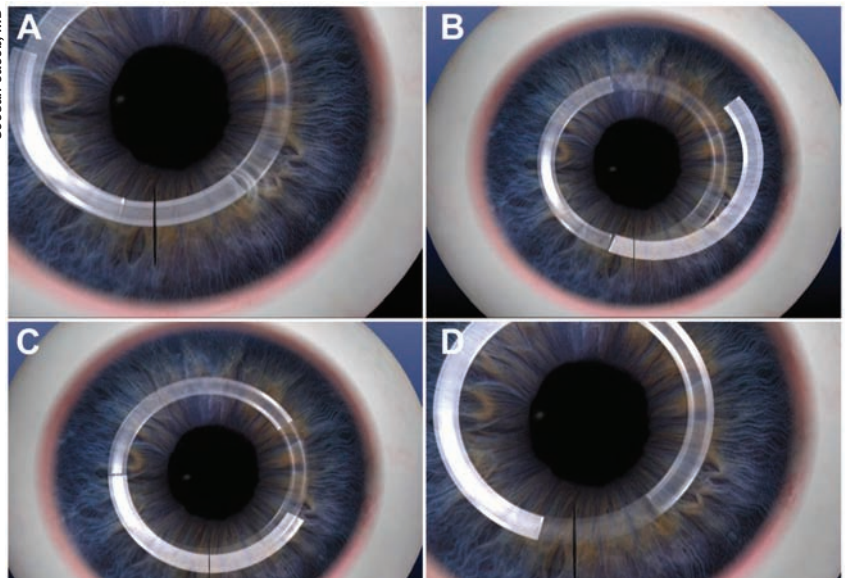
Like many endeavors, surgeons say where you start often determines where you finish with Intacs.

"In planning, we go off of the corneal topography and refraction," says Peter Hersh, MD, of Teaneck, N.J. "We try to get the best idea of where the cone is. It's easiest when the refractive axis and topographic axis align and, if that's the case, we take the steep axis and that's where we make our incision. If the refractive and topographic astigmatism axes are not in accord, though, it's a little more confusing. In those cases, I study the topography maps and even go back and study Scheimpflug maps on the Pentacam or OCT images. I find that by scrolling through these and looking at the maps, one can get a very good idea of the geographic depiction of the cone location, because what we're doing, essentially, is trying to straddle the cone location.

"Then, I look at the difference between the steep and flat axes," Dr. Hersh continues. "For this, we're looking at the steepness of the cone and then, 180 degrees away, at the flatness of the cornea. Looking at this difference and the patient's refraction tells me if I want to use two segments or one and, if I'm going to use two, do I want to use symmetrical segments or asymmetrical segments. For example, if a patient has a relatively low cone, there's a big difference in the inferior to superior topographic power and the patient has a preponderance of astigmatism—mixed astigmatism in particular—then I'll typically use one single segment aligned beneath the cone. If there's asymmetry and more myopia, then I'll consider asymmetric segments. And, if there's mostly myopia and little astigmatism with a central cone—meaning not much of an inferior/superior difference—then I'll use symmetrical segments, because if you use a single segment or two asymmetrical ones there tends to be coupling. Particularly with a single segment, coupling will flatten the cone inferiorly where the cone is located and simultaneously steepen it superiorly, with the effect being greater corneal symmetry and improved best-corrected vision."

Getting the proper depth for segment placement is also key. "With Intacs, probably the most important thing is not to go too shallow," says Dr. Hersh. "The flip side, however, is you don't want to go too deep because if you do, rather than elevating the anterior surface you can instead push out Descemet's into the anterior chamber and not get as much effect. So, I typically try to go as deep as I can while leaving 100 microns of residual stroma between the Intacs and Descemet's at the thinnest point that I'm going around. Other measurements I use: I look at 75 percent depth at the entry site and 85 percent at the thinnest point. I also look at the thickest point to make sure I'm not going too shallow for the thickest point. Taking all those together, I make my plan for

the incision depth." Istanbul, Turkey, corneal surgeon Efekan Coskunseven also takes care in planning the depth. "Today I use the Pentacam and ultrasonic pachymetry at the tunnel location and use the thinnest pachymetry as my reference," he says. "I then use 80 percent of that reference point. Or, another method is to determine the minimum thickness of the cornea and then stay 90 microns away from the endothelium based on that measurement. For example, if the minimum thickness is 450 microns, I plan to use 360 microns for the depth of the channel. In over 4,000 surgeries, I have never had an endothelial perforation with this technique."



Soosan Jacob, MD

The turnaround technique for overcoming a false channel: A) The presence of undue resistance to insertion of segment indicates false channel creation. B) The segment is removed and reinserted from the opposite direction, using another segment to push it. C) As the first segment approaches the obstruction from the opposite side, it flattens the lip of the false channel and opens up the original IntraLase-dissected channel. D) The segment is then pulled into position using a reverse Sinskey hook.

## Creating the Channels

To create the channels where the Intac or Intacs will sit, surgeons can choose a manual or a femtosecond method.

"One of the major problems with manual channel creation is it's not very predictable," says Chennai, India, surgeon Soosan Jacob. "You can't be exactly sure about the depth of the Intacs' placement. With manual, it's easier to get a decentration or to go more superficial or deep than you'd been planning for. There can be variations in the centration of the channel with respect to the pupil as well as the depth of the cornea."

Although, like Dr. Jacob, Dr. Hersh uses the femtosecond for almost all of his Intacs cases, he says it's not foolproof. "In some cases it can be more difficult to place the Intac with the femtosecond-created channel than a mechanical one because, with a mechanical, you're completely separating a smooth channel," Dr. Hersh says. "But, when you use the femtosecond, you still have some residual anchors that haven't been split by the femtosecond, so it might be a little more difficult to pass the Intac through."

Dr. Jacob says that, in some cases, the laser may make the 360-degree circumferential cut but not the entry incision you need to introduce the segment into the corneal channel. "If this occurs, take a 15 blade and cut down to the depth of the channel," she says. "You need to know when to stop, however, since you might go below it or stop short of the actual channel. If either of those situations occurs, when you put the segment in you might create a false channel by inserting it at the wrong depth. To make sure you cut down to the proper depth, do so before the bubbles that were created when the channel was formed by the femtosecond dissipate. When your blade reaches the plane of the bubbles, they will escape through the incision and you'll know you're at the proper plane of the channel. If you delay, however, and the bubbles disappear, you won't know where the channel is and it will be very difficult to locate.

"In case you anticipate a delay," Dr. Jacob adds, "make sure you mark 360 degrees over the channel with a marker pen so that there is no confusion regarding the location of the channel."

## Placement Issues

Once the channel is created, surgeons say you still have to remain vigilant for complications as you slide the segments in.

"You have to be meticulous, going little by little, as you push the segment through the channel," says Dr. Hersh. "I've found it helpful if you provide counter traction at the end of the Intac to give a little stretch as it's going through. You do this by using your other hand to manipulate the periphery of the cornea in that area." Even when a surgeon is careful, however, a segment can occasionally go off-course and start creating a false channel by driving into the corneal lamellae next to the real channel. The false channel can be in any direction from the main channel.

"You'll know you're getting a false channel because you'll feel increased resistance as you insert the Intacs segment," Dr. Jacob says. "At that point, you must stop pushing, because the

more you push, the larger the false channel will be. Another way to detect the creation of a false channel is you will begin to see radiating folds around the leading edge of the segment."

If a false channel occurs, Dr. Jacob performs what she calls the turnaround technique. "With a false channel, an internal lip is formed from some of the stromal lamellae that you cleaved into with the segment," Dr. Jacob explains. "That lip separates the true channel from the false one, and the more you push, the more you enlarge the lip. At this point, you will never be able to regain the true channel in that direction, since the segment will always slide into the false channel. However, with the turnaround technique that I developed, you come around from the opposite direction and the lip flattens, allowing you to regain the original channel." (For a video of the turnaround technique, visit http://goo.gl/t9L2fR.)

