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REVIEW[®] of Ophthalmology

March 2019

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ANNUAL CATARACT SURGERY ISSUE



Refining Postop Infection Prevention

*Combining drops in one bottle and
the use of postop injections are just
part of the discussion. P. 26*

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Indications and Usage

BromSite® (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

Recommended Dosing

One drop of BromSite® should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite®, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite®.

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

- **Increased Bleeding Time of Ocular Tissue:** With some NSAIDs, including BromSite®, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that BromSite® be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- **Keratitis and 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. Patients with evidence

The **FIRST** and **ONLY** NSAID indicated to prevent ocular pain in cataract surgery patients¹

A DROP OF PREVENTION

FOR YOUR CATARACT SURGERY PATIENTS

Defend against ocular pain and combat postoperative inflammation with the penetrating power of BromSite® formulated with DuraSite®¹

- DuraSite® increases ocular surface retention time, resulting in increased bromfenac absorption²⁻⁵
- Provides 24-hour coverage with BID dosing¹
- Available in 5 mL bottle

Visit bromsite.com to find out more.

BromSITE®
(bromfenac ophthalmic solution) 0.075%

Formulated with **DURASITE® DELIVERY SYSTEM**

of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite®, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

- **Contact Lens Wear:** BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.

- **Adverse Reactions:** The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

Please see brief summary of Full Prescribing Information on the adjacent page.

NSAID=nonsteroidal anti-inflammatory drug.

References: **1.** BromSite® [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. **2.** Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 5-9, 2013; Seattle, Washington. **3.** ClinicalTrials.gov. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. <https://clinicaltrials.gov/ct2/show/results/NCT01387464?sect=X70156&term=insite+vision&rank=1>. Accessed March 2, 2017. **4.** Si EC, Bowman LM, Hosseini K. Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *J Ocul Pharmacol Ther.* 2011;27(1):61-66. **5.** Bowman LM, Si E, Pang J, et al. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133-139.

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BromSite® (bromfenac ophthalmic solution) 0.075%

Brief Summary

INDICATIONS AND USAGE

BromSite® (bromfenac ophthalmic solution) 0.075% is indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Slow or Delayed Healing

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Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time of Ocular Tissue

With some NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that BromSite® be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear

BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.

ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the Brief Summary:

- Slow or Delayed Healing
- Potential for Cross-Sensitivity
- Increased Bleeding Time of Ocular Tissue
- Keratitis and Corneal Reactions
- Contact Lens Wear

Clinical Trial Experience

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

The most commonly reported adverse reactions in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

Clinical Considerations

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

Data

Animal Data

Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m² basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m² basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m² basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m² basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (195 and 65 times a unilateral daily dose, respectively, on a mg/m² basis).

Rx Only

Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512

Lawmakers in Washington Push for Drug-price Reform

The Prescription Drug Price Relief Act of 2019 was recently introduced to lawmakers, aiming to allow generic drug companies to enter into competition with patent-holding drug manufacturers after a petitioned drug's price is deemed excessive. With hearings on drug prices under way, all constituents are being heard, from doctors and patients to members of the pharmaceutical industry.

The bill would allow the Secretary of Health and Human Services to deem a petitioned drug excessively priced if its U.S. price is higher than that of its median price in the United Kingdom, Canada, Germany, France and Japan. However, if that stipulation is not met, the Secretary can still judge the price excessively high by taking into account factors such as the following:

- size of the affected patient population;
- value of the drug to patients;
- costs associated with development of the drug;
- whether the drug produces a significant improvement in health outcomes; and
- cumulative global revenues generated by the drug.

Once confirmed to be excessively high, the pharmaceutical company would have to lower the drug's price. Otherwise, the government would allow a generic manufacturer to enter production by waiving or voiding any

government-granted exclusivities. However, the generic manufacturer would pay a reasonable royalty to the company that holds the patent. This could be a percentage of sales or



an amount that's determined by the Secretary based on factors similar to those already listed.

According to Michael Repka, MD, the AAO Medical Director for Government Affairs, this kind of sweeping legislation doesn't seem likely. While industry and doctors can somewhat agree that drug prices are too high, both parties highlight issues associated with the bill. "Setting our prices based upon what [drugs] cost in Europe or other parts of the world is an idea that doesn't seem politically palatable to anyone," Dr. Repka says. However, he acknowledges that relief is necessary. "As a physician-advocate for our patients, drug prices are high and many consumers can't afford them."

The Pharmaceutical Research and Manufacturers of America sees

the bill as flawed. The organization says that patients won't benefit from the legislation, and that it may affect America's position as a pharmaceutical leader. "Circumventing patent and other intellectual property rights on medical innovation, and allowing foreign governments to set U.S. prices, would be disastrous for patients," PhRMA said in a prepared statement. The organization is concerned that reduced investment in research and development may slow progress in creating tomorrow's cures, and could result in Americans having access to fewer new medicines. PhRMA adds that there's no evidence the bill would benefit

patient access or affordability of the medicine. "Patients in countries whose governments set prices wait years for new medicines and have far fewer treatment options," the organization's statement added.

PhRMA also feels the bill could harm America's competitive pharmaceutical status on the world stage. "No countries that are leaders in innovation have taken such drastic measures," it remarked. "These policies would threaten America's ability to remain competitive and instead, replicate flawed policies of countries where patient needs are brushed aside."

Dr. Repka details several of the factors that will go into any legislation affecting drug prices. First, he notes that different nations bear different costs associated with pharma-

Editor in Chief

Walter C. Bethke
(610) 492-1024
wbethke@jobson.com

Senior Editor

Christopher Kent
(814) 861-5559
ckent@jobson.com

Associate Editor

Alexandra Skinner
(610) 492-1025
askinner@jobson.com

Chief Medical Editor

Mark H. Blecher, MD

Art Director

Jared Araujo
(610) 492-1032
jaraujo@jobson.com

Senior Graphic Designer

Matt Egger
(610) 492-1029
megger@jobson.com

Graphic Designer

Ashley Schmouder
(610) 492-101048
aschmouder@jobson.com

International coordinator, Japan

Mitz Kaminuma
Reviewophthalgo@aol.com

Business Offices

11 Campus Boulevard, Suite 100
Newtown Square, PA 19073
(610) 492-1000
Fax: (610) 492-1039

Subscription inquiries:

United States — (877) 529-1746
Outside U.S. — (845) 267-3065

E-mail:

revophthalmology@cambeywest.com

Website: www.reviewofophthalmology.com



ceuticals. “Industry has research and development but they also have marketing and advertising and, in some countries, these costs may not exist at the same levels,” he says. “Choosing average overseas pricing as a vehicle to price medications in our own economy doesn’t seem consistent with a market-based economy.”

Feasibility of producing additional generic drugs is another potential issue. “Part of this bill seeks to move branded drugs to the generic space,” Dr. Repka says, “but we may not have the generic capacity to produce [them]. We have problems of shortages in the generic space, and ramping up production for a limited market can be very expensive.” He says that this could pose a risk to patients if medications aren’t sufficiently profitable. “We have to have a price that’s high enough that industry is willing to bring it to market, but also a price that the consumer can afford,” he adds.

When asked if patients who take medication for chronic conditions (i.e., patients with dry eye or glaucoma) may opt for medical treatment instead of surgical intervention if drug prices were to come down, Dr. Repka says it’s possible. “In general, pharmacotherapy is used before surgical therapy,” he notes, “but lower pricing could cause patients to be willing to continue long-term pharmacotherapy or a multidrug plan.”

On the question of whether drug prices are fair or if there’s an alternative solution, PhRMA notes that large rebates are often required for a medicine to be covered. “Forty percent of the list price of medicines is

given as rebates or discounts to insurance companies, the government, Pharmacy Benefit Managers and other entities in the supply chain,” the organization says. PhRMA notes that these savings are often not shared with patients, whose out-of-pocket costs soar as rebates and discounts grow every year. “We need to ensure that more of the negotiated rebates and discounts are resulting in lower costs for patients at the pharmacy,” the industry group says. Dr. Repka acknowledges that rebates could be a subject to explore, noting, “They’re generally not transparent to the consumer.”

In terms of alternative solutions, Dr. Repka says improved transparency in drug-pricing reform is needed to protect patients. “Any drug-price legislation in the U.S. has to help the consumer understand where their payments go so that they buy the right plan,” he says. “Weakening patient protection or shortening the period it takes for generic companies to gain access to producing these medications is the only thing I could see happening. This bill does that, but with a very sharp knife. Changing the patent process or changing exclusivity terms seem to be very significant changes in how we go about protecting intellectual property. There would have to be enough protections for the manufacturer’s rights.” Dr. Repka concludes, “I think that everyone recognizes that prices are too high. We need [both] pricing and availability—so it’s a very difficult needle to thread.”

At press time, hearings had just
(Continued on page 16)

Clarification

In the January 2019 Cornea/Anterior Segment column about pterygium repair using amniotic membrane, an oversight led to the author’s financial disclosure being omitted from the article. To clarify, the author, Thomas John, MD, has a financial interest in Bio-Tissue and Tissue Tech. *Review* regrets the omission.

Experiencing zero-energy lens fragmentation.

ZEISS miLOOP



Keep the zonules intact

The new miLOOP® from ZEISS is a micro-interventional device, developed to deliver zero-energy¹ lens fragmentation and achieve full-thickness lens fragmentation. The dissecting action of ZEISS miLOOP is designed to reduce force on the delicate capsular bag and zonules.

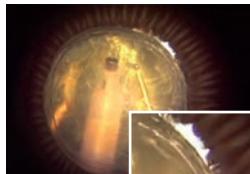


¹ without the need to apply energy from phacoemulsification

Lens cracking



Lens cracking

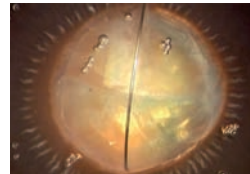


Broken zonules

Lens fragmentation with ZEISS miLOOP



Lens fragmentation



Preserved zonules

More product information:
www.zeiss.com/miloop



CONTRIBUTORS

CHIEF MEDICAL EDITOR

Mark H. Blecher, MD

CONTACT LENSES

Penny Asbell, MD

CORNEA / ANTERIOR SEGMENT

Thomas John, MD

GLAUCOMA MANAGEMENT

Peter Netland, MD, PHD
Kuldev Singh, MD

MASTERS OF SURGERY

Taliva D. Martin, MD
Sara J. Haug, MD, PhD

MEDICARE Q & A

Paul M. Larson, MBA

PEDIATRIC PATIENT

Wendy Huang, MD

PLASTIC POINTERS

Ann P. Murchison, MD, MPH

REFRACTIVE SURGERY

Arturo S. Chayet, MD

RETINAL INSIDER

Carl Regillo, MD, FACS
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STEPHEN PASCUCCI, MD, BONITA SPRINGS, FLA.

PAUL PENDER, MD, BEDFORD, N.H.

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ROBERT G. WILEY, MD, CLEVELAND

FRANK WEINSTOCK, MD, CANTON, OHIO

BUSINESS OFFICES

11 CAMPUS BOULEVARD, SUITE 100
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF

PUBLISHER

JAMES HENNE

(610) 492-1017 JHENNE@JOBSON.COM

REGIONAL SALES MANAGER

MICHELE BARRETT

(610) 492-1014 MBARRETT@JOBSON.COM

REGIONAL SALES MANAGER

MICHAEL HOSTER

(610) 492-1028 MHOSTER@JOBSON.COM

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VICE PRESIDENT OF OPERATIONS

CASEY FOSTER

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CIRCULATION

PO BOX 71, CONGERS, NY 10920-0071
(877) 529-1746

OUTSIDE USA: (845) 267-3065

SENIOR CIRCULATION MANAGER

HAMILTON MAHER

(212) 219-7870 hmaher@jhihealth.com

CEO, INFORMATION GROUP SERVICES

MARC FERRARA

SENIOR VICE PRESIDENT, OPERATIONS

JEFF LEVITZ

VICE PRESIDENT, HUMAN RESOURCES

TAMMY GARCIA

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION

MONICA TETTAMANZI

CORPORATE PRODUCTION DIRECTOR

JOHN ANTHONY CAGGIANO

VICE PRESIDENT, CIRCULATION

EVELDA BAREA



440 Ninth Avenue, 14th Floor
New York, N.Y. 10001

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DELIVER THE PROLENSA[®] EFFECT¹⁻³

Achieve **POWERFUL CORNEAL PENETRATION** with the
#1 prescribed branded ocular NSAID, PROLENSA[®].

The only branded formulation of bromfenac approved for once-daily use.¹

*IQVIA NPA Monthly, November 2018

INDICATIONS AND USAGE

PROLENSA[®] (bromfenac ophthalmic solution) 0.07% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA[®]

- PROLENSA[®] contains sodium sulfite, a sulfite that may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.
- All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Use with caution in patients who have previously exhibited sensitivities to these drugs.
- There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Use with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.
- PROLENSA[®] should not be instilled while wearing contact lenses. The preservative in PROLENSA[®], benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA[®].
- The most commonly reported adverse reactions in 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

Please see brief summary of full Prescribing Information for PROLENSA[®] on adjacent page.

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

BAUSCH + LOMB

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PROLENSA[®]
(bromfenac ophthalmic
solution) 0.07%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe Prolensa safely and effectively. See full prescribing information for Prolensa.

PROLENSA (bromfenac ophthalmic solution) 0.07%

Rx only

Initial Rx Approval: 1997

INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is indicated for the treatment of postoperative inflammation and reduction of pain in patients who have undergone cataract surgery.