Other issues that can occur are incision gaping and migration of the Intacs postop. "If I'm planning on using a single segment, I'll make my incision site a little more distant from the head of the segment than I would for double segments," Dr. Hersh says. "What this does is bring the incision site farther away from the ultimate Intacs placement. I think this mitigates potential problems that one might have with gaping of the incision, potential infection of the incision site and also possible migration out of the incision site. Specifically, I set my laser to create the entry incision site 10 degrees distal to where the head of the Intacs will be."

In a study of 850 eyes of 531 patients, Dr. Coskunseven says the segments were displaced postop in 11 cases (0.8 percent).[1] In seven of the cases the segments migrated in the channel and a suture placed at the incision stopped any further movement. Four segments moved toward the surface, though, and had to be removed before any perforation occurred. Dr. Jacob says superficial migration is possible if a false channel occurs, but the surgeon finishes the case. "It's possible to leave it in such a way that it straddles the incision," she says. "However, I don't do this because if the tip of the Intacs is underlying the incision, there's a higher chance of foreign body complications such as neovascularization, migration, extrusion and stromal erosion." REVIEW

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# Update on Intravitreal Injection Techniques

On the anniversary of the consensus guidelines, a look at what evidence gathered over the decade has taught us.

*By Peter A. Karth, MD, MBA, and Mark S. Blumenkranz, MD, Palo Alto, Calif.*

**It has been** a decade since Lloyd P. Aiello, MD, and colleagues published their consensus guidelines on the technical aspects of intravitreal injections.[1] In 2004, only one agent was approved for intravitreal injection, and anti-VEGF agents had not yet been approved in ophthalmology. Since that time, intravitreal injections have become a cornerstone of retinal care and one of the most commonly performed procedures across all specialties. We have seen practices change dramatically and evidence on this topic mount. The 10-year anniversary of the guidelines is a good opportunity to examine the evidence in this area. Herein, we consider several of the critical technical aspects of IVI, broadly examining the literature and offering evidence-based suggestions based upon the available literature *(See Table 1)*.

## Anesthesia

Current techniques of pre-injection anesthetics vary widely and have been well-studied. In one randomized prospective trial of 24 patients, no difference in intravitreal injection pain scores was found between topical proparacaine and tetracaine, lidocaine pledget, and subconjunctival lidocaine for pre-injection anesthesia.[2] Another randomized, prospective study of 28 patients showed significantly lower patient pain scores with subconjunctival 4% lidocaine versus topical 4% lidocaine for the IVI portion of the procedure; however, the combined pain score of the subconjunctival injection and IVI together was equivalent in both groups.[3] Alternatively many retina surgeons employ lidocaine gel for pre-injection anesthesia. In a prospective, randomized study of 120 patients comparing proparacaine 0.5% drops, proparacaine + 4% lidocaine-soaked cotton tipped swabs held against the injection site for 20 seconds, and 3.5%

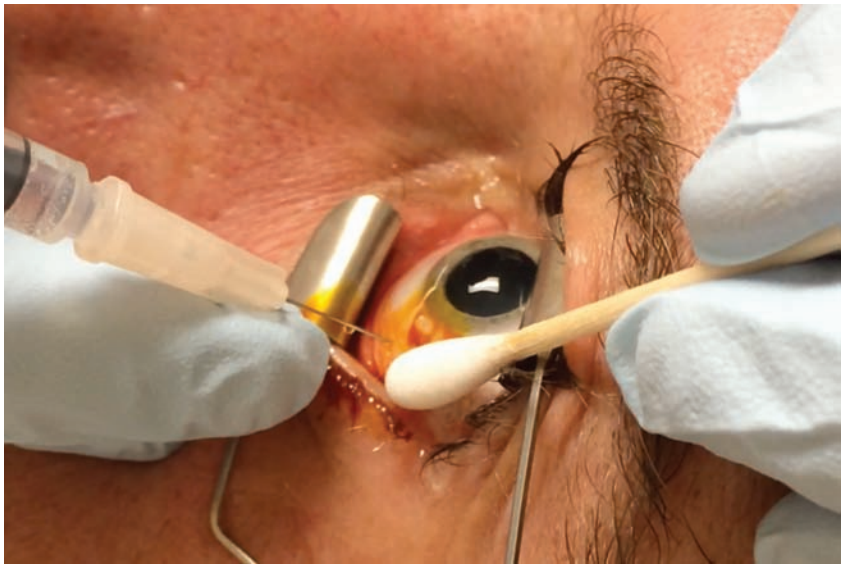

Figure 1. Intravitreal injection, showing use of a lid speculum and local application of providone-iodine to the conjunctival surface at the intended site of injection, thus minimizing corneal exposure/toxicity.

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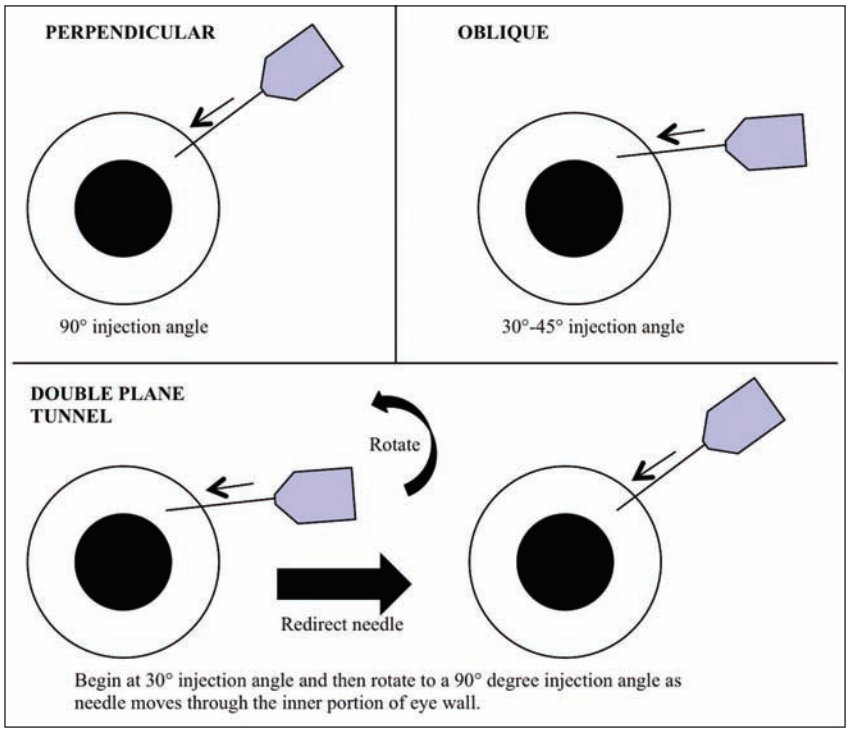


Figure 2. Schematic illustration of three different needle path penetration techniques —perpendicular, oblique and double-plane.

lidocaine gel, no difference in pain scores was found between these methods.[4] In another prospective, randomized study of 120 patients comparing topical lidocaine 2% gel and subconjunctival lidocaine 2% injection, they found no difference in pain scores.[5] Based on this evidence, we suggest one of the above lidocaine-based methods, but feel there is a lack of evidence to support recommending one technique over another.

## Povidine-iodine Eye Prep

Providone-iodine is the mainstay of conjunctival antibacterial surface preparation and is widely considered part of the standard of care for IVI *(See Figure 1)*. Typically, 5% PI solution is used. There are two additional important issues in this area: 1) the length of time the PI should be in contact with the conjunctiva; and 2) the order in which anesthetic gel and PI should be applied.

One laboratory study looking at common pathogens in endophthalmitis showed that bacterial kill time for PI ranges from 30 to 120 seconds, and that 15 seconds was inadequate.[6] In another study, exposure to 5% PI for 15 seconds failed to yield significant reduction in conjunctival bacteria, with only a 42-percent reduction in bacteria; significant reduction was observed after 30 seconds.[7] In another study, 5% PI showed 96.7-percent bacterial kill rates achieved with 60 seconds of contact. The authors also note that 5% PI is more effective than 1% PI.[8]

One laboratory study showed that if the PI was placed on culture plates before the lidocaine gel, the bacterial counts were equivalent to PI only (no growth); however, if PI was placed onto the plates after the lidocaine gel, bacterial growth was similar to plates which had no PI applied at all.[9] Another laboratory study demonstrated that applying lidocaine gel before 5% PI severely decreased effectiveness against common endophthalmitis pathogens versus 5% PI in direct contact.[10] We feel the literature shows strong evidence supporting application of PI directly to the conjunctival surface for at least 30 seconds after administration of aqueous topical anesthetic but prior to administration of gel, if used.

Interestingly, a recent study incubated common endophthalmitis pathogens with and without lidocaine 2%/methylparaben 0.1% and showed a 90- to 95-percent reduction in colonies in the lidocaine group, suggesting an antibacterial effect of this agent. The authors also presented a chart review of IVIs either with subconjunctival lidocaine or without; they found a statistically significant reduction in endophthalmitis rates in those with subconjunctival lidocaine.[11]

## Peri-injection Topical Antibiotics

In 2004, Dr. Aiello and colleagues refrained from recommending peri-IVI antibiotics, due to lack of evidence.[1] Ten years later, there has been sufficient study of routine peri-injection antibiotic use to suggest that they should not be considered standard of care and may preferably be avoided.

Regarding antibiotic resistance, in a randomized, controlled study of 24 patients receiving IVI, participants received four monthly IVIs along with one of four topical antibiotics (ofloxacin, gatifloxacin, moxifloxacin or azithromycin) at the time of IVI and four days later. The conjunctiva was cultured before and after the injection. In positive cultures, the strain was identified and tested for susceptibility. In untreated control eyes, resistance to the antibiotics was in the range of 26 to 59 percent, while resistance in eyes treated with antibiotic was higher, in the range of 42 to 82 percent.[12] Another group showed that treated eyes had an 87.5-percent resistance rate to fluoroquinolones com-

pared with 25 percent in non-treated matched control eyes ($p$=0.04).[13] Also, IVI eyes treated with topical fluoroquinolones rapidly developed multidrug-resistant conjunctival flora (90 percent *Staph epidermidis*) compared with untreated controls (70 percent, $p$<0.02).[14] Stephen J. Kim, MD, and colleagues also showed that the percentage of *S. epidermidis* in conjunctival bacteria also increases with peri-IVI antibiotic use.[15]

No incremental benefit of peri-IVI antibiotics has been shown, if PI is appropriately used for prep.16 Also, neither topical moxifloxacin nor gatifloxacin achieves therapeutic levels in the vitreous. *(Costello P. Vitreous penetration of moxifloxacin and gatifloxacin after topical administration in humans. Paper presented at Annual meeting of the American Academy of Ophthalmology October 23, 2004; New Orleans.)* Additional cost for this common procedure is also an issue. We feel there is a preponderance of evidence suggesting the avoidance of routine peri-IVI topical antibiotics, assuming proper PI prep is employed.

## Needle Diameter

With respect to needle size, three important potential complications have been investigated: vitreous incarceration; fluid reflux; and patient discomfort for needles ranging from 27- to 32-ga.

• ***Vitreous incarceration.*** Vitreous incarceration (wick) may be a risk factor for endophthalmitis.[17] In a laboratory *ex vivo* study, 32-ga. needles demonstrated less vitreous incarceration at the tract site than either 27- or 30-ga. needles ($p$<0.01) with endoscopic investigation.[18]

• ***Fluid reflux.*** Fluid backflow through the needle tract may result in reduced volume of drug delivery.[19] Laboratory studies have shown that 27-ga. needles are associated with the formation of subconjunctival blebs or reflux post IVI at a greater rate than 30- or 32-ga. needles. [18,20]

• ***Patient discomfort.*** In one survey study of 60 IVI patients comparing 27-, 30 and 32-ga. needles, the gauge of the needle was not found to affect pain scores to a statistically significant level.[21] However, in another study, statistically significant lower pain scores were found with smaller gauges, comparing 26- or 27-ga. needles to 29- and 30-ga. needles ($p$<0.001).[22]

Importantly, no reports of significant disadvantages of smaller gauge needles have been published. However, reduced fluid reflux associated with smaller needles likely leads to higher post-injection intraocular pressure elevations compared with larger needles; this important point is discussed below. We feel the data shows significant advantages with 30-ga. or smaller needles and trends towards advantages with even smaller-gauge needles for IVI.

## Needle Angle

The angle of penetration of the needle in relation to the sclera is an important, but often overlooked, aspect of IVI. Significant variation of fluid reflux has been shown with various needle angles. The consequence of fluid reflux may be reduced effective medication dose, vitreous wicking and IOP fluctuation. For proper perspective, a well-structured rabbit study evaluated reflux using PET/CT after IVI of I-124-labelled anti-VEGF. Straight perpendicular injection with a 32-ga. needle with a cotton swab placed as the needle was withdrawn was used in this protocol. Immediately following injection, each subject was imaged with micro PET/CT. The subconjunctival bleb at the injection site was clearly visible by PET/CT and therefore contained the labeled anti-VEGF, showing that drug does reflux—in this experimental setting.[19]

In a study of 105 patients randomly assigned to either straight perpendicular (90°), shallow oblique (30° to 45°), or double-plane tunnel injection (beginning at 30° and redirecting to 90°), the occurrence of fluid reflux was recorded *(See Figure 2)*. In the straight injection group, 51.4 percent of patients had reflux; 34.3 percent did so in the oblique group, and only 17.1 percent did so in the double-plane tunnel group.[23] In another non-randomized prospective study of 88 eyes, the mean measured reflux bleb was statistically less with a double-plane tunneled injection versus eyes undergoing the straight perpendicular injection ($p$<0.001).[24] Another randomized study of 60 patients comparing straight or tunneled needle paths noted no difference in IOP after five minutes and equivalent patient pain scores between groups; however, less reflux was found in the tunneled group.[25]

We feel there is significant evidence suggesting that a tunneled or shallow needle angle will reduce reflux of drug or vitreous back through the sclerotomy, maximizing actual delivered dose of medication and minimizing wicking. Of note, the amount and occurrence of fluid reflux with any needle angle is inconsistent and variable between patients (17 to 51 percent, shown above). As further discussed below, if IOP modulation is deemed beneficial to a patient, we feel that more consistent IOP-modulating methods should be employed and the needle angle which appears to reduce uncontrolled fluid reflux (either drug or vitreous) should be chosen.

## Post-Injection IOP

Significant, although short-lived, elevation in intraocular pressure occurs after IVI, even with 0.05 ml of injection volume. The long-term effects of this transient elevation are not known, though there may be risk of late prolonged intraocular elevation.[26,27] In

**Table 1. Evidence-Based Suggested Techniques for IVI**

| | |
|---|---|
| Anesthesia | The evidence supports the use lidocaine-based anesthesia (topical drops, gel, pledgets or sub-conjunctival injection), but there is a lack evidence supporting one technique over another. |
| Povidine-iodine Eye Prep | The literature shows strong evidence supporting PI prep applied directly to the conjunctival surface for at least 30 seconds prior to injection. |
| Peri-injection Topical Antibiotics | There is a preponderance of evidence suggesting cessation of routine peri-injection topical antibiotics, assuming proper PI prep. |
| Needle Gauge | The data shows significant advantages with 30-gauge or smaller needles and trends towards advantages with even smaller-gauge needles. |
| Needle Angle | There is significant evidence suggesting a tunneled or shallow angle of needle penetration will reduce reflux of drug or vitreous, maximizing actual delivered dose of medication and minimizing vitreous wicking. |
| Post-Injection Intraocular Pressure | • It is not wise to withhold indicated intravitreal treatment due to a patient's existing glaucoma.<br>• Tempering of post-injection IOP spike, if desired, is best accomplished by consistent methods (AC tap, etc.) rather than relying on variable fluid reflux.<br>• There is not sufficient evidence to recommend routine post-injection evaluation. |

patients with advanced glaucoma or other optic neuropathy, special consideration may be warranted.