DOSAGE AND ADMINISTRATION

Recommended Dosing

One drop of PROLENSA ophthalmic solution should be applied to the affected eye once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

Use with Other Topical Ophthalmic Medications

PROLENSA ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time

With some NSAIDs, including bromfenac, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that PROLENSA ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to

rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Treatment of rats at oral doses up to 0.9 mg/kg/day (systemic exposure 90 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and rabbits at oral doses up to 7.5 mg/kg/day (150 times the predicted human systemic exposure) produced no treatment-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3 mg/kg/day (30 times the predicted human exposure), and caused dystocia, increased neonatal mortality, and reduced postnatal growth at 0.9 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (systemic exposure 30 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and 5 mg/kg/day (340 times the predicted human systemic exposure), respectively, revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests. Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (systemic exposure 90 and 30 times the predicted human exposure, respectively).

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

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

Sterility of Dropper Tip

Advise patients to replace bottle cap after using and to not touch dropper tip to any surface, as this may contaminate the contents. Advise patients that a single bottle of PROLENSA be used to treat only one eye.

Concomitant Use of Contact Lenses

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

Concomitant Topical Ocular Therapy

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

Rx Only

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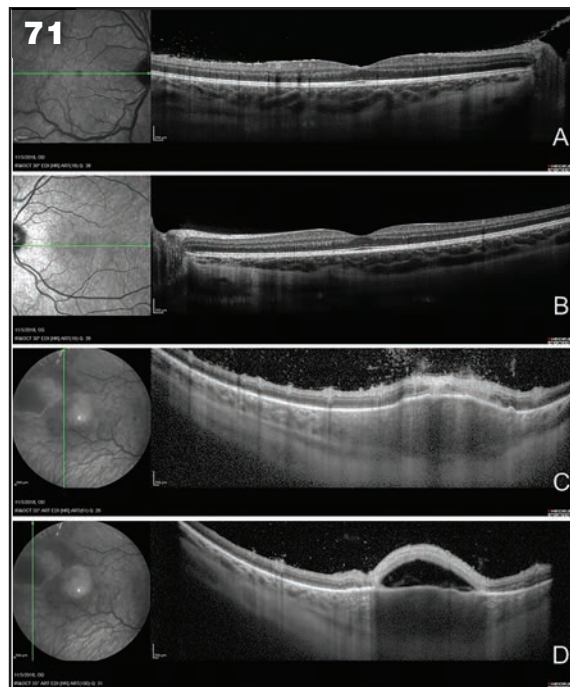
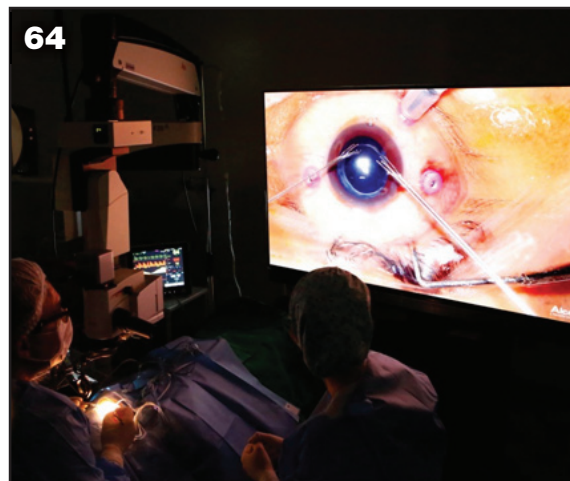
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INDICATIONS AND IMPORTANT SAFETY INFORMATION

Rx Only

ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information. **INDICATIONS:** The TECNIS® 1-Piece Lens is indicated for the visual correction of aphakia in adult patients in whom a cataractous lens has been removed by extracapsular cataract extraction. These devices are intended to be placed in the capsular bag. **WARNINGS:** Physicians considering lens implantation should weigh the potential risk/benefit ratio for any conditions described in the TECNIS® 1-Piece IOL Directions for Use that could increase complications or impact patient outcomes. The TECNIS® 1-Piece IOL should not be placed in the ciliary sulcus. **PRECAUTIONS:** Do not reuse, resterilize, or autoclave. **ADVERSE EVENTS:** In 3.3% of patients, reported adverse events of cataract surgery with the 1-Piece IOL included macular edema. Other reported reactions occurring in less than 1% of patients were secondary surgical intervention (pars plana vitrectomy with membrane peel) and lens exchange (due to torn lens haptic).

*Compared against AcrySof® IQ (SN60WF), HOYA AF-1™ FY-60AD and enVista® IOLs (MX60).

Reference: 1. Data on file. Chromatic aberration of the TECNIS® Symphony IOL. Johnson & Johnson Surgical Vision, Inc. Santa Ana, CA.

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Cornea/Anterior Segment Criticisms

To the Editor:

I am writing to respond to the January 2019 article, “Amniotic Membrane Use in Pterygium Surgery” (Thomas John, MD). The article contains inaccuracies related to the processing, protein profile and clinical effectiveness of dehydrated amniotic membrane technologies (such as Ambio Amniotic Membrane Grafts [Katena]).

Dr. John states that dehydration of the amniotic membrane “involves high-temperature processing to remove the water content of the tissue; this has been shown to potentially cause protein denaturation, loss of function and possibly irreparable damage to the tissue, with the possible loss of active components and, hence, their associated biological functions.”

The process employed to clean and dehydrate the Ambio Amniotic Membrane grafts does not expose the native tissue to high temperatures. Additionally, laboratory tests have been conducted to prove that the Ambio graft does contain native growth factors and cytokines. These data were published by Koob et al.¹

Dr. John also claims that, when compared to dehydrated amniotic grafts, “cryopreserved amniotic membrane is usually a preferred choice for clinical use in ophthalmology and pterygium surgery.” Ambio grafts have been widely used by eye surgeons since 2002 to treat pterygium and a range of other ocular surface disorders and

diseases. According to Katena, more than 125,000 Ambio grafts have been supplied to the ophthalmic surgical community.

I have used both dehydrated and cryopreserved amniotic membrane to treat thousands of patients with pterygium and other forms of ocular surface disease. Both methods of membrane preparation and both types of product work well to preserve the anti-inflammatory, anti-fibrotic properties of this special tissue. There are no published studies that demonstrate the clinical superiority of one preparation method or one product over another. Like many colleagues, I prefer dehydrated amniotic membrane grafts because they can be stored at room temperature for five years. The dry configuration of the tissue also allows for easier cutting, manipulation, placement and fixation. And finally, the cost of dehydrated amniotic membrane is considerably lower than cryopreserved tissue.

I will appreciate your sharing these facts with your readers to provide more accurate reporting on this topic.

*John Hovanesian, MD
Harvard Eye Associates
Laguna Hills, Calif.*

Financial Disclosure: Dr. Hovanesian serves Katena as its medical director.

1. T. Koob, J. Lim, N. Zabeck, M. Massee. “Cytokines in single layer amnion allografts compared to multilayer amnion/chorion

allografts for wound healing.” *Journal of Biomedical Materials Research B: Applied Biomaterials*. 2014.

Dr. John responds:

I thank Dr. Hovanesian for his interest in my recent article which reviews pterygia and the best surgical approach in managing them.

As I mentioned in the article, amniotic membrane grafts possess anti-inflammatory and anti-scarring properties that theoretically make it an optimal tissue graft during pterygium surgery. Although the aforementioned is true in general, different processing techniques (e.g. cryopreservation and dehydration) of the amniotic tissue have varying impacts on the biochemical composition and anti-inflammatory properties of the tissue.¹ In fact, cryopreservation, but not dehydration, was shown to retain the HC-HA/PTX3 complex, which has been identified as an active matrix component responsible for the observed anti-inflammatory and anti-scarring properties of amniotic tissue.² This is one potential reason why, in one study, dehydrated amniotic membrane (Ambiodry 2) was not effective in controlling inflammation and scarring in rabbit eyes after extraocular muscle surgery, as the authors of the study mention.³ Hence, despite the presence of some growth factors and the ability to “work well,” dehydrated amniotic tissue lacks the maximal properties that one would expect

(Continued on page 16)

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INDICATION

DEXTENZA is a corticosteroid indicated for the treatment of ocular pain following ophthalmic surgery.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

WARNINGS AND PRECAUTIONS

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. Intraocular pressure should be monitored during treatment.

Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

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.

Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation

ADVERSE REACTIONS

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (9%); intraocular pressure increased (5%); visual acuity reduced (2%); eye pain (1%); cystoid macular edema (1%); corneal edema (1%); and conjunctival hyperemia (1%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

Please see brief summary of full Prescribing Information on adjacent page.

*73.6% of physicians in Study 1 and 76.4% in Study 2 rated DEXTENZA as easy to insert.

References: 1. Sawhney AS et al, inventors; Incept LLC, assignee. US patent 8,409,606 B2. April 2, 2013. 2. DEXTENZA [package insert]. Bedford, MA: Ocular Therapeutix, Inc; 2018. 3. Walters T et al. *J Clin Exp Ophthalmol.* 2016;7(4):1-11.

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BRIEF SUMMARY: Please see the DEXTENZA Package Insert for full prescribing information for DEXTENZA (11/2018)

1 INDICATIONS AND USAGE

DEXTENZA® (dexamethasone ophthalmic insert) is a corticosteroid indicated for the treatment of ocular pain following ophthalmic surgery (1).

4 CONTRAINDICATIONS

DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

5 WARNINGS AND PRECAUTIONS

5.1 Intraocular Pressure 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. Intraocular pressure should be monitored during the course of the treatment.

5.2 Bacterial Infection

Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection [see Contraindications (4)].

5.3 Viral Infections

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex) [see Contraindications (4)].

5.4 Fungal Infections

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 [see Contraindications (4)].

5.5 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Intraocular Pressure Increase [see Warnings and Precautions (5.1)]
- Bacterial Infection [see Warnings and Precautions (5.2)]
- Viral Infection [see Warnings and Precautions (5.3)]
- Fungal Infection [see Warnings and Precautions (5.4)]
- Delayed Healing [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. 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; delayed wound healing; secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera [see Warnings and Precautions (5)].

DEXTENZA was studied in three randomized, vehicle-controlled studies (n = 351). The mean age of the population was 68 years (range 43 to 87 years), 62% were female, and 85% were white. Forty-six percent had brown iris color and 31% had blue iris color. The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (9%); intraocular pressure increased (5%); visual acuity reduced (2%); eye pain (1%); cystoid macular edema (1%); corneal edema (1%); and conjunctival hyperemia (1%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate or well-controlled studies with DEXTENZA in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, administration of topical ocular dexamethasone to pregnant mice and rabbits during organogenesis produced embryofetal lethality, cleft palate and multiple visceral malformations [see Animal Data].

Data

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.75 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in a mouse study. A daily dose of 0.75 mg/kg/day in the mouse is approximately 5 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis. In a rabbit study, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.36 mg /day, on gestational day 6 followed by 0.24 mg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A daily dose of 0.24 mg/day is approximately 6 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis.

8.2 Lactation

Systemically administered corticosteroids appear in human milk and could suppress growth and interfere with endogenous corticosteroid production; however the systemic concentration of dexamethasone following administration of DEXTENZA is low [see Clinical Pharmacology (12.3)]. There is no information regarding the presence of DEXTENZA in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production to inform risk of DEXTENZA to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DEXTENZA and any potential adverse effects on the breastfed child from DEXTENZA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

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

17 PATIENT COUNSELING INFORMATION

Advise patients to consult their surgeon if pain, redness, or itching develops.

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REVIEW | Letters to the Editor

(Continued from page 14)

with amniotic tissue. Also, cryopreserved amniotic tissue may be preferred by some surgeons due to its handling properties in the OR; in addition, it's FDA-recognized as demonstrating anti-scarring and anti-inflammatory functions.⁴

Thomas John, MD

Thomas John Vision Institute
16532 South Oak Park Ave Suite 201
Tinley Park, IL 60477

Financial disclosure: Dr. John has a small equity interest in, is consultant/advisor to, and has received lecture fees and grant support from Bio-Tissue and Tissue Tech.

1. Cooke M, Tan EK, Mandrycky C, He H, O'Connell J and Tseng SC. Comparison of cryopreserved amniotic membrane and umbilical cord tissue with dehydrated amniotic membrane/chorion tissue. *J Wound Care* 2014;23:465-76.
2. Tseng SC. HC-HA/PTX3 Purified from amniotic membrane as novel regenerative matrix: Insight into relationship between inflammation and regeneration. *Investigative Ophthalmol Vis Sci* 2016 Apr 1;57:5:ORSFh1-8.
3. Chun BY, Kim HK and Shin JP. Dried human amniotic membrane does not alleviate inflammation and fibrosis in experimental strabismus surgery. *J Ophthalmol* 2013;2013:369126.
4. Bio-Tissue 2001 RFD, available at: <https://www.fda.gov/downloads/CombinationProducts/JurisdictionalInformation/RFDJurisdictionalDecisions/RedactedDecisionLetters/UCM113701.pdf>

REVIEW | News

(Continued from page 6)

begun on Capitol Hill to investigate why prescription drug prices are rising and how this development is affecting Americans.

Witnesses at the hearing seek to clarify research costs, inflation vs. drug prices, the prescription percentage of patent-protected drugs vs. drug spending, and patent policy regarding the length of time before generic manufacturers can enter into competition.

In testimony, Aaron S. Kesselheim, MD, an associate professor of medicine at Harvard Medical School, stated that the pharmaceutical marketplace is fractured and inefficient.