In a study of 106 eyes undergoing IVI with 30-ga. needles, including those with well-controlled glaucoma, 51 percent had elevation above 25 mmHg immediately after injection and only 2 percent were elevated after 30 minutes. Significantly fewer eyes in which vitreous reflux was seen had elevation above 25 mmHg immediately after injection (50 percent less, $p<0.001$).[28] Another study showed the mean post-injection IOP immediately after the injection in 45 eyes without glaucoma was 47.9 mmHg (range 23 to 82), with 71.1 percent elevated >40 mmHg and 42.2 percent elevated over 50 mmHg. After only 10 minutes post-injection, the mean difference between pre- and post-injection IOP was +4.6 mmHg (range -9 to +26, $p<0.001$). Eyes without subconjunctival reflux had a higher increase in IOP than eyes with reflux.[29]

Needle path affects post-IVI intraocular pressure. In 45 eyes, the mean IOP in eyes receiving a standard, straight scleral incision was 21.9 ±14.2 mmHg (median 22.3) versus 33.5 ±7.2 mmHg (median 34.7) in the tunneled scleral incision group ($p=0.001$).[30] However, as the occurrence of reflux is variable between patients and the reflux may consist of drug, we do not recommend using a straight needle path in an attempt to mitigate IOP spike.

Another study examined post-IVI IOP with or without application of moderate pressure to the globe with cotton swab before injection (for anesthetic purposes). The authors found this technique lowered the mean IOP change immediately after injection, with 35 percent of eyes without pre-injection pressure having post-injection IOP ≥50 mmHg compared with only 10 percent of eyes that had pre-injection pressure ($p<0.001$).[31]

At this time, long-term effects of frequent/monthly IOP spikes are not known. However, in patients in whom vision may be more sensitive to IOP insult, employing consistent techniques to mitigate IOP spikes may be advisable, such as pre-injection anterior chamber paracentesis. Relying on fluid reflux to mitigate IOP spikes is not advisable due to the variability of the reflux volume and the possibility that refluxed fluid is drug. Therefore, we suggest using a small-gauge needle and an oblique needle angle, thus minimizing reflux and assuring delivered dose and employing other methods of IOP mitigation, if desired.

An editorial by Dennis P. Han, MD, and Dale K. Heuer, MD, stated, "If intravitreal therapy is deemed appropriate, the physician should proceed with the knowledge that its risks are manageable and that visual outcome, not IOP, should be the final arbiter in the decision-making process."[32] We agree it is not wise to withhold indicated intravitreal treatment due to a patient's existing glaucoma.

Interestingly, a recent survey of retinal specialists showed that nearly 30 percent do not perform immediate post-IVI ocular assessment,[33] and we expect this number to decrease as injections become safer and our knowledge base increases. We feel there is not sufficient evidence to recommend routine post-injection evaluation.

With the advent of ocular anti-VEGF agents we have seen dramatic improvements in treatment of retinal disease. With continued study of IVIs, the goal must be to continually improve methods of drug delivery and provide even safer and more efficacious treatments with these medications. We encourage ophthalmologists to carefully consider the work done in this area and rely on evidence to guide practice, rather than habit REVIEW

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# A middle-aged man's short history of a worsening and migrating blind spot initiates an emergency room visit.

*Brynn N. Wajda, MD*

## Presentation

A 51-year-old white male presented to the Wills Eye Hospital Emergency Room with a chief complaint of a five-day history of a worsening, migrating blind spot in his right eye. It started in the upper right corner of his vision and then migrated centrally. He had similar visual disturbances in the left eye approximately one month prior, which improved with eye rubbing.

The patient denied redness, pain or diplopia. Review of systems was notable for a chronic cough and intermittent headache. He denied any fever, chills, meningitis-like symptoms or rash.

## Medical History

Past medical history was significant for arthritis, hepatitis, HIV for the past 23 years and a many pack-year history of smoking. His only chronic medication was HAART medication Complera. After the initiation of the Complera a few months prior, his CD4 had decreased to less than 160 cells/mm$^3$ but was steadily climbing. He had never been on any prophylactic antivirals or antibiotics. Family history was noncontributory.

## Examination

Vital signs were stable and within normal limits. Visual acuity was 20/200 in the right eye and 20/20 in the left eye. Color vision was full in the left eye, but the patient could not see the test plate with the right eye. Pupils were equal and reactive without an afferent pupillary defect. Extraocular motility was full, and intraocular pressure was normal in both eyes.

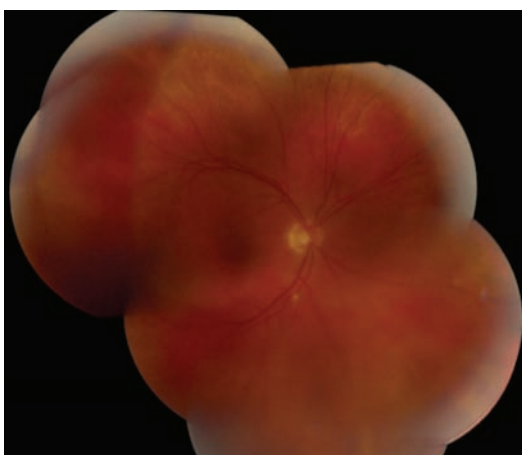

Figure 1. Fundus photo of the right eye, which showed a large, pale-yellow placoid lesion in the posterior pole and a discrete, deep, yellow-white lesion located inferior to the disc.

Visual fields were diffusely depressed and the patient could not see an Amsler grid. Both tests were normal in the left eye.

External exam was normal without any mass, ptosis or proptosis. Anterior segment exam was only remarkable for anterior chamber and vitreous cell in both eyes. Funduscopic exam was significant for a large, pale-yellow placoid lesion involving the macula and posterior pole in both eyes and a discrete, yellow-white lesion near the optic disc in the right *(See Figure 1)*. A maculopapular rash was also noted on the patient's hands *(See Figure 2)*.

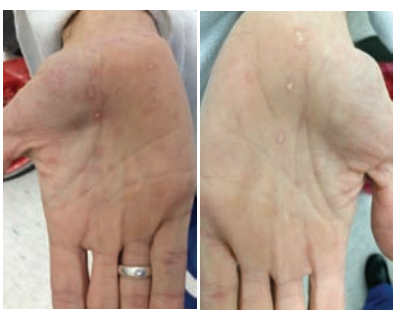

Figure 2. The patient's hands demonstrate a scattered, scaly maculopapular rash on both palms.

***What is your differential diagnosis? What further workup would you pursue? Please turn to p. 68***

## Diagnosis, Workup and Treatment

Based on the clinical history and exam, the differential diagnosis included infectious conditions such as syphilis, tuberculosis, Lyme disease, toxoplasmosis or fungal infections. The differential diagnosis also included inflammatory and neoplastic conditions such as sarcoidosis, persistent placoid maculopathy, lymphoma or metastasis.

An anterior chamber paracentesis and intravitreal injection of foscarnet, ganciclovir and clindamycin were performed in the Wills ER. The aqueous fluid was sent for toxoplasmosis, herpes zoster, herpes simplex and cytomegalovirus PCR, and all were within normal limits. Additional workup included blood cultures, ACE and lysozyme levels, a head CT looking for calcifications, and a chest X-ray, which were all unremarkable. Laboratory investigation for infectious causes included a PPD, RPR/FTA serum analyses and Lyme studies. The RPR titer came back positive.