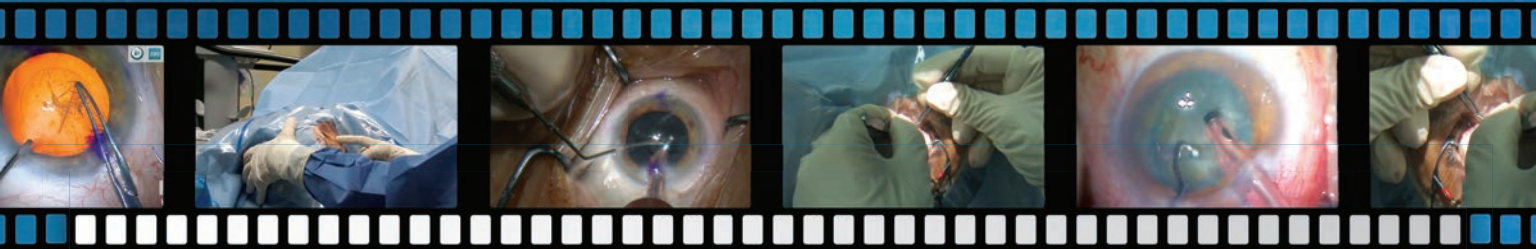
“The solution to this problem involves intelligent legislation and regulation to ensure that U.S. patients and payers pay prices commensurate with the clinical value that the drugs provide,” Dr. Kesselheim said, “and to ensure that even expensive drugs face generic or biosimilar competition after a reasonable and fair time frame.” **REVIEW**



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Surgical Video by:
Richard J. Mackool, MD

Video Overview:

After posting so many complicated cases, I thought it may be time to review my standard procedure with this one-eyed patient showing some slight macular degenerative changes. Leaving this patient myopic for better reading vision quality, my chopping technique, settings, and the benefits of vacuuming the posterior capsule are all discussed.

MackoolOnlineCME.com MONTHLY Video Series



Richard J. Mackool, MD

We are excited to continue into our fourth year of Mackool Online CME. With the generous support of several ophthalmic companies, I am honored to have our viewers join me in the operating room as I demonstrate the technology and techniques that I have found to be most valuable, and that I hope are helpful to many of my colleagues. We continue to edit the videos only to either change camera perspective or to reduce down time - allowing you to observe every step of the procedure.

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I thank the many surgeons who have told us that they have found our CME program to be interesting and instructive; I appreciate your comments, suggestions and questions. Thanks again for joining us on Mackool Online CME.



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Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical techniques using a variety of instrumentation and settings.

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After completion of this educational activity, participants should be able to:

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2019 (Year 3) MIPS Changes

What you can do in the coming year to help ensure that your practice earns a bonus—and avoids a penalty.

Year three of the Quality Payment Program is here! There are some significant changes to be aware of as you plan what to do in 2019 to earn a bonus and avoid a penalty. Most eye-care providers will be in the Merit-Based Incentive Program, or MIPS. The program's complexity for year three scoring is much higher since the scoring bar for penalty avoidance was raised to 30 points, which was doubled from the 2018 level. Year one of MIPS had a penalty avoidance of only three points.

QWhat are the four main parts of MIPS and how has the weight of each changed for year three?

A The weight of each year-three MIPS component (adding up to 100 percent) is as follows:

- Quality = 45 percent
- Resource Use (Cost) = 15 percent
- Improvement Activities (IA) = 15 percent
- Program Interoperability (PI) = 25 percent.

Program Interoperability might seem like a new MIPS category, but it was renamed mid-2018 by CMS. It was formerly known as Advancing

Care Information, but it's still the electronic medical record portion of MIPS. If you don't have an electronic medical record system in your practice and have no exemption, your maximum score is limited to 75 points since you can't score in Program Interoperability.

Two of the categories, Quality and Resource Use, have had their emphases/weighting changed every year since the program's inception in 2017. In the second year, Quality was worth 50 percent, while the Resource Use category was worth 10 percent.

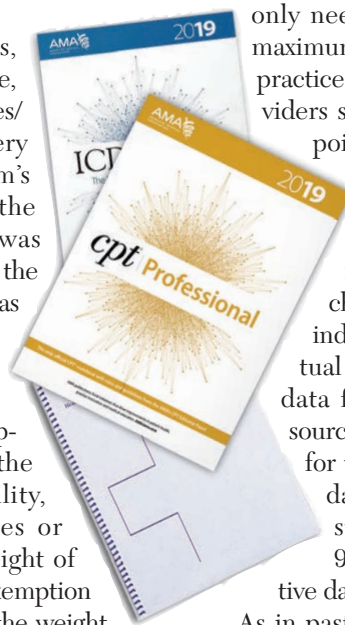
In some instances, when a provider or group receives an exemption or no score from the Program Interoperability, Improvement Activities or Cost categories, the weight of the category with the exemption or no score is added to the weight of the Quality category. For example, if a practice had a hardship exception for Program Interoperability, then the associated 25 percent would be added to Quality's 45 percent value, making the new weight 70 percent.

QWhat hasn't changed for 2019 MIPS?

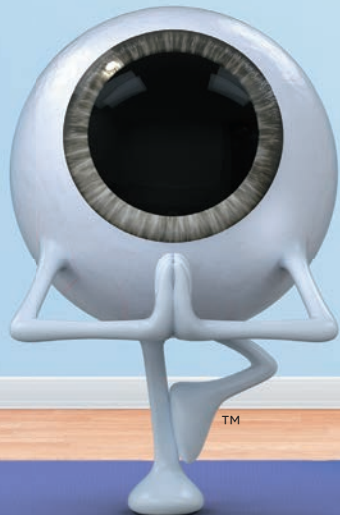
A If you're considered a small practice (fewer than 16 providers) then CMS retains the IA score-doubling effect. To get 100 percent, you only need to reach half the maximum score of 40. Large practices of 16 or more providers still have to reach 40 points the normal way.

Other 2019 MIPS provisions that haven't changed include the ability to choose to report as an individual, group or virtual group. Additionally, data for Quality and Resource Use is still collected for the entire year, while data for PI and IA is still collected for any 90 or more consecutive days.

As in past years, what you do this year has the potential to affect your Medicare payments two years later; so, the 2019 MIPS component affects 2021 payments. CMS refers to these as the "Performance Year" and "Payment Year."



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Published and presented clinical studies report that in post-launch (i.e., not included in current labeling), prospective and retrospective, double-masked and open-label, cohort and case-controlled, single- and multi-center analyses, the use of OMIDRIA, compared to the surgeons' standard of care, statistically significantly:

- Prevents Intraoperative Floppy Iris Syndrome (IFIS)¹
- Reduces complication rates (epinephrine comparator)²
- Decreases use of pupil-expanding devices (epinephrine comparator)²⁻⁷
- Reduces surgical times (epinephrine comparator)^{2,4,6,7}
- Prevents miosis during femtosecond laser-assisted surgery (epinephrine comparator)^{5,8}
- Improves uncorrected visual acuity on day after surgery (epinephrine comparator)²
- Delivers NSAID to the anterior chamber and related structures better than routine preoperative topical drug administration, resulting in effectively complete postoperative inhibition of COX-1 and COX-2^{9,10}

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IMPORTANT SAFETY INFORMATION

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

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

Systemic exposure of phenylephrine may cause elevations in blood pressure.

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

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

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

You are encouraged to report Suspected Adverse Reactions to the FDA.

Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

References: 1. Silverstein SM, Rana V, Stephens R, Segars L, Pankratz J, Shivani R, et al. Effect of phenylephrine 1.0%-ketorolac 0.3% injection on tamsulosin-associated intraoperative floppy-iris syndrome. *J Cataract Refract Surg.* 2018;44(9):1103-1108. 2. Rosenberg ED, Nattis AS, Alevi D, et al. Visual outcomes, efficacy, and surgical complications associated with intracameral phenylephrine 1.0%/ketorolac 0.3% administered during cataract surgery. *Clin Ophthalmol.* 2018;12:21-28. 3. Bucci FA Jr, Michalek B, Fluet AT. Comparison of the frequency of use of a pupil expansion device with and without an intracameral phenylephrine and ketorolac injection 1%/0.3% at the time of routine cataract surgery. *Clin Ophthalmol.* 2017;11:1039-1043. 4. Visco D. Effect of phenylephrine/ketorolac on iris fixation ring use and surgical times in patients at risk of intraoperative miosis. *Clin Ophthalmol.* 2018;12:301-305. 5. Walter K, Delwadia N. Miosis prevention in femtosecond cataract surgery using a continuous infusion of phenylephrine and ketorolac. Presented at: 2018 American Society of Cataract and Refractive Surgery (ASCRS) and American Society of Ophthalmic Administrators (ASOA) Annual Meeting; April 13-17, 2018; Washington, DC. 6. Matossian C. Clinical outcomes of phenylephrine/ketorolac vs. epinephrine in cataract surgery in a real-world setting. Presented at: American Society of Cataract and Refractive Surgery (ASCRS) and American Society of Ophthalmic Administrators (ASOA) Annual Meeting; April 13-17, 2018; Washington, DC. 7. Al-Hashimi S, Donaldson K, Davidson R, et al. Medical and surgical management of the small pupil during cataract surgery. *J Cataract Refract Surg.* 2018;44:1032-1041. 8. Gayton JL. E-poster presented at: 15th International Congress on Vision Science and Eye; 2017 Aug 10-11; London, UK. 9. Katshev DA, Katshev CC, Pinnow J, Lockhart CM. Intracameral ketorolac concentration at the beginning and end of cataract surgery following preoperative topical ketorolac administration. *Clin Ophthalmol.* 2017;11:1897-1901. 10. Waterbury LD. Alternative drug delivery for patients undergoing cataract surgery as demonstrated in a canine model. *J Ocul Pharmacol Ther.* 2018;34:154-160.



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Q I reported MIPS via a registry in 2017 and 2018. Have the submission methods changed?

A No. You can still submit via Claims if you're a small group, and the Direct EMR and Registry options remain for anyone. If you submit the same MIPS category using multiple methods (for example, if you report Quality via both Claims and Registry), your highest score will count.

Q For 2018, I'm receiving a small-practice bonus of five points, which will be added to my MIPS Composite score. Is this bonus still available in 2019?

A The bonus is now six points, but instead of applying that to the Composite score, it all goes to Quality, which has the effect of diluting the bonus points.

Q Did any of the areas undergo changes I should know about that aren't noted above?

A Yes. Both PI and Resource Use changed in significant ways. The 2018 method of reporting PI involved having a "Base" that you had to meet before going to a "Performance" score. That was changed; there's just one level now. In 2018, there were more than 150 possible PI points, and you only had to reach 100 to max out that category and get 100 percent. For 2019, there are only 100 possible points. There are some bonus points in PI, which can total 10 points, but they are unlikely to be achieved by ophthalmologists, who won't have prescription drug monitoring programs and opioid treatment agreements. As a result of these changes, getting a perfect score of 100 percent may be more difficult.

For Resource Use, if your office does cataract surgery in an ASC or HOPD, this is the biggest change of

all. There's a new "Episode of Cost" measure which takes into account uncomplicated cataract with intraocular lens surgery and all of the associated costs. At the end of the year, CMS will calculate a normalized value for 66984, which takes into account regional differences, site of surgery and other factors. That value is then multiplied by the number of cases, if you reach the case minimum.

Here are a few important specifics that you should know regarding this change:

- Only items/amounts paid by Medicare for uncomplicated CPT 66984 are counted. Claims to other payers are not part of this; neither are patient-pay, noncovered services such as premium IOLs.

- You need to have been paid for 20 or more 66984 claims to Medicare for 2019 surgery that are not otherwise excluded (*see below*).

- Anything paid by Medicare related to cataract within a window of 60 to 90 days before the surgery can count.

- All costs paid by Medicare related to the cataract surgery count, which includes all of the related exams, diagnostic tests, reoperations (for example early YAG capsulotomy or IOL repositions, even if not done by the initial surgeon), any drugs used during the surgery or in the office that are separately paid, and anesthesia payments.

- Patients who have concomitant ocular disease which might limit best-corrected visual acuity aren't counted (such as situations where the patient has a corneal scar or significant posterior segment disease). The Centers for Medicare and Medicaid Services dictates the exclusions by looking at diagnosis codes for the eye that's having surgery as well as the "time window" above.

The two-step attribution process for "primary-care services," which was always unlikely to apply to eye doctors, still remains.

If any costs are attributed to a sur-

geon—or the surgeon's group, if reporting that way—using either or both of the methods described above, then you are compared to the national norm for cost and scored accordingly. Those who are low-cost would be given a higher Resource Use score. If both two-step and cataract are attributed, each scores in this category. If only one of these applies, then that counts in full for the category. Here, a perfect score would be 10 points on each part scored, which is multiplied by the 2019 weight of 15 percent.

Q I've heard that some medical practices could receive an exemption for some or all of MIPS. Is that true?

A Yes, if a large natural disaster affects the practice. This was true in both 2017 and 2018 and is likely for 2019, too. However, as we are barely into the year, CMS has not issued any information for 2019 disasters at the time of this writing, since none have occurred.

Those practices who are affected by wildfires or other natural disasters (CMS calls these "extreme and uncontrollable circumstances") are likely to be given a "pass" on part or all of 2019 MIPS reporting and will therefore receive no penalty in 2021 unless they are able to and elect to submit MIPS data. CMS automatically identifies these areas by their payment ZIP codes. There are other exemptions published by CMS but they are far less likely to apply to the average practice.

Ultimately, what it comes down to is that 2019 MIPS is more complicated this year, and diligence is warranted in order for your practice to avoid a 2021 penalty. **REVIEW**

Mr. Larson is a senior consultant at the Corcoran Consulting Group in San Bernardino, California. He can be contacted at plarson@corcoranccg.com.

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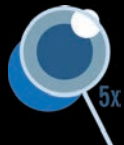
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Monitoring IOP at Home: A Work in Progress

Now that technology has made home IOP measurement feasible, doctors are beginning to uncover its real-world pros and cons.

Sharon F. Freedman, MD, Durham, N.C.

As physicians managing patients with glaucoma, we face numerous practical challenges. One of them is accurately monitoring intraocular pressure. Most of us only get to check our patients' pressures every few months in the clinic, which is far from ideal, since we know that pressure fluctuates over time.

It's no secret that researchers are striving to make 24/7, high-tech IOP-monitoring a reality. That technology will bring us new challenges, including figuring out what to do with the enormous amount of data it will produce for every patient. But in the meantime, it's possible to improve on our current, sparse supply of data by asking selected patients to monitor their pressure at home. This offers the possibility of getting several readings each day over a period of weeks or months—enough information to make us aware of what's happening to our patient outside of the office without drowning us in data points.

Home monitoring of IOP is still in its early stages, but as a pediatric glaucoma specialist, I now have several years of experience using rebound tonometry in clinic and at

home with young patients. I believe my experience with childhood glaucoma can help to shed some light on the challenges and benefits that lie ahead when this technology becomes more widely used—hopefully in appropriate adult glaucoma patients as well as children.

Benefits of Home Monitoring

The theoretical advantages of having IOP measurements taken outside the office are not hard to see:

- **A more accurate measurement of peak IOP.** The variability of IOP over time sometimes surprises us; occasionally, the pressure we measure in the office is very different from the previous visit. So it shouldn't be a surprise—and it has been my experience—that multiple measurements taken outside of the office frequently reveal much higher pressures than we measured in the office.

- **Catching pressure fluctuations.** It's been shown that pressure fluctuations—even those measured during periodic office visits—are associated with progression in adult open-angle glaucoma. (This stands in

contrast to patients whose IOPs are at target and stable.) We also know that pressure fluctuations can happen outside of office hours. Measuring IOP over a larger range of time offers the possibility of catching those fluctuations.

That raises another point:

- **Some fluctuations caused by surgery can be dangerous when they're not carefully monitored.**

Sometimes the treatments we provide—including surgery—cause dramatic IOP fluctuations. In the pediatric world, situations prone to such fluctuations might include doing angle surgery and having a little blood in the eye; putting the child on steroids; or putting in a Baerveldt drainage device where we purposely tie the tube off, knowing that it's going to open when the stitch dissolves. In the latter situation, the pressure may be very high until the stitch dissolves; then it may drop very low. In the adult world, some MIGS procedures are also associated with pressure spikes.

If IOP is being monitored at home during such high-risk times in vulnerable patients, we'll know when there's an abrupt pressure change that

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Indication

INVELTYS (loteprednol etabonate ophthalmic suspension) 1% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information

INVELTYS 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.

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.

Use of corticosteroids may result in posterior subcapsular cataract formation.

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.

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.

Use 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 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.

In clinical trials, the most common adverse drug reactions were eye pain (1%) and posterior capsular opacification (1%). These reactions may have been the consequence of the surgical procedure.

Please see Brief Summary of Prescribing Information for INVELTYS on the next page.

INVELTYS™

(loteprednol etabonate
ophthalmic suspension) 1%

**INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1%,
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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

INVELTYS 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, as well as 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—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—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 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—The preservative in INVELTYS may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of INVELTYS and may be reinserted 15 minutes following administration.

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.

Clinical Trial Experience—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse drug reactions in the clinical trials with INVELTYS were eye pain and posterior capsular opacification, both reported in 1% of patients. These reactions may have been the consequence of the surgical procedure.

USE IN SPECIFIC POPULATIONS

Pregnancy—Risk Summary: INVELTYS is not absorbed systemically following topical ophthalmic administration and maternal use is not expected to result in fetal exposure to the drug.

Lactation—Risk Summary: INVELTYS is not absorbed systemically by the mother following topical ophthalmic administration, and breastfeeding is not expected to result in exposure of the child to INVELTYS.

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.

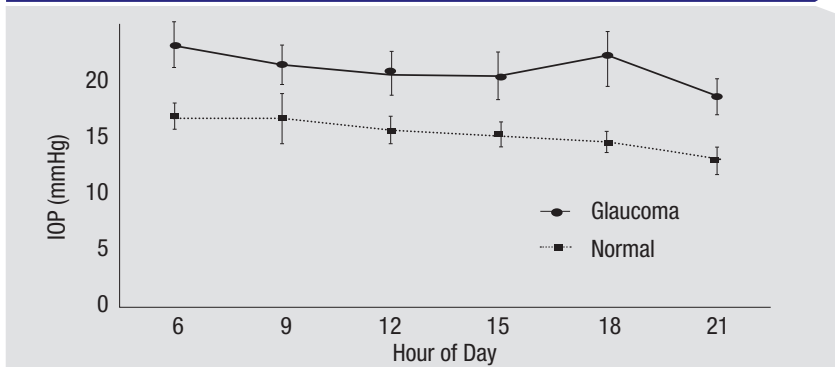
NONCLINICAL TOXICOLOGY

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 thymidine kinase (tk) assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay.

For a copy of the Full Prescribing Information, please visit www.INVELTYS.com.

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Home Rebound Tonometry for Pediatric Glaucoma



IOPs tended to be higher in the mornings and lower in the evenings for both normal and glaucoma patients. (Flemmons, Hsaio et al. 2011')

needs to be addressed.

• **Fewer concerns about patients missing office visits.** Patients who need to have their pressure checked sometimes can't come to the office when, or as often, as we'd like. For a patient measuring IOP at home, some office visits purely for IOP checks might actually be unnecessary.

• **A single in-office diurnal curve measurement may not tell the whole story.** It's helpful to measure a diurnal pressure curve over the course of a day in the clinic (if the patient can manage this), but some studies have shown that in adults the diurnal fluctuation may not be exactly the same from one day to the next.

What's Taking So long?

Despite the promise of home IOP monitoring, a number of obstacles have caused this idea to get off to a slow start. The first obstacle has only recently been overcome: Having available technology that can safely be used by patients at home.

Most tonometers aren't suited to home tonometry because they require anesthetizing the cornea. Any physician will be reluctant to let a patient use an anesthetic at home, because if the eye is anesthetized for a home-based reading, there's a risk that the person taking the pressure

will injure the cornea. Neither person would know anything had happened until the anesthetic wore off.

Tonometers that can accurately measure IOP at home without topical anesthetic are not common. In theory, parents could use an air puff device of some type to take the readings, but most patients—young or old—don't enjoy that experience. In fact, the lack of multiple FDA-approved options for home IOP monitoring is largely the result of the fact that most IOP-measuring technologies don't lend themselves to home use.

In my experience, the only technology that can easily be used to measure pressure without an anesthetic at home—at least for now—is rebound tonometry, because it touches the eye so gently. I first became interested in this technology when a colleague mentioned a new tonometer that didn't require a topical anesthetic. In the pediatric world, that's huge; by the time you put in the topical anesthetic and the child has had a meltdown, you're starting from scratch, convincing the child to let you check the pressure. Even the Tonopen, which has been the standby for pediatric patients, often proves challenging to use in young children for the same reason.

The first rebound tonometry I tried was the TAO1i from Icare,

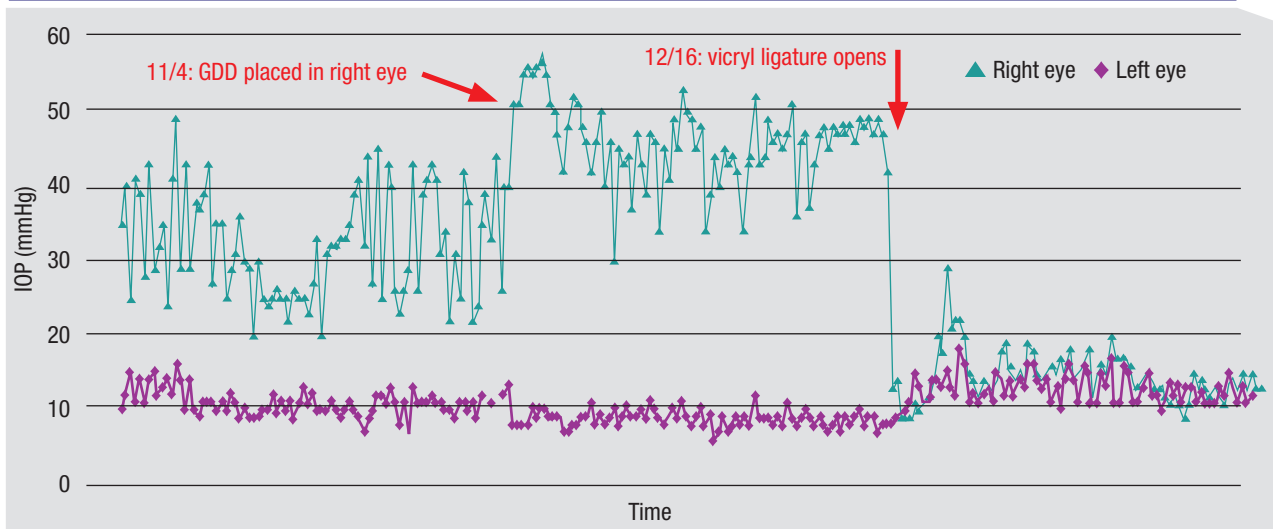
the company's first model; our early studies were conducted using that device. It provides a reliability index with each reading and it's pretty easy to use, but it doesn't store any data. The next model, the ic100, has a display on it and a few extra bells and whistles. The Icare Pro version (not commercially available in the United States) has storage capability and can be used upright or flat, so you could use it on a patient lying down, making it feasible for use in the OR.

Recently, the Food and Drug Administration approved the Icare HOME model, designed specifically to allow an older patient to use it on himself, thus making home IOP measurement feasible. The device knows whether you're measuring the left or right eye, and it has a red-light-green-light display that lets patients know when they're at the right distance from the instrument and the device is angled correctly. When the patient is finished taking a reading, it shows either a repeat indicator or a checkmark, so the patient knows when it's time to do the other eye. (Notably, it doesn't let the patient see the pressure reading.)

If the reading was reliable, the machine will store the data, including which eye was measured, the date and the time, the reliability index and the measured pressure. Currently, the device has to be plugged in to a computer to upload the data, but the company plans to upgrade the software to allow the device to wirelessly upload data to the cloud, where it would theoretically be downloadable by anyone with appropriate permission to access it.

Obviously, there will be other technologies that can be used by the patient at home—including high-tech options such as contact-lens-based monitors like the Triggerfish—in the future. I chose to study rebound tonometry because it was available and well-suited for this type of application.

Long-term Home Monitoring of IOP in an Aphakic Patient Receiving a Baerveldt Implant



This patient's left eye had already undergone successful Baerveldt implantation. Surgery in the right eye during the home measurement period caused a short-term increase in pressure; a few weeks later when the ligature opened, pressure dropped. Being able to identify the actual timing of the ligature opening made it possible to manage the sudden pressure drop without guesswork. (Bitner et al. 2016³)

Getting Our Questions Answered

Because the idea of home IOP monitoring was relatively new, we set out to answer some key questions. Initially, we wanted to find out what rebound tonometry could and couldn't do when used in the clinic, so we conducted a study in the clinic involving 71 children with known or suspected glaucoma.¹ All of these children could tolerate Goldmann applanation, allowing us to compare the applanation and rebound tonometry IOP readings in a masked fashion. We found that the TAO1i usually read higher than Goldmann, by a little more than 2 mmHg. Occasionally the readings would be significantly different, for reasons we couldn't determine; we never found one specific thing, such as corneal thickness, that might explain this. We also noted that the device didn't hurt the cornea. When we stained the cornea, we couldn't even tell that it had been used.

Next, we set out to see whether families could use the Icare (original model) for home tonometry in chil-

dren. We studied it under a research protocol with 17 affected children (17 eyes) and 11 normal siblings.² We found that caregivers obtained reliable readings 70 percent of the time. The data showed that daily IOP fluctuation occurred in both groups, and the pressures tended to be higher in the morning and lower in the evening. (See graph, p. 26.) Perhaps most significant, peak IOPs were sometimes much different from those measured in the clinic. In five subjects (31 percent) the peak IOP measured at home was more than 6 mmHg higher than that measured in the clinic. This caused us to alter our management of several of these patients, meaning we either performed surgery or changed medications.

Long-term Use at Home

Next, we wanted to know how long we needed to send a device home in order to catch pressure spikes. To get an answer, we examined data from seven children (average age: 9) enrolled to do home rebound to-

nometry three times a day for more than 30 days.³ On average, the monitoring lasted for about six months. The parents entered the data into an Excel spreadsheet or used our online entry form. Ultimately, we found that two weeks of monitoring in the children caught more than 90 percent of all pressure spikes, so we concluded that two weeks might be a good minimum length of time to have a child's pressure monitored if the goal was specifically to find a pressure spike on a given treatment regimen.