The patient was diagnosed with acute ocular syphilis. He had a documented allergy to penicillin, and, thus, was admitted to the hospital for co-management with the Infectious Disease and Medicine Services. An inpatient lumbar puncture showed pleocytosis (>10 WBC/mm3) and an elevated protein level of 76 mg/dL. He underwent penicillin desensitization and then received IV penicillin in standard neurosyphilis therapeutic doses. He was also given topical steroid prednisolone eye drops four times a day in both eyes. Marked reduction in his uveitic cellular reaction occurred within one week of treatment initiation. His visual acuity improved to 20/30 in the right eye and was stable at 20/20 in the left.

## Discussion

Referred to as "The Great Masquerader," syphilis has many clinical stages and manifestations, which are nicely summarized and outlined in the table taken from Lutchman, Weisbrod, and Schwartz *(See Table 1)*.[1] It is most commonly spread during sexual contact, exposure to infected lesions, or via transplacental transmission.[2] While the U.S. incidence of syphilis decreased from 1990 to 2000, the rate steadily increased throughout the next decade. In 2012, the total number of syphilis cases reported to the U.S. Centers for Disease Control and Prevention was slightly over 49,900.[3] Interestingly, since 2006, younger males (aged 20 to 29 years) and men who have sex with men have accounted for approximately two-thirds of early stage syphilis cases in the United States.[3,4]

The eye can be affected in any stage of the disease, and ocular involvement has a wide range of manifestations including: papulosquamous lid lesions; loss of eyebrows; papillary conjunctivitis; sclerokeratitis; interstitial keratitis; granulomatous anterior uveitis; vitritis; vasculitis; neuroretinitis; choroiditis; papillitis; and serous retinal detachment.[4-6]

While ocular syphilis is classically described under the secondary stage of the disease, during which there is hematologic dissemination of spirochetes, the presence of ocular involvement suggests central nervous system activity. As a result, it is advised that patients with ocular involvement receive a lumbar puncture. The CDC defines "confirmed" cases of neurosyphilis by a positive CSF-VDRL in a patient with known syphilis. Likewise, the CDC deems neurosyphilis probable or "presumptive" in patients with signs and symptoms of the disease and either CSF pleocytosis or elevated CSF protein without a positive CSF-VDRL.[7] The lumbar puncture not only aids in diagnosis and quantification of disease activity but also allows for physicians to establish baseline CSF titers against which response to therapy can be measured.[4]

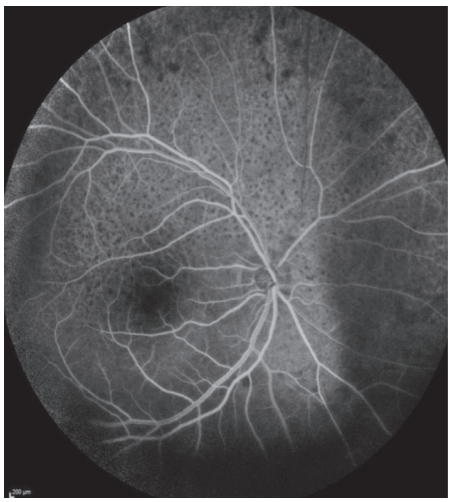

Figure 3. Fluorescein angiography of the patient's right eye demonstrating the "leopard spot" pattern seen in acute syphilitic posterior placoid chorioretinitis.

The treatment regimen for neurosyphilis is 10 to 21 days of IV penicillin (dose 12 to 24 million units).[8] While responses to therapy are often rapid in onset, many physicians feel that retreatment is warranted if CSF has failed to normalize after two years.

It is important to consider HIV screening in patients with syphilitic uveitis. A 2005 study noted that ocular symptoms in syphilis led to the discovery of HIV seropositivity in 25 to 50 percent of patients.[4] When considering the subset of ocular

## Table 1. Clinical Stages and Selected Manifestations of Syphilis

| Stage | Clinical Manifestations | Incubation Period |
|---|---|---|
| Primary | Chancre, regional lymph adenopathy | Three weeks (three to 90 days) |
| Secondary | Rash, fever, lymphadenopathy, mucous lesions, condyloma lata, alopecia<br>Hepatic (jaundice, hepatitis)<br>Renal (proteinuria)<br>Neurologic (meningitis, headaches)<br>Ocular (uveitis, retinitis) | Two to 12 weeks (two weeks to six months) |
| Latent | Asymptomatic | Early (less than one year) to late (more than one year) |
| Tertiary | | |
| • Cardiovascular syphilis | Aortic aneurysm<br>Aortic regurgitation<br>Coronary ostial stenosis | 10 to 30 years |
| • Neurosyphilis | Meningoencephalitis, locomotor ataxia, generalized paresis. Can range from asymptomatic to headache, cranial nerve palsies, vertigo, personality changes, dementia, intention tremor, ataxia, presence of Argyll Robertson pupil, areflexia, loss of proprioception | Two to 20 years |
| • Gumma | Tissue destruction of any organ<br>Manifestations depend on site involved | 15 years (one to 36 years) |

Clinical stages and manifestations of syphilis. Note that ocular manifestations are listed under the secondary stage, however many ophthalmologists feel that ocular involvement is synonymous with neurosyphilis. *(Adapted from Lutchman C, et al.[1])*

syphilis cases in patients co-infected with HIV, some studies have shown that HIV patients are subject to higher rates of treatment failure and relapse despite appropriate therapy.[9] In addition, some sources advise a neurosyphilis regimen of systemic penicillin in all HIV-positive patients with syphilitic uveitis since the progression to neurosyphilis is high in this subgroup of patients.[6,9]

Interestingly, this particular case report demonstrated an entity known as acute syphilitic posterior placoid chorioretinitis (ASPPC), one of the more unique manifestations of ocular syphilis originally described by J. Donald Gass, MD, and colleagues in 1990.[8,10] ASPPC is characterized by large solitary placoid lesions in the area of the macula that are pale yellow. The lesions may have faded centers and coarsely stippled spots of hyperpigmentation.[4,8,9,12] Fluorescein angiography of ASPPC shows a distinct pattern of irregular early hypofluorescence with progressive hyperfluorescence overlying persistently less bright foci referred to as "leopard spots"[13] *(See Figure 3)*. Optical coherence tomography can also be used to demonstrate changes that occur in ASPPC, including disruption of the outer retinal layers (especially within the region of the photoreceptors), loss of the external limiting membrane, hyperreflective and nodular thickening of the retinal pigment epithelium, accumulation of subretinal fluid, loss of normal choroidal vascular detail and diffuse choroidal infiltration[8,14,15] *(See Figure 4)*.

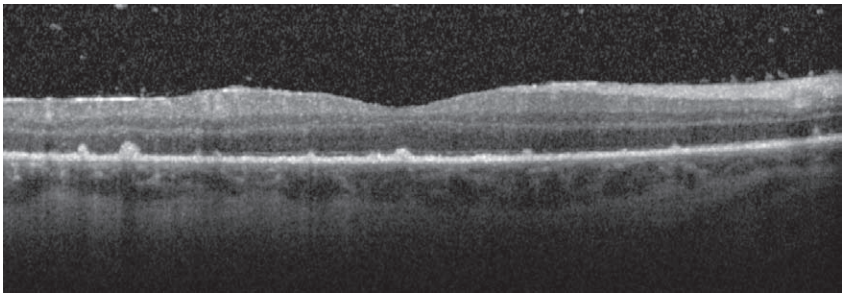

Figure 4. Optical coherence tomography of the patient's right macula demonstrates the characteristic outer retinal abnormalities of ASPPC. Note the characteristic hyperreflective, nodular thickening of the RPE and disrupted photoreceptor layer.