We also were able to monitor the impact of our treatment, especially relating to surgical intervention in this small group of childhood glaucoma patients. On average, surgery lowered pressure by 10 mmHg. Perhaps most interesting, we found that the mean variation in pressure over the course of a day decreased when we improved aqueous outflow. Before the intervention, the average daily pressure fluctuation in those eyes was 8 mmHg; after surgery it was 5 mmHg. So not only did we lower the pressure by an average of 10 points, we also decreased the amount of daily

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pressure fluctuation.

One situation in which we found ongoing monitoring at home to be especially useful was following the implant of a Baerveldt drainage device, when we ligated the tube to prevent early hypotony. That turned out to be valuable for several reasons:

- First, we found that if we added steroids or surgery while the tube was ligated, the pressure usually went up before it went down. (This was not a surprise, but it was useful to know that the data confirmed our expectations.)

- We saw tremendous variations in pressure while we were waiting for the tube to open, sometimes prompting unplanned therapy changes for unusually high IOPs caught at home.

- Perhaps most useful, the parents could precisely pinpoint the moment when the tube opened because the measured pressure would drop. It's important to know when this has happened because as soon as the tube opens and the pressure plummets, the patient needs to stop using the glaucoma drops for a while or the pressure could get dangerously low.

Knowing when the tube has opened is especially important in some patients, such as those with Sturge-Weber-associated glaucoma, where there's a choroidal hemangioma in the eye along with the glaucoma. Kids in this situation may get choroidal effusions—leakage from the choroidal hemangioma—and even serous retinal detachments if they have a dramatic pressure drop. If we can more precisely monitor the pressure as it's changing, we can help to mitigate some of that. For that reason I now routinely use home monitoring in this situation.

Convinced that home IOP monitoring of selected childhood glaucoma patients was helpful in their care, we were interested in exploring attitudes towards home tonometry, both from our patients and our colleagues who treat childhood glaucoma. To that

end, we recently sent a survey to 83 parents (or the patients themselves, if they had been treated as children but were now adults), and pediatric ophthalmologists and glaucoma specialists who care for kids with glaucoma. Eighty-four percent of the parents said they were very interested in using this technology; most felt it would improve their physician's ability to monitor their glaucoma. Eighty percent of the surgeons who responded to our survey indicated interest and saw the potential benefit for patient care, but only 14 percent were actually using any form of home tonometry, demonstrating that this approach to IOP monitoring is by no means widespread.⁴

We also asked doctors in which situations they'd use home tonometry. Most physicians said they'd use it to try to catch IOP peaks or fluctuations that they suspected were occurring, either because readings were inconsistent or they couldn't do enough clinic visits to be sure. Some said it might help them provide better postoperative care. Overall, most physicians felt there would be a benefit to using home tonometry in selected patients.

Barriers to Use

Despite its potential, a number of barriers to widespread use of home tonometry remain:

- **Managing the information.** One of the challenges that comes with implementing any kind of home tonometry is processing the resulting data. How do you collect it and make sense of it? How do you make sure you haven't missed something?

- **Opening up new areas of liability.** When the patient is being measured at home, who is responsible for interpreting and responding to those measurements, and by what methodology?

- **Cost to the physician/practice.** Physicians and offices would have

to spend money to own or rent the devices, to care for the devices, to train patients to use the devices, and to process all of the data. Currently, there are no treatment codes that would allow physicians to be reimbursed for these costs, although nothing would prevent them from renting the equipment to the patient.

One related thing we discovered is that patients get very attached to using the instrument! They (or their families) often don't want to give it back. To make home tonometry feasible, one needs to own several (or more) of these devices—at a non-trivial initial cost. Fortunately, through generous support from Saving Kids' Sight, we've been able to purchase several dozen tonometers to loan out (again, under IRB protocol). We've now reached out to several other institutions, sharing our protocol and tonometers, to help expand the reach of our Icare Lending Library Project.

- **A lack of supporting evidence, especially in adult populations.** There's some evidence in the literature that this technology can be helpful when managing children, and my own experience supports that. However, as far as I know, there's little published in the adult glaucoma literature demonstrating improved outcomes as a result of measuring pressures at home. I think that such supporting evidence will be needed to increase interest and the use of home tonometry for adult glaucoma patients.

The bottom line is that home tonometry is not likely to sweep the field of glaucoma in the near future. In fact, I suspect most busy clinicians will not want to do this except under select circumstances.

Onward and Upward

Studies involving home tonometry are now appearing in the literature, and some doctors are already using

the Icare Home. Although this is currently mostly used in pediatric populations, the studies indicate that there's interest in home tonometry in the adult world as well. Nevertheless, I think we're quite far from widespread implementation at this point. And that may be reasonable: Based on our experience, home tonometry is not appropriate for every patient, nor is it necessary.

In the meantime, the technology continues to improve, and I believe the future for home monitoring is bright, for many reasons. The instruments are getting more user-friendly, and cloud-based storage of data is now on the near horizon. I can imagine a situation in the future in which electronic medical record systems will be able to seamlessly download and integrate the IOP measurements, much as can be done today with home telemetry for arrhythmia monitoring. Perhaps the device could even have an alarm that would alert the patient that her pressure is high and ask whether she remembered to use her drops, thus improving adherence.

In addition, once this technology becomes easy to use and is implemented in more practices, it may actually save doctors time by eliminating the need for patient visits that happen primarily just for a pressure check. Of course, once we have proof that this technology improves outcomes, we're going to need some kind of reimbursement. And we'll need to do a lot more research to find out which patients it can help the most, and how best to implement it.

In the meantime, our experience and data so far relate to caring for a very tiny subset of glaucoma patients—kids with childhood glaucoma. The rest of the iceberg, of course, is the adult community. I wouldn't presume to tell doctors dealing with adult patients how or whether to use home tonometry, but I suspect that what we're doing with kids is of interest to those doctors who are managing adults. Yes, implementing this technology in an adult practice with a large number of patients could be more daunting than what I'm dealing with, but I'm hopeful that our experience can act as a starting point for studies involving adults. [REVIEW](#)

Dr. Freedman is a professor of ophthalmology and pediatrics and chief of the Pediatric Ophthalmology and Strabismus Division at Duke Eye Center in Durham, North Carolina. She reports no financial ties to Icare or its products.

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IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.
- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.
- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.
- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

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IMPORTANT SAFETY INFORMATION (CONT'D)

- The most common adverse reactions (incidence \geq 5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity

Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see a brief summary of the US Full Prescribing Information on the following pages.


Reference: 1. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc; 2017.

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1 INDICATIONS AND USAGE

LUXTURNA (voretigene neparvovect-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physicians.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis

Endophthalmitis may occur following any intraocular surgical procedure or injection. Proper aseptic injection technique should be used when administering LUXTURNA. Following the injection, patients should be monitored to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

5.2 Permanent decline in visual acuity

Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal abnormalities

Retinal abnormalities may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. LUXTURNA must not be administered in the immediate vicinity of the fovea. [See Dosage and Administration (2.3) in full prescribing information]

Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

5.4 Increased intraocular pressure

Increased intraocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

5.5 Expansion of intraocular air bubbles

Instruct patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

5.6 Cataract

Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

6 ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 5\%$) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellens (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

6.1 Clinical Trials Experience

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

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5×10^{11} vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety [see Clinical Studies (14) in full prescribing information]. The average age of the 41 subjects was 17 years, ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellens (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection.

Immunogenicity

At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary: There is no information regarding the presence of LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential

No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 [see Clinical Studies (14) in full prescribing information] that included 25 pediatric patients with biallelic RPE65 mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use

The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

17 PATIENT COUNSELING INFORMATION

Advise patients and/or their caregivers of the following risks:

Endophthalmitis and other eye infections: Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new floaters, eye pain, or any change in vision.

Permanent decline in visual acuity: Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

Retinal abnormalities: Treatment with LUXTURNA may cause some defects in the retina such as a small tear or a hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms, such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

Increased intraocular pressure: Treatment with LUXTURNA may cause transient or persistent increase in intraocular pressure. If untreated, such increases in intraocular pressure may cause blindness. Advise patients to follow up with their healthcare provider to detect and treat any increase in intraocular pressure.

Expansion of intraocular air bubbles: Advise patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. A change in altitude while the air bubble is still present may cause irreversible damage.

Cataract: Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

Shedding of LUXTURNA: Transient and low-level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

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Refining Postop Infection Prevention

Christopher Kent, Senior Editor

There are many ways—new and old—to prevent post-surgery inflammation and endophthalmitis.

Surgery always comes with some amount of risk, and removing a cataract is no exception. Postoperative inflammation—and more concerning, endophthalmitis—are potential consequences that cataract surgeons go to great lengths to prevent. Today, with technology advancing rapidly, new options for preventing these undesirable outcomes are appearing. Nevertheless, many surgeons are hesitant to abandon current protocols, and some surgeons say that many effective low-tech precautions are still frequently overlooked.

Here, surgeons share their experience and advice regarding how to do the best possible job of preventing postoperative inflammation and endophthalmitis—whether or not you’ve adopted any of the cutting-edge protocols.

To Drop or Not to Drop?

The biggest debate right now centers around how to manage the patient at the end of surgery and into the postoperative period. Although giving the patient a battery of preop and postop eye drops has been the standard approach for a number of years, there are two clear arguments for switching to an injection of antibiotic (and possibly other drugs) at the conclusion of

surgery: First, evidence is mounting that injecting antibiotics is effective at preventing postop infection—possible more effective than having the patient use drops. Second, drops are a huge burden for the patient and the practice, so the fewer drops the patient has to use, the better.

“Don’t expect to reduce your risk of endophthalmitis by having the patient use antibiotic drops for a week before, or two weeks after, surgery,” says Robert M. Kershner, MD, MS, FACS, professor and chairman of the Department of Ophthalmic Medical Technology at Palm Beach State College, and president and CEO of Eye Laser Consulting in Palm Beach Gardens, Florida. “There’s not a single study showing that this has any substantive effect. The only solid evidence that shows antibiotics to be of any benefit is when they get inside the eye at the time of surgery. In addition, there’s a moderate amount of evidence that suggests that using postoperative antibiotic drops in addition to an intraoperative intracameral or intravitreal injection may lower the incidence of endophthalmitis, compared to using injections or eye drops alone. So it’s probably best to use a combination.”

“We’re at the forefront of a huge paradigm shift in postoperative drug

delivery,” says Cynthia Matossian, MD, FACS, founder and chief medical officer of Matossian Eye Associates, and a clinical assistant professor of ophthalmology (adjunct) at Temple University School of Medicine in Philadelphia. “By eliminating drops, we’re going to take compliance out of the patient’s hands. We’ll eliminate the confusion and difficulty of managing the drops, and decrease the burden for the patient and the patient’s family. In addition, we’ll be putting the drugs closer to the target tissue.

“The average cataract patient in the United States is in his or her late 60s or early 70s,” she notes. “Managing a complicated schedule of drops can be very challenging for some patients. For example, a steroid drop is tapered over a period of several weeks; an antibiotic drop is stopped earlier than the steroid and the NSAID. A brand-name NSAID is used once a day, but if the pharmacist substitutes a generic drop, it may be used four times a day. This creates a lot of confusion—and this is just the first eye. After few weeks we do eye two, which has a different schedule that’s not aligned with whatever remains for eye one. To complicate matters, some patients are forgetful. They may be confused; they may have arthritis in their hands and not be able to squeeze the bottle appropriately; they may contaminate the tip; and they may think they put the drop in when it actually ended up on their forehead or eyelid.

“In addition, the cost of the drops is becoming prohibitive,” she continues. “The cost can be as much as \$400 or \$500. With higher deductibles and a greater percentage of responsibility being placed on the patient by insurance carriers, patients are experiencing sticker shock when they go to pick up their drops. And when they have sticker shock, guess what they do? They call our offices and yell at our staff. They believe we’re the cause of the high prices, even though we have

Making the Preop Period Count

It’s fairly common for cataract surgeons to put their patients on drops prior to surgery, but many surgeons are questioning the value of that protocol. Nick Mamalis, MD, a professor of ophthalmology and director of ocular pathology at the University of Utah in Salt Lake City, says he hasn’t found the use of antibiotic drops prior to surgery to make a significant difference in the incidence of postop endophthalmitis. “We’ve had issues getting patients to be compliant with the use of drops preoperatively, so we don’t start anything until the patient arrives at the surgery center,” he says.

“After they arrive, patients get three sets of a fourth-generation fluoroquinolone, like moxifloxacin or gatifloxacin, several minutes apart, while they’re receiving dilating drops and topical NSAIDs,” he says. “We include the NSAID because there’s some evidence that having an NSAID onboard before making your incisions will decrease the breakdown of the blood-aqueous barrier in the anterior chamber during cataract surgery. In fact, if the patient has an increased risk of inflammation after surgery—for example, if the patient has a history of uveitis or inflammation in the eye—we’ll often start the patient on NSAID treatment up to a week prior to surgery to reduce the chance of a breakdown of the blood-aqueous barrier.”

Dr. Mamalis believes that preoperative povidone iodine is much more effective at ensuring sterility than preoperative antibiotics. “There’s very good evidence that 5% povidone iodine is helpful,” he says. “So, when patients are in the preop holding area we give them a drop of topical povidone iodine. However, it’s important to do this before giving the patient any lidocaine gel to anesthetize the surface of the eye. If you put the gel in first, it will prevent the povidone iodine from spreading out and covering the surface of the eye as it should. Once the patient is in the OR undergoing prep for surgery, the skin is prepped with 10% betadine, but we also put another drop of the 5% betadine on the surface of the eye. By this point the gel has been in the eye for 10 or 15 minutes and has dissipated a bit, so it doesn’t interfere with the coverage of the iodine.”

—CK

nothing to do with it. Furthermore, when the pharmacist substitutes generic drops, the frequency protocol changes; that confuses the patients even more, so they call us to get clarification. Aside from having unhappy patients, the number of incoming calls about these issues is becoming burdensome. Dealing with upset patients, tying up our phone lines and technician time, is a cost to the practice.

“For all of these reasons,” she concludes, “minimizing the drop-instillation regimen is the way to go.”

Going Intracameral

“There’s good evidence from multiple studies around the world that intracameral antibiotics are effective at preventing endophthalmitis,” says

Nick Mamalis, MD, a professor of ophthalmology and director of ocular pathology at the University of Utah in Salt Lake City. “So, we put one-tenth of a cc of preservative-free 0.5% moxifloxacin into the anterior chamber at the conclusion of the case. Also, after we take the speculum out and peel the covers off, I like to put an additional drop of a fourth-generation fluoroquinolone on the eye, along with another drop of betadine, before we put the shield on.”

It’s clear that despite mounting evidence that intracameral injection of antibiotics is effective, many American surgeons are hesitant to switch to this protocol. Dr. Mamalis points out that one reason many surgeons haven’t switched is that there’s no drug that’s FDA-approved for this purpose.



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¹ Schanzlin, Olkowski, Coble, Gross. NuLids II Study, April 2018



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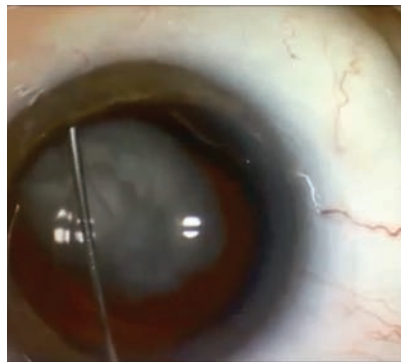


“Surgeons would prefer to have an approved postoperative antibiotic that comes in a single-use vial, specifically made for injection following cataract surgery for prevention of endophthalmitis,” he says. “A lot of people have said that without this, they’re concerned about the formulation and how you get it made. I think that’s keeping many surgeons from switching. I’m lucky to be at a university, because we have our own pharmacy. They’ll put a preservative-free antibiotic into a syringe for us under sterile conditions, so we can just inject it directly. Without that advantage, surgeons have to find an outside source on their own.”

Even some surgeons who have switched to intracameral antibiotics are still using postoperative drops as a safety measure. Dr. Mamalis admits he hasn’t committed to eliminating postoperative antibiotic drops yet, despite his use of an intracameral antibiotic. “I’m not sure if it’s because we’re creatures of habit, or simply still worried about postoperative endophthalmitis, but we use a belt-and-suspenders approach,” he says. “We use the intracameral antibiotic but also have the patient use a topical fourth-generation fluoroquinolone for a week postoperatively. I think this is reasonable, because we don’t know for sure whether there might be a problem several days after the surgery. I prefer to err on the side of caution.”

Sheri Rowen, MD, who practices at NVision Eye Centers in Newport Beach, California, and is a clinical assistant professor of ophthalmology at the University of Maryland, notes that even though there is telling evidence throughout the world supporting the postop injection of antibiotics, she hasn’t seen any long-term studies confirming the efficacy of this approach.

“We’ve seen some debate about which antibiotic can be used, and some cases of hemorrhagic occlusive retinal vasculitis (HORV) have occurred,” she points out. “Many surgeons using this



Cynthia Matossian, MD, FACS

One approach to placing drugs inside the eye has been to place a bolus of drug into the vitreous, usually by inserting a cannula through the zonules (as shown above). Given the potential for complications—and patients often dealing with floaters for a period of time afterwards—many surgeons have been unwilling to adopt this approach.

protocol are injecting non-preserved moxifloxacin, but a lot of people are trying other alternatives internationally. When we’re at American meetings and we raise hands to see who’s using this approach, it’s not a compelling majority of cataract surgeons yet—at least in the U.S.”

Dr. Mamalis notes that the American Society of Cataract and Refractive Surgery has put together a research council to conduct a series of research studies that could potentially lead to FDA approval of an intracameral antibiotic. “A study like this could only be done through a large group with a large number of surgeons involved,” he says.

“The first project we’re tackling is a masked study comparing an intracameral injection of a fourth-generation fluoroquinolone to topical drops for prevention of endophthalmitis,” he explains. “Because endophthalmitis is rare, we’ll need to enlist as many as 75,000 patients. But if this study proves that an injection of intracameral antibiotic is efficacious, it will allow companies to get approval to make a preservative-free antibiotic for single use after cataract surgery. This will go a long way toward making surgeons

more willing to use an intracameral antibiotic.”

Can We Go Dropless?

Dr. Matossian says she’s been doing everything possible to avoid giving the patient postoperative drops for the past two years. “At the conclusion of cataract surgery, just before I seal the incision, I put a steroid and antibiotic combination into the anterior chamber with a 25-ga. bent cannula,” she explains. “I use Dex-Moxi, which is dexamethasone and moxifloxacin; it’s clear, like water. Once it’s placed inside the eye, I seal the incision in the normal way.” Dr. Matossian notes that the downside to her current approach is that neither version of Dex-Moxi (one from Imprimis, one from Ocular Sciences) is FDA-approved. “The combination drugs are manufactured by a 503-A or -B pharmacy,” she explains. “We order it per patient, and the formulation is sent to the ASC.”

Dr. Matossian adds that she still has patients use an NSAID once a day postoperatively. “That’s far easier for the patient than the multi-drop protocol,” she points out. “The exception is if I’ve done a limbal relaxing incision. In that situation the patient also needs topical antibiotics, which I prescribe b.i.d. for five days. In addition, if it was a complex case in which I went in and out of the eye more than normal, or I used a pupil dilating device or the case was prolonged, I might add a topical steroid for just a few days in addition to what I’ve placed intracamerally.”

Dr. Mamalis acknowledges that few or no postoperative drops would be good for both patients and practices. “The problem is that there’s not enough data out there for us to really know how well this works,” he says. “In addition, there’s no commercially available approved medication to inject for this purpose. That means you have to go through a compounding pharmacy to get the medication made

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up. Furthermore, you can't just put it in the anterior chamber; you have to leave a depot of this medication in the eye, either placing it through the zonules or in the anterior vitreous."

Dr. Rowen says she thinks the jury is still out on how surgeons will use intraocular antibiotics. "Everybody's trying to figure out exactly what they're comfortable with and what they feel they need," she says. "If you haven't had a case of endophthalmitis in 20 years, you might feel like you're doing OK with your current protocol. I think if anything new will be adopted, it will be an intracameral injection done at the end of the case—but I can't tell you what the majority of doctors will do. There's no consensus yet. We all want to be in line with the accepted standard of care, but I don't know that we have an accepted standard of care in this area."

Stop Infection Before It Starts

Dr. Kershner emphasizes something that's often omitted from the discussion: If a postop infection occurs, it started during the surgery. In fact, he points out that the term "postoperative endophthalmitis" is misleading. He says the best way to prevent endophthalmitis is to do everything humanly possible to ensure that sterility is maintained during the procedure, rather than focusing on postoperative fallbacks.

"We're probably infecting many more patients than we realize," he says. "Fortunately, in most cases the end result isn't endophthalmitis. The result may be inflammation that we interpret as a low-grade sterile inflammation, when in fact the postoperative cell and flare is secondary to intraocular organisms. Even if that happens, in most patients with a normal immune system—though not all—receiving intraoperative antibiotics will likely ensure that a contamination doesn't turn into an inadvertent adverse event.



Robert M. Kershner, MD, MS, FACS

The best way to prevent endophthalmitis is to make sure sterile protocols are followed to the letter during surgery, including a thorough preoperative scrub.

"The point is that what goes on during the surgery is a lot more important than what happens before or after the surgery," he says. "Preoperative and postoperative antibiotic drops or injections can minimize the chances of endophthalmitis, but preventing it during surgery makes the most sense. That will always be your best insurance policy."

Dr. Kershner notes that some ophthalmologists might be lulled into the illusion that contamination is unavoidable, and if an infection occurs an antibiotic will take care of the problem. "Let me disabuse them of that notion," says Dr. Kershner. "Many times the organism is not identified right away, and a frightening number of bugs are now resistant to most of the antibiotics we've used in the past. Surgeons must keep in mind that no amount of antibiotic is going to be a substitute for strict adherence to preoperative and intraoperative attention to sterile technique. All ophthalmologists need to take this into account when deciding what they're going to do to prevent endophthalmitis.

"In the past, when a patient developed an infection, a team of infectious disease experts would be brought in to examine everything associated with that surgery to determine where the bacteria came from," he recalls. "With good sleuthing, we usually could identify the source. Normally,

the ocular surface is already colonized with a variety of resident surface flora, including the common bacteria *Propionibacterium acnes* followed by coagulase-negative *Staphylococcus*, *Corynebacterium*, *Streptococcus sp.*, *Enterococcus sp.*, and to a lesser extent gram-negative bacteria and fungi. In one case I was made aware of, an eye had become infected with the intestinal microflora *Morganella morganii*, which is not a common organism to find inside the eye, to say the least. How could an organism get from below the waist into the eye? The answer: poor hygiene. Not on the part of the patient, but a member of the surgical team.

"The infectious disease team came in and swabbed everything, including all body parts of the patient and everyone who was in the OR," he continues. "In this instance, the patient didn't carry the organism, but one technician did. Apparently, after multiple cases, the tech went to relieve herself and was not scrupulous enough about thorough washing of her hands, and rescrubbing as if it were the first case of the day."

Ensuring Sterility

Dr. Kershner points out that there are a number of steps every practice should take to minimize the chance of contamination during surgery. First, policies designed for this purpose should be stated and enforced.

- **Make sure your techs understand that they have to be scrupulous about sterility.** Dr. Kershner notes that when the patient load is heavy, people may drop their guard. "In many surgical centers, they're turning over those rooms pretty fast, and it's easy to skip a step in the preoperative scrub routine, such as rushing the scrub or using an antiseptic lotion as a substitute for a thorough hand scrub done with antiseptic soap and a brush," he says. "Of course, the one

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The Transzonular Approach

One approach to placing a drug, or drugs, inside the eye has been to place a bolus of drugs into the vitreous, usually by inserting a cannula through the zonules. Cynthia Matossian, MD, FACS, founder and chief medical officer of Matossian Eye Associates, says she used to follow that protocol, placing an antibiotic and steroid combination through the zonules into the vitreous. However, she eventually stopped. “It’s a bit of a blind maneuver, because you have to pop the cannula through the zonules under the iris without direct visualization,” she explains. “Then you place the product, which is like a white milkshake, into the anterior vitreous. There’s a learning curve for the injection technique, and not many ophthalmic surgeons feel comfortable doing it.”

Like many surgeons, Sheri Rowen, MD, who practices at NVision Eye Centers in Newport Beach, California, says she was never comfortable with the idea of placing a bolus of triamcinolone and antibiotic into the eye through the zonules. “Some people found that approach to be within their comfort level, but a lot of us didn’t,” she notes. “One reason I never used that protocol is that it can cause floaters; the patient has to see through the triamcinolone for a while. Retinal detachments have also been reported. I wasn’t comfortable with that, nor did I feel I needed that in order to give the patient a good outcome. In addition, some doctors have had problems with some compounding pharmacies.”

“Now we have two FDA-approved products [available soon] that can deliver a steroid in the post-cataract period,” Dr. Matossian adds. “I’d rather use one of these two options than a non-FDA-approved product—and they won’t require placing anything into the vitreous.”

—CK

time you don’t do a proper scrub is the one time that you’re going to contaminate the patient and end up with an infection.”

- **Create a written protocol describing exactly how every eye should be prepped.** “You should have a written protocol specifying how to properly prep an eye for surgery,” says Dr. Kershner. “I’ve seen all kinds of poor protocol. I’ve seen the OR crew put in a couple of drops of betadine followed by a half-hearted wipe of the eyelids with a cotton swab, and then decide that’s good enough. I’ve seen doctors fail to exclude the eyelashes and eyelid margin from the operative field and then drag instruments over them. These types of mistakes will eventually get you into trouble.

“In fact, if you want to go after the resident flora, or more importantly, the transient microbial flora, you have to be meticulous about the preoperative preparation of the patient—what

touches the eye, what gets into the eye, what gets out of the eye, and how and what is used to assure strict antisepsis,” he continues. “Antisepsis doesn’t work unless the antiseptic agent reaches every surface of the skin, eyelashes, and bulbar, palpebral, perilimbal and forniceal conjunctiva, and is left on those surfaces for a significant amount of time.”

- **Take the time to train your techs to follow sterile procedure, yourself.** “I don’t leave technician training to someone else,” says Dr. Kershner. “Maybe they received good training before working with me, maybe they didn’t. But the surgeon is the one who has to make sure everything is done correctly. So, I show my ophthalmic medical technologists, scrubs and OR nurses exactly how I expect them to scrub before surgery.”

- **Set an example.** Dr. Kershner says that he always makes sure to follow his protocol to the letter. “I make

sure that I’m a good example—that I always scrub properly and for long enough to make a real difference,” he says. “I never scrub halfheartedly and throw on some sanitizing gel as a substitute for a thorough scrub.”