In summary, ASPPC is a distinctive ocular manifestation of syphilis with unique imaging findings. Because risk factors for contracting HIV and syphilis are similar and since co-infection is relatively common, patients diagnosed with syphilis should also be tested for HIV. Penicillin is the treatment of choice for patients with either neurosyphilis or co-infection with HIV. Fortunately, early recognition and appropriate treatment often result in successful

control of the disease, but patients with HIV and syphilis should be closely monitored for treatment failure or recurrence. REVIEW

*The author would like to thank Sonia Mehta, MD, assistant professor, Vitreoretinal Diseases and Surgery, Wills Eye Hospital, for her time and assistance in preparing this case report.*

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*(continued from page 75)*

mediating adjuvant effects for vaccines, and as therapeutic targets in their own right. For example, the IL1-receptor antagonist Anakinra showed efficacy against a rare disease linked to NLRP3 mutation, Muckle-Wells syndrome. Trials of this agent for several other conditions known to involve NLRP3 dysfunction (familial cold urticaria and gout) also demonstrated significant efficacy.[32] This is an example of how elucidation of underlying mechanisms can suggest new therapies whose utility would not otherwise be apparent.

Targeting PRR signaling has great potential in a number of ocular diseases, including conditions involving ocular surface inflammation,[3] uveitis[14] and retinal degenerative diseases.[16] While we are still building on the foundation established long ago by Celsus, the expanded list of potential therapeutic targets generated by recent discoveries in immunity research may provide the tools to answer these questions. With these tools, there is substantial reason for optimism that future novel therapies will act to re-establish the homeostatic balance of our innate immune system. REVIEW

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# AREDS: Ten-year AMD Follow-up

**In order to** provide long-term follow-up on the natural history of age-related macular degeneration and associated risk factors, the Age-Related Eye Disease Study Group tracked surviving AREDS participants for an additional five years after the randomized clinical trial of antioxidant vitamins and minerals was completed. Their results indicate a relentless loss of vision in persons who develop advanced AMD.

Following the completion of AREDS, 3,549 of the surviving 4,203 participants were followed for an additional five years, with researchers focusing on the development of varying stages of AMD and changes in visual acuity. The rates of progression to large drusen and advanced AMD (neovascular AMD or central geographic atrophy) were evaluated using annual fundus photographs assessed centrally. Best-corrected visual acuity was measured at annual study visits.

The risk of progression to advanced AMD increased with age ($p$=0.01) and severity of drusen. Women ($p$=0.005) and current smokers ($p$<0.001) were at increased risk of neovascular AMD. In the oldest participants with the most severe AMD at baseline, the risks of developing neovascular AMD and central geographic atrophy by 10 years were 48.1 percent and 26 percent, respectively. Similarly, rates of progression to large drusen increased with increasing severity of drusen at baseline, with 70.9 percent of participants with bilateral medium drusen progressing to large drusen and 13.8 percent to advanced AMD in 10 years. Median visual acuity at 10 years in eyes that had large drusen at baseline but never developed advanced AMD was 20/25; eyes that developed advanced AMD had a median visual acuity of 20/200.

*JAMA Ophthalmol 2014;132: 272-277.*

Chew E, Clemons T, Agron E, Sperduto R, et al.

## Axial Length Not Predictor of Elevated IOP After IVI

**Researchers have determined** that there is no association of axial length or postinjection reflux with transient or sustained intraocular pressure elevation in patients with neovascular age-related macular degeneration who are receiving anti-VEGF injections.

One hundred and forty-seven eyes from 74 consecutive patients with neovascular AMD who presented to a single physician over a two-month period had their axial lengths measured by IOLMaster. Of these, 21 patients had preinjection and immediate postinjection IOP measured and their immediate reflux assessed.

In a previous study, 9.5 percent of eyes had been identified with sustained IOP elevation. Axial length did not significantly differ between eyes that had and had not experienced sustained IOP elevation (axial length, 23.96 ±0.66 mm; n=14 and axial length 23.44 ±1.24 mm; n=133; $p$=0.12). By linear regression analysis, the relationship between experiencing sustained IOP elevation and axial length was not statistically significant (R2=0.0165; $p$=0.121). The relationship between axial length and immediate postinjection IOP elevation was also not statistically significant (R2=0.0001; $p$=0.97). Immediate postinjection IOP increase did differ between eyes without reflux (30.2 ±9.3 mmHg; n=12) and those with reflux (1.1 ±7.2; n=9; $p$<0.001).

*Retina 2014;34:519-524.*

Hoang Q, Jung J, Mrejen S, Freund K.

## Relationship Between Pathologic Myopia and Dry Eye Examined

**A Turkish study** investigating the relationship between pathologic myopia and dry-eye syndrome found that patients with pathological myopia have lower tear breakup time and higher ocular surface disease index scores compared to healthy individuals.

Forty-five patients with a spherical equivalence greater than -6 D and an axial length >26.5 mm were assigned to the pathological myopia group (Group 1). Forty-four healthy individuals were selected from subjects with emmetropia whose spherical equivalence values ranged from -1 to +1 D (Group 2). OSDI scores of all the patients were

determined, with all participants undergoing the following: Schirmer 1 test without anesthesia; corneal staining; TBUT; Schirmer test with anesthesia; and axial length measurement.

The mean ages of Group 1 and Group 2 patients were 40.2 ±12.3 and 38.8 ±9.3 years. The mean values of spherical equivalence, keratometry and axial length were -9.6 ±3.8 D, 43.9 ±1.1 D and 27.4 ±0.6 mm in Group 1 and -0.1 ±0.5 D, 42.3 ±1.4 D and 23 ±0.2 mm in Group 2. The mean values of the Schirmer 1 test without and with anesthesia were 14.4 ±6.1 and 9.5 ±4.5 mm in Group 1 and 16.7 ±6.2 and 11.4 ±6 mm in Group 2. The mean TBUT in Group 1 was 7.2 ±3.4 seconds, whereas the mean TBUT in Group 2 was 13.6 ±3.7 seconds. There was a significant difference between the groups in spherical equivalence, keratometry, axial length, TBUT and OSDI scores ($p<0.001$).

*Cornea 2014;33:169-171.*
Ilhan N, Ilhan O, Tuzcu E, Daglioglu M, et al.

## Goldman Applanation Tonometry Underestimates POAG IOP

**Ohio researchers have** determined that the delta differences between Goldman applanation tonometry and newer measures of intraocular pressure are greater in magnitude in patients with primary open-angle glaucoma than in normal control groups, regardless of central corneal thickness. This is likely due to differences in corneal biomechanical properties, with POAG corneas being softer than healthy corneas, causing greater underestimation of IOP by GAT in POAG than in controls.

Thirteen eyes of 13 POAG patients and 15 eyes of 15 control patients underwent corneal topography; IOP measurement using GAT, dynamic contour tonometry (DCT) and corneal compensated IOP (IOPcc) using the Reichert ocular response analyzer (ORA); corneal hysteresis; and CCT. Results from POAG and control eyes were then compared using *t* tests.

Ages in the POAG group were slightly greater than those of the control group. CCT was also closely matched between groups. However, significant differences were found between GAT vs. DCT and GAT vs. IOPcc within both groups: Mean GAT IOP was not significantly different between POAG and controls, whereas mean DCT IOP did show a significant difference between groups, as did mean IOPcc. The delta differences, GATΔDCT and GATΔIOPcc, were of greater magnitude in POAG subjects when compared with controls. Corneal hysteresis was also significantly lower in POAG subjects.

*J Glaucoma 2014;23:69-74.*
Costin B, Fleming G, Weber P, Mahmoud A, et al.

## Glaucoma Screening Using Relative Afferent Pupillary Defect

**Stanford doctors assessed** the relative afferent pupillary defect observed during the swinging flashlight test as a quick, inexpensive, easily performed screening test for glaucomatous optic neuropathy, finding that RAPD screening with neutral density filters was moderately sensitive and strongly specific for glaucoma. Sensitivity, specificity and predictive value improved when patients who had previously undergone cataract surgery were removed from the analysis.