- **Make it clear that being the cause of contamination is grounds for dismissal.** “I explain that if anyone doesn’t follow this routine each and every time, they can look for a job elsewhere,” Dr. Kershner says. “I tell them, ‘If we get a case of endophthalmitis, we’re going to go looking for the culprit, and if it’s you, you’ll lose your job.’”

Preoperative Pearls

Once the basic rules regarding sterility have been established, these strategies will help ensure that no unnecessary sources of contamination make their way into the OR:

- **Examine the patient preoperatively.** “I’ve always believed that the surgeon should see the patient before the surgery—and not just after the patient has been prepped and is in the OR,” says Dr. Kershner. “Sometimes the surgeon hasn’t seen the patient for weeks. I’ve had patients say they wanted to finish the golf tournament, or go up north and visit the kids and think about surgery; then they call two months later and say, ‘OK, let’s do it.’ If that happens, my staff will tell the patient we have to see him again to re-examine and go over everything. The patient may have developed a cutaneous inflammation or infection—acne rosacea, seborrhea or blepharitis. Perhaps the signs of these were missed during the last examination, but those conditions need to be addressed before contemplating surgery. The patient may now be on antibiotics for some reason, or have recently had dental surgery, or have a pulmonary or urinary infection. It can get pretty expensive and time-consuming to discover this kind of thing at the

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last minute when the patient is in the holding area ready for surgery—not to mention the patient’s disappointment. Or worse, we may put the patient at risk by not discovering it at all.”



• **Look carefully at the patient’s chart.** “As the surgeon, you need to stop before and between cases, take a breath, and look carefully at the history of the patient you’re about to operate on before commencing surgery,” notes Dr. Kershner. “I’ve seen cases in which concerns regarding symptoms and signs were noted in the chart, but the surgeon who reviewed the chart missed them. I’ve reviewed other cases where the surgeon did see the patient prior to surgery, but zoomed in and out without doing a careful exam,” he says. “As a result, the surgeon missed something that could have put the patient at risk. A little time spent in advance of the surgery could make all the difference between an uneventful surgical case and a courtroom.”

• **Check for infections elsewhere in the body.** “Doctors often don’t ask about or check to see if the patient has an infection elsewhere in the body, such as a urinary tract infection,” notes Dr. Kershner. “These individuals have a certain degree of bacteremia; they’re already contaminated. Infections elsewhere can end up becoming systemic infections, and those organisms sometimes can show up in the eye. If these factors are not reviewed by the surgeon, and noted in the patient’s record, then they can be missed.”

• **Train your staff to note potential problems and bring them to your attention.** “I always remind my personnel that if anything is discovered—even at the last minute—I want to hear about it,” he says. “Unfortunately, taking the history is usually relegated to the lowest person on the totem pole, so the person who does ask the right questions may not want to bother the doctor with the information—information that may be critical to the patient’s well-being. Tell your

staff, ‘If the patient has a systemic infection, let me know. If the patient just had a boil on his neck lanced, point that out to me.’”

• **Talk to the patient prior to surgery.** Dr. Kershner advises: “Ask the patient: ‘How are you feeling? Have you been sick recently? Have you had any procedures performed, such as dermatological, dental or urinary tract procedures? Have you had a colonoscopy? Are you on any medications that you weren’t on the last time I saw you?’ This is part of our job as doctors. It’s the surgeon who doesn’t take the time to do this before surgery who gets in trouble after surgery.”


*“It’s critical that
your injection be
preservative-free and
the proper dose.”*
—Nick Mamalis, MD


Dr. Kershner adds that you shouldn’t wear a mask when talking to the patient. “Let the patient see that it’s you, and make it clear to the patient by your demeanor and the questions you ask that you’re concerned about his or her welfare,” he says. “Finally, don’t wait until the patient is prepped and in the OR to have this conversation. If that’s the norm for you, think about changing your approach. Talking to the patient in the OR is too late.”

During the Surgery

These intraoperative strategies will help reduce any chance of infection:

• **Minimize your instrumentation.** “There’s usually no need to put instruments in and out of the eye multiple times during cataract surgery,” notes Dr. Kershner. “Every time you

do that you increase the risk that bacteria will get inside the eye.

“In general, you should always use the minimum number of instruments you can use,” he continues. “This has multiple advantages. First, fewer instruments means less sterilizing and managing of tools before, during and after the procedure. Second, the less often you introduce foreign objects into the eye, the safer the procedure becomes. Third, it’s efficient, meaning it takes less time to complete your surgical task and the patient spends less time under the microscope. That’s important because the less time the procedure takes to complete, the lower the risk that something bad will happen while you’re working in the eye.

“An efficient and well-executed procedure also translates into faster recovery and a better outcome for the patient,” he continues. “Show me a doctor who uses 15 instruments and takes 20 minutes to do the surgery, and I’ll show you a patient with corneal and macular edema and weeks before they achieve clear vision. Of course, being efficient doesn’t mean you have to rush. Hurrying is never in the patient’s best interest.

“If you need a special instrument,” he adds, “the tech can easily grab a sterile, sealed blister pack with the additional tool.”

• **Know exactly what you’re injecting.** “It’s critical that your injection be preservative-free, and the proper dose,” says Dr. Mamalis. “If you’re going to inject moxifloxacin, some studies have shown that one-tenth of a cc of preservative-free 0.5% moxifloxacin is safe and nontoxic.”

• **Inject through the side-port incision.** “First of all, make sure that your primary wound is watertight,” says Dr. Mamalis. “Then, at the conclusion of the case, you can make the injection through the side-port incision into the anterior chamber. Injecting through the small, less-than-1-mm side-port incision avoids disturbing

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the main incision.”

- **Make sure your wound is absolutely watertight.** “A leaky wound is the most serious risk factor for post-operative endophthalmitis,” notes Dr. Mamalis. “Studies, including some done at our institution, have found that a wound leak increases the risk of endophthalmitis 44 times. Not 44 percent, but 44 times! For that reason, we’re very compulsive about checking this before we leave the OR.

“To ensure that the wounds are watertight, we hydrate the wound and stab incisions,” he explains. “Then we bring the anterior chamber up to physiological pressure, dry the incisions with a Weck-Cel sponge, and put gentle pressure on the eye at the limbus on the opposite side. Under high-power microscopy we make sure there’s absolutely no leak. If there’s any question, you can put a little fluorescein on there and perform a Seidel test. In the uncommon situation that we can’t get the wound to seal, we’ll put in a suture.”

Two Final Thoughts

Last but not least, these two strategies will help make sure that you’re giving your patients the greatest chance of an excellent outcome:

- **Accept responsibility for any less-than-ideal outcomes.** Dr. Kershner says this was ingrained in him when he trained as a general surgeon before going into ophthalmology. “We were taught that the surgeon is responsible for everything that happens to the patient,” he says. “If you had an infection postoperatively, it was your fault and most likely secondary to poor surgical technique. The surgeon simply did not blame the patient. Assuming responsibility for any problems that might occur following surgery will ensure that you go the extra mile to prevent every type of contamination that’s within your ability to control.”

- **When new options appear, try**

them—and share your experience.

“The only way we can really know what works best in our hands is to try it on our patients,” says Dr. Rowen. “We can read how well something worked in an FDA study, but that doesn’t necessarily reflect how well it will work in the real world. I prefer to stick with products that are approved, but once they’re approved, I think it’s important to try them and share what we learn. That’s how we decide what persists in our field.”

Dr. Matossian notes two new products that are FDA-approved that should be available shortly. “One is called Dexycu [Eyepoint]; it’s a 9% dexamethasone intracameral ophthalmic steroid suspension that’s placed under the iris using a 25-ga. bent cannula at the conclusion of cataract surgery,” she explains. “Through its ‘Verisome’ technology, it delivers more steroid at the beginning; then over a 30-day period, it bio-erodes and disappears. Thus, it mirrors our steroid tapering schedule.” This may allow surgeons to eliminate the steroid drop with an FDA-approved alternative.

“The second approved product that should be available soon is called Dextenza,” Dr. Matossian says. “It’s an intracanalicular insert that contains dexamethasone 0.4%; it’s placed into the inferior punctum like a punctal plug at the conclusion of cataract surgery. It elutes dexamethasone for 30 days to treat postoperative pain. It’s another option that will allow us to eliminate postoperative steroid drops. Of course, there will be some situations in which the punctal anatomy may not be suitable for inserting the Dextenza plug. I think that with experience, we’ll know which product is better suited in specific circumstances.”

She adds that the possibility of skipping an NSAID drop is also on the horizon. “There’s a punctal plug in the pipeline that contains an NSAID that elutes over time, but that’s not available yet; it’s still in clinical trials,” she

says. “If that comes out, we could place the antibiotic and steroid in the eye and put the NSAID-eluting plug in the inferior puncta. Or, we could put the NSAID-eluting plug in the superior puncta and put a Dextenza plug in the inferior puncta. Either way, the procedure would be totally dropless, postop.”

Dr. Rowen adds that new lotepred-nol nanoparticle formulations are now available in drop form. “Those include Inveltys 1% ophthalmic suspension [Kala Pharmaceuticals] and Lotemax sub-micron ophthalmic gel 0.38% [Bausch + Lomb],” she says. “These have novel formulations and are designed to work for a longer time than previous modalities.”

Dr. Kershner points out that ophthalmologists—like people in general—tend to be resistant to trying new things. “It’s difficult to get doctors to change their habits, even when the proof that they should is staring them in the face,” he says. “Doctors like to make decisions based upon their clinical experience, but their clinical experience is often not based on real data. If surgeons have always done it a certain way and it seems to be working, then they don’t change. But ophthalmologists need evidence-based studies for doing what they do.

“Surgeons should be constantly re-evaluating their protocols to see if there’s a better way to do things,” he adds. “Review the literature. Go to the meetings. Look at what other surgeons are doing. Just because you’ve always done it that way doesn’t mean you should continue to do it that way.” **REVIEW**

Drs. Kershner and Mamalis report no financial ties to any product discussed. Dr. Rowen has consulted for Bausch + Lomb, Kala, Sun Pharma and Eyepoint. Dr. Matossian is a consultant for Eyepoint, Ocular Therapeutics, Ocular Sciences and Impri-

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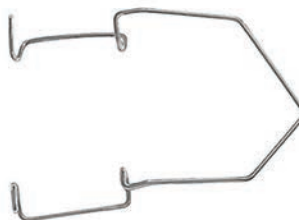
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Cataract Surgeons Eye New Techniques

Walter Bethke, Editor in Chief

On our annual survey, surgeons share their best practices for safe, effective results.

Today, cataract surgeons have more options than ever. They have multiple ways of making a capsulotomy, attacking the nucleus and even controlling miosis during surgery. The results of this year's cataract surgery survey may give you a clearer picture of how some of your colleagues are adopting these new methods. This year, for example, a slightly higher percentage of surgeons than in previous years say they're giving femtosecond a try; some are still hesitant to dive into intraoperative wavefront aberrometry; and quadrant division is the preferred way to break up a cataract.

These are just some of the results from this year's survey on cataract surgery. This month, 2,001 surgeons of the 12,509 who received the survey opened it (16 percent open rate) and, of those, 110 fully completed the survey. To see how your preferences jibe with theirs, read on.

Femto Use Creeps Up

This year, a slightly higher percentage of respondents said they use the femtosecond laser for some phase of their cataract surgeries. Thirty-nine percent of the surgeons say they use the femtosecond (up from last year's 36 percent), and 1 percent (one sur-

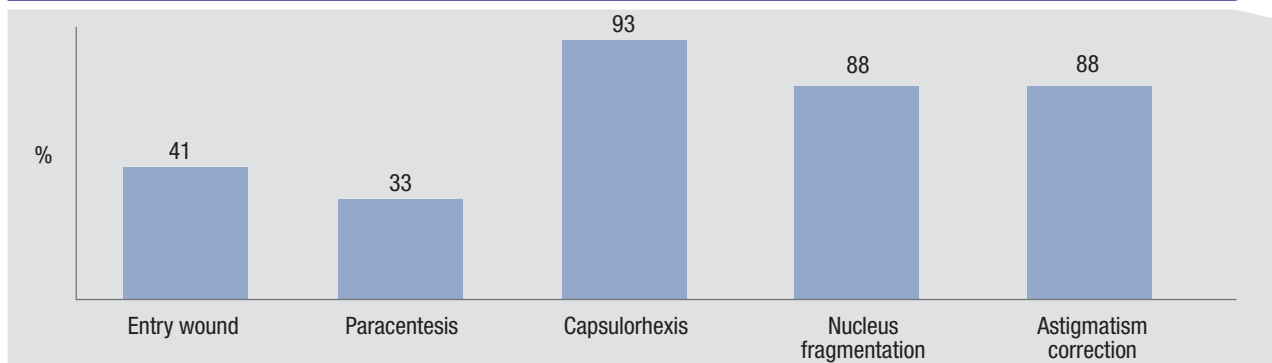
geon) says he uses the Zepto capsulotomy device. Among the femto users, it's used most commonly to create the capsulorhexis (chosen by 37 percent). The popularity of its other uses appears in the graph on the facing page. The surgeons who use this technology say they appreciate the precision, and its usefulness in certain cases.

A surgeon from Pennsylvania lists what he likes about the technology: "Lower phaco energy, great astigmatism correction (especially with-the-rule) and a good patient experience," he says. An ophthalmologist from Louisiana agrees, saying, "Femto is safer, creates a more precise capsulotomy and allows the management of mild astigmatism. Femto is essential for a very dense nuclear sclerotic cataract and I will use it in 100 percent of these cases, regardless of reimbursement."