The doctors recruited 107 subjects from a mixed population of glaucomatous and nonglaucomatous patients. All subjects underwent a swinging flashlight test with, when necessary, the aid of a neutral density filter, to determine whether or not RAPD was present. A determination of glaucoma diagnosis, as well as classification of disease stage, was subsequently assessed based upon review of history and ophthalmic examination. The non-ophthalmologist performing the swinging flashlight test was masked to disease presence, and the clinical information regarding glaucomatous disease was ascertained without knowledge of study RAPD status.

Statistical analysis demonstrated an odds ratio of 9.71 (95 percent CI, 3.72 to 25.4) for glaucomatous disease if RAPD was present, with a sensitivity of 66.7 percent and a specificity of 82.9 percent. Patients who had not previously undergone cataract surgery revealed an odds ratio of 17.05 percent (95 percent CI, 4.73 to 61.44) for glaucomatous disease if a RAPD was present, with a sensitivity of 68.8 percent and a specificity of 88.6 percent.

*J Glaucoma 2014;23:169-173.*
Charalel R, Lin S, Singh K.

## Long-term Follow-up After LVC in Physicians

**A cohort study** sent to physicians who had refractive surgery at the Cole Eye Institute between 2000 and 2012 indicates that, despite high visual demands, physicians who had laser vision correction had a high percentage of good visual outcomes, satisfaction and quality of life improvements.

A 12-question survey targeted toward physicians and their experiences with refractive surgery was sent to 226 physicians (439 eyes). Of those, 132 (58 percent) responded, reporting an overall satisfaction rate of 95.3 percent. Respondents included surgeons (28 percent), physicians who perform procedures but not surgery (43.2 percent) and physicians who do not perform procedures or surgeries (28.8 percent). Of the physicians, 84.8 percent reported an improvement in the quality of vision compared with corrected preoperative vision, 39 percent reported that their ability to perform procedures accurately had improved and 1.6 percent said they believed their ability to perform procedures was less. The majority of physicians (96 percent) said that they would have the procedure again.

*J Cataract Refract Surg 2014; 40:395-402.*
Pasquali T, Smadja D, Savetsky M, Reggiani G, et al.

# FDA Clearance for B+L Stellaris PC System

**Bausch + Lomb's** Stellaris PC Vision Enhancement System received 510(k) clearance from the Food and Drug Administration for the integrated 532-nm laser and software. With this new capability, the Stellaris PC now provides one of the most complete ophthalmic surgical systems for posterior segment, anterior segment and combined procedures, the company says.

With this advance, the Stellaris PC now offers the following advantages to surgeon's facilities:

• A fully integrated 532-nm green laser, which is upgradable for existing Stellaris PC Vision Enhancement Systems, and connects within the sterile field.

• A first-of-its-kind wireless, dual linear foot pedal that features integrated laser control and improved design offering greater versatility and flexibility for procedural needs. The pedal and ergonomic foot rest improve comfort for longer procedures by reducing pitch. An optional LIO foot pedal, cable and headset are also available.

• A full portfolio of multifunction laser fibers that meet a wide range of procedural needs, including straight, curved, illuminated and aspirating probes with a soft tip for added security when working close to the retina.

• A redesigned interface and laser control software that offer improved clarity, enhanced contrast and ease of use for both surgeons and staff.

For information, visit bausch.com.

## Ocusoft Continues to Add to New Cosmetic Line

**Ocusoft Inc. has** announced its continued expansion into the skin-care field with the launch of Zoria Recovery Bruise and Scar Cream, specially formulated to promote healing and minimize the unsightly post-operative effects of eyelid/facial surgical procedures or bruising from injections. Thepatent-pending formula contains a unique blend of ingredients that support the skin's natural healing process, including arnica to reduce bruising, vitamin K (phytonadione) to minimize skin discoloration, escin (from horse chestnut) to improve circulation and moisturizers to hydrate delicate, dry skin. Simply apply on affected areas prior to and immediately after the procedure or injury and reapply as needed.

Zoria Recovery Bruise and Scar Cream will only be promoted through physician specialties at a discounted price to encourage direct dispensing to patients.

Orders may be placed through Ocusoft's customer service number below or from local Ocusoft representatives. The Zoria Cosmetics line includes Zoria Boost Lash Intensifying Serum and Zoria Mascara for sensitive eyes.

For information, visit zoriacosmetics.com or call 1 (800) 233-5469.

## Nidek Microscope Granted FDA Clearance

**Nidek received 510(k)** clearance for its CEM-530 Specular Microscope. Nidek says the instrument, with auto-tracking capability, acquires images of the corneal endothelium and provides analysis quickly and easily.

Features include paracentral specular microscopy as well as peripheral



*This article has no commercial sponsorship.*

images; two-second auto analysis; automatic indication of the optimal image; 3-D auto tracking; auto shot; a tiltable touch screen; and a built-in printer.

The paracentral images are captured at eight points at a five-degree visual angle within a 0.25 mm x 0.55 mm field and enable enhanced assessment surrounding the central image.

Sixteen images are captured and automatically sorted based on quality.

Once the best image is selected, complete analysis is automatically performed in two seconds. The analysis screen allows visualization of the endothelial cells in four modes: trace; photo; area; and apex. This enables the clinician to verify analysis values with the corresponding cell images. An LED light source is used for illumination, which reduces power consumption and lasts longer.

The CEM-350 can seamlessly integrate with most EMR systems without the need for an additional computer or software.

For information, visit usa.nidek.com.

## Gulden Website Offers Instructional Videos

**Gulden Ophthalmics has** introduced a new series of instructive videos that are easily accessed on the Gulden website. The videos cover a range of solutions to many ophthalmic diagnostics testing, surgical and challenging situations in eye care, using cost-saving and time-saving tools and techniques.

Topics include:

- Saving surgical costs and time with sterilized, surgery-ready spheres and conformers.
- Practicing ophthalmic procedures and demonstrating products with Practice Eyes.
- Using eye models to demonstrate and instruct patients and staff.
- Testing color deficiencies using D-15 testing tools.
- Practicing indirect ophthalmoscopy and photocoagulation with the Reti Eye tool.
- Elevating and treating patients' eyelids with an eyelid plate expression tool.
- Cleaning tonometer tips effectively and easily.
- Helping patients treat dry eye and lagophthalmos without messy tape glue.
- A simple and inexpensive way to measure PD with a new digital PD Ruler.
- Overcoming the disadvantages of previous near cards that are prone to wear and tear, aging and yellowing and scratches, and require a lamp or illumination source with an Illuminated Near Card.

For information, call (215) 884-8105 or visit gulden ophthalmics.com. REVIEW

# REVIEW Advertising Index

## Equipment and Supplies



## EquipmentandSupplies

## Professional Opportunities

### Ophthalmology Opportunity

**Geisinger Health System (GHS) is seeking a BC/BE Cornea/Refractive Surgery Ophthalmologist for Geisinger–Scenery Park, State College, Pa.**

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- Opportunity to start up a new practice and develop new programs
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**Geisinger Health System** serves more than 3 million people in central and northeastern Pennsylvania and is nationally recognized for innovative practices and quality care. A mature electronic health record connects a comprehensive network of 5 hospitals, 43 community practice sites and more than 900 Geisinger primary and specialty care physicians.

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**For more information, please visit geisinger.org/careers or contact: Autum Ellis, Department of Professional Staffing, at 1-800-845-7112 or amellis1@geisinger.edu.**

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# LUMIGAN® 0.01% AND 0.03%
## (bimatoprost ophthalmic solution)

**Brief Summary—Please see the LUMIGAN® 0.01% and 0.03% package insert for full Prescribing Information.**

### INDICATIONS AND USAGE

**LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

### CONTRAINDICATIONS

None

### WARNINGS AND PRECAUTIONS

**Pigmentation:** Bimatoprost 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 bimatoprost 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 bimatoprost, 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 **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

**Eyelash Changes: LUMIGAN®** 0.01% and 0.03% 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: LUMIGAN®** 0.01% and 0.03% 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 bimatoprost ophthalmic solution. **LUMIGAN®** 0.01% and 0.03% 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: LUMIGAN®** 0.01% and 0.03% 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 **LUMIGAN®** 0.01% and 0.03% 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.

In clinical studies with bimatoprost ophthalmic solutions (0.01% or 0.03%) the most common adverse reaction was conjunctival hyperemia (range 25%–45%). Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia with 0.01% or 0.03% bimatoprost ophthalmic solutions. Other common reactions (>10%) included growth of eyelashes, and ocular pruritus.

Additional ocular adverse reactions (reported in 1 to 10% of patients) with bimatoprost ophthalmic solutions included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, periorbital erythema, ocular irritation, eyelash darkening, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema, conjunctival hemorrhage, and abnormal hair growth. Intraocular inflammation, reported as iritis, was reported in less than 1% of patients.

Systemic adverse reactions reported in approximately 10% of patients with bimatoprost ophthalmic solutions were infections (primarily colds and upper respiratory tract infections). Other systemic adverse reactions (reported in 1 to 5% of patients) included headaches, abnormal liver function tests, and asthenia.

**Postmarketing Experience:** The following reactions have been identified during postmarketing use of **LUMIGAN®** 0.01% and 0.03% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **LUMIGAN®**, or a combination of these factors, include: dizziness, eyelid edema, hypertension, nausea, and periorbital and lid changes associated with a deepening of the eyelid sulcus.

### USE IN SPECIFIC POPULATIONS

**Pregnancy:** Pregnancy Category C

Teratogenic effects: In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the maximum intended human exposure based on blood AUC levels.

At doses at least 41 times the maximum intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) administration in pregnant women. Because animal reproductive studies are not always predictive of human response **LUMIGAN®** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether **LUMIGAN®** 0.01% and 0.03% is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN®** 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 Impairment:** In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

### OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m2 is at least 70 times higher than the accidental dose of one bottle of **LUMIGAN®** 0.03% for a 10 kg child.

### NONCLINICAL TOXICOLOGY

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels).

### 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 **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution).

**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 **LUMIGAN®** 0.01% and 0.03%. 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 **LUMIGAN®** 0.01% and 0.03%.

**Use with Contact Lenses:** Patients should be advised that **LUMIGAN®** 0.01% and 0.03% contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN®** and may be reinserted 15 minutes following its administration.

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


APC70EN12 based on 71807US13.

**Rx only**

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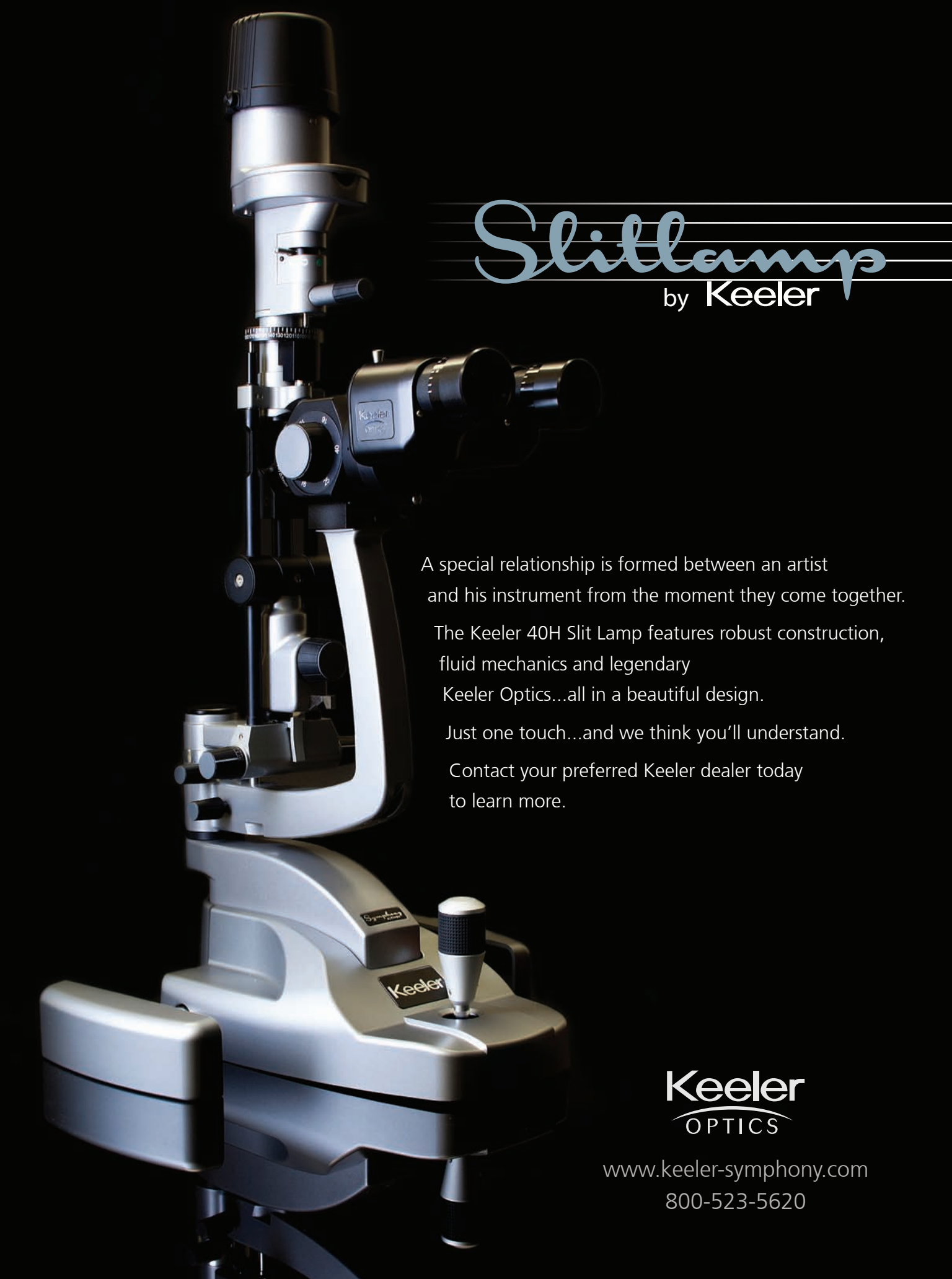
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# Monotherapy Maintained.

Proven IOP reduction[1]

•

Established tolerability with low discontinuation rate[2]

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Comprehensive patient support

**Indication:** LUMIGAN® (bimatoprost ophthalmic solution) 0.01% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

**Important Safety Information**

**Warnings and Precautions:** LUMIGAN® 0.01% causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® 0.01% is administered. Iris color change may not be noticeable for several months to years. After discontinuation of bimatoprost, iris pigmentation is likely to be permanent, while eyelid and eyelash changes have been reported to be reversible in some patients. Patients should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

LUMIGAN® 0.01% should be used with caution in patients with active intraocular inflammation (eg, uveitis) because the inflammation may be exacerbated. Macular edema, including cystoid macular edema, has been reported with LUMIGAN® 0.01%. LUMIGAN® 0.01% 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. LUMIGAN® 0.01% has not been studied to treat types of glaucoma other than open-angle glaucoma. Remove contact lenses prior to instillation of LUMIGAN® 0.01% and reinsert after 15 minutes.

**Adverse Reactions:** The most common (25%-45%) adverse event with LUMIGAN® 0.01% was conjunctival hyperemia. Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia. Other common events (> 10%) included growth of eyelashes and ocular pruritus.

**Please see Brief Summary of the full Prescribing Information on adjacent page.**

**1.** LUMIGAN® Prescribing Information. **2.** Katz LJ, Cohen JS, Batoosingh AL, Felix C, Shu V, Schiffman RM. Twelve-month, randomized, controlled trial of bimatoprost 0.01%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. *Am J Ophthalmol*. 2010;149(4):661-671. **3.** Managed Markets Insight & Technology, LLC, database, as of November 2013.


LUMIGAN® 0.01%
(bimatoprost ophthalmic solution) 0.01%

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