Kerry Hunt, MD, of Raleigh, North Carolina, says he thinks the femto is most useful in complicated cases. "I do like the 'perfect' capsulorhexis but I don't need it for that," he says. "Fragmentation is not possible in the most difficult cases where it would ideally be the most helpful. I think its greatest utility is in the setting of zonulopathy to get a good rhexis."

Other surgeons are less impressed

Surgeons' Use of Femtosecond for Cataract Surgery (Among Those Who Use it Regularly)



by femtosecond technology, for a variety of reasons, including the high cost.

“It’s useful for capsulorhexis for mature white cataracts,” says a New York surgeon. “Otherwise I do not find it valuable as compared to my standard technique. Time and expense are significant issues as well.” William E. Holcomb, MD, from Cullman, Alabama, needs to see more data. “There is no peer-reviewed evidence showing that either device improves clinical outcomes vs. a procedure performed by a good, experienced cataract surgeon,” he says. A surgeon from Oregon feels similarly. “Femtosecond cataract surgery and Zepto are solutions looking for a problem,” he says. “[It’s] more expensive to be borne by the ambulatory surgery center and the patient without demonstrable benefit.”

“I have performed [femtosecond cataract surgery] in the past but no longer do it,” says a surgeon from Mis-

souri. “I found it cumbersome. Positioning of the incisions was problematic at times. I also had two episodes of posterior capsule rupture due to gas buildup behind the cataract.”

Breaking up the Nucleus

One of the primary areas where the art and science of cataract surgery come together is in the fragmentation of the nucleus. Many surgeons have their own particular way of attacking it that they feel works best for them.

On this year’s survey, the most popular nucleofracture technique was quadrant division, chosen by 41 percent of the respondents. The next two most popular techniques were phaco chop (19 percent) and stop-and-chop (18 percent). All of the techniques chosen appear in the graph on p. 48.

“It’s simple, and I can use it on all grades of cataracts,” says a quadrant-division proponent from New Jersey.

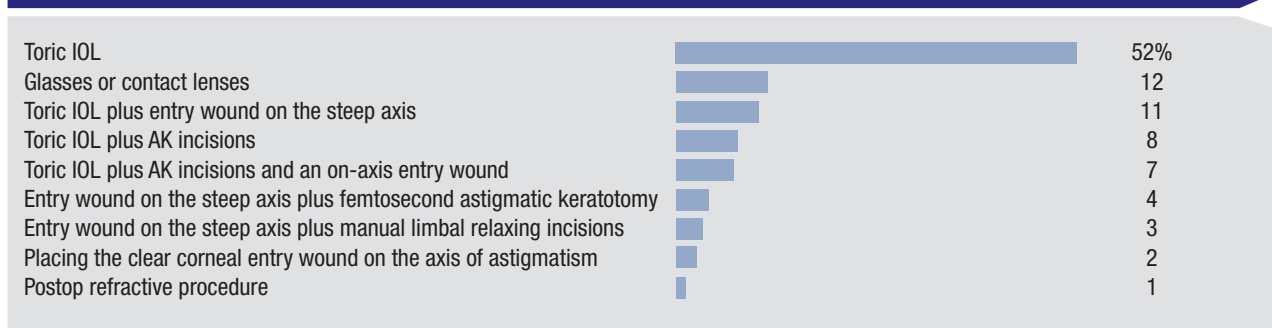
Alan Baribeau, MD, a surgeon from San Antonio, also likes the mechanical benefits of the technique: “It controls the fraction and phaco-ing best for the wide range of cataracts I have in my practice,” he says.

Several surgeons like the safety of quadrant division. “It works very well without passing instruments posterior to the lens equator,” an Arizona surgeon avers. “It puts less stress on the capsule zonules,” adds a doctor from Ohio.

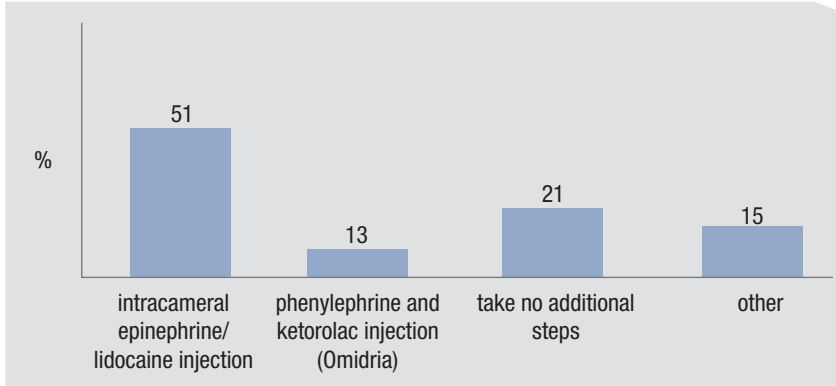
Surgeons who prefer phaco chop say they use it because it minimizes the phaco power used in the eye.

“[I like] the speed of the nucleus disassembly and low ultrasound energy into the eye,” says Ivan Mac, MD, Charlotte, North Carolina, who uses phaco chop. A surgeon from Utah is thinking along the same lines: “It allows almost all the ultrasound to be expended at the iris plane or below, and wastes no energy with unneces-

Management of Pre-existing Astigmatism



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sary, inefficient sculpting,” she says. “One can adjust fragment size to density. I prefer cross-action vertical chop with circumferential disassembly for brunescient nuclei.”

“Phaco chop allows me to perform my cases with minimal phaco energy and minimal stress on the cornea,” says Robert Bullington Jr., MD, of Phoenix.

Ben Hasty, MD, of Panama City, Florida, details his technique: “Phaco chop works in soft and hard lenses, and uses familiar tools, with the Seibel chopper already used as a ‘finger.’”

For the stop-and-chop adherents, the safety and stability of the technique are important to them.

“Debulking the nucleus with the central trough decreases overall cumulative dispersed energy, and helps protect the endothelium by allowing better control of chopped pieces,” says Alabama’s Dr. Holcomb. A Connecticut surgeon agrees, saying, “It’s

easiest to perform efficiently with little energy.”

“I like to see the tip of the instrument at all times,” says an Illinois ophthalmologist. “I cannot do that with horizontal chop.”

Tackling Cylinder

As in previous years, the most popular way surgeons correct astigmatism is with toric intraocular lenses, chosen by 52 percent of the respondents (53 percent in 2018). The second most popular choice was glasses and contact lenses (12 percent), followed by the combination of a toric IOL and the entry wound on the steep axis (11 percent). The full range of options selected by surgeons appear in the graph on p. 47.

A Pennsylvania surgeon likes the toric IOL’s predictability in certain cases. “It’s most predictable for moderate or severe astigmatism,” he says.

“I generally use femto [AK] for mild astigmatism.” Eileen Wayne, MD, Moline, Illinois, agrees that “it’s very accurate.” Gregory Cox, MD, of Hamilton, New Jersey, calls toric IOLs “accurate and predictable.”

“The toric IOL is safe, reliable and predictable,” says Dr. Holcomb. “I’ll use it if the preop keratometric cylinder is 0.75 D or greater against-the-rule, or 1.25 D or greater with-the-rule.” Greensboro, North Carolina, surgeon Karl Stonecipher also shares his protocol: “For 0.75 D or less I do on-axis incisions and laser astigmatic incisions,” he says. “For 1 D or more I do toric IOLs.”

“I have generally seen very good to excellent results using this technology,” says Phoenix’s Dr. Bullington.

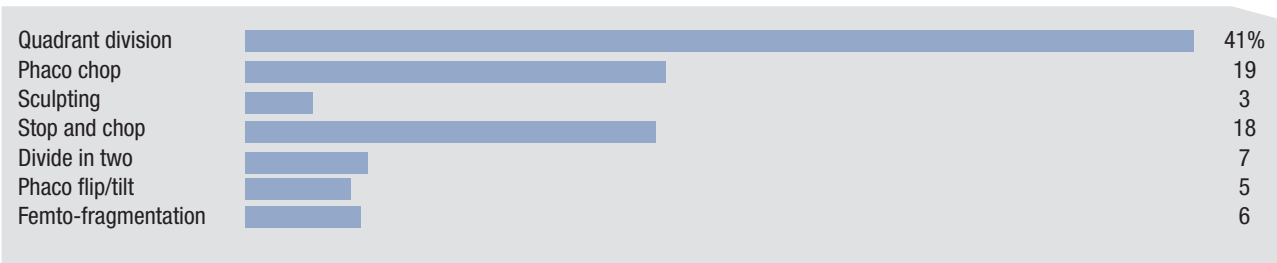
As for the tried-and-true options of spectacles and contact lenses, surgeons say it’s usually a matter of price. “Patients don’t want to pay for a toric lens,” says Christopher Papp, MD, of South Lyon, Michigan, who adds that he does provide toric lenses and limbal relaxing incisions for some patients who, presumably, are willing to pay for them.

Items of Interest

Surgeons also weighed in on other aspects of surgery, such as intraoperative wavefront aberrometry and maintaining an adequately sized pupil.

• **Intraoperative aberrometry.** On the survey, a third of the respondents use this technology to help select an IOL, with 11 percent deeming it

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Intraocular injection of combined antibiotic/steroid	7
Combined topical mixture of antibiotic/anti-inflammatory	9
Topical antibiotic and a combined topical mixture of steroid and NSAID	16
Topical steroid plus intraocular antibiotic injection	7
Other	13

excellent, 13 percent saying it's good, 8 percent calling it fair and 0.9 percent (one surgeon) saying that it's poor.

"This technology provides IOL power verification for post-refractive patients and adds confidence to my decision-making when choosing premium IOLs," says a surgeon from Missouri.

Dr. Mac says he's seen an improvement in his results. "I have objective clinical data that proves an improvement in my refractive clinical outcomes," he says.

For the surgeons who only rate it as fair, they say it hasn't separated itself from conventional methods.

"It hasn't proven to be superior to calculations from the ASCRS website in my patients," says Raleigh's Dr. Hunt. "I use it only in post-refractive cases to avoid big errors." A surgeon from Utah agrees, saying, "Most of the time there is very little value [to the technology]. The in-office measurements are good. It is beneficial in post-refractive cases [however]."

• **Pupil dilation.** Fifty-one percent of surgeons say they use a mixture of epinephrine and lidocaine, injected intracamerally; 21 percent take no additional steps; 13 percent use Omidria (Omeros, Seattle); and 15 percent use another method of pupil management (including phenylephrine/lidocaine injections, Malyugin rings and epinephrine in the irrigation bottle).

• **Infection/inflammation prophylaxis.** Here, the most popular answer was the conventional use of a topical anti-inflammatory and antibiotic postop (48 percent), followed

by the use of a topical antibiotic and a combined topical mixture of a steroid and an NSAID (16 percent). Thirteen percent use another method (usually some permutation of intracameral drug combined with a topical drug or mixture postop). Nine percent use a combined mixture of antibiotics and anti-inflammatories, and 7 percent inject a combined antibiotic/steroid. The respondents' answers appear in the graph above.

Surgical Pearls

The surgeons also provided their number-one piece of advice.

"Have the patient's head in exactly the right position for their particular orbital/lid/head/neck configuration before ever touching the eye," recommends Dr. Holcomb. A surgeon from Utah shares a safety tip: "Don't allow the chamber to bounce around, and prevent both collapse and over-deepening," she says.

A couple of surgeons have thoughts on the removal of cortex: "Remove subincisional cortex first during I/A before proceeding to other areas of cortex," says a Pennsylvania ophthalmologist. And Jeff Whitman, MD, of Dallas, advises, "Irrigate/aspirate cortex centripetally—not with radial pulling."

Though there are many techniques a surgeon can use, a doctor from New York says it's better to simplify. "Learn a technique. Perfect it," he says. "Your patients will be happy—and so will you!" **REVIEW**

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How to Manage MIGS Complications

Alexandra Skinner, Associate Editor

Surgeons offer mitigation techniques for common MIGS complications.

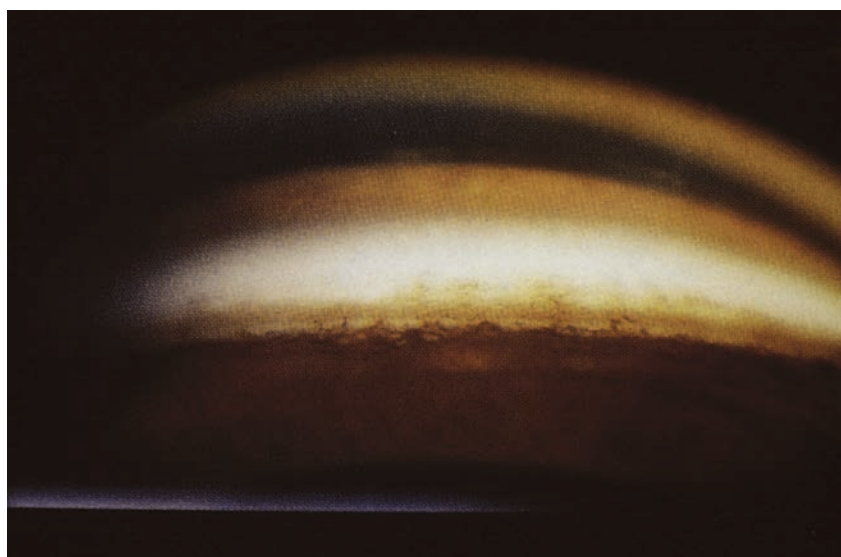
The goal of minimally-invasive glaucoma surgery is a noble one: Offer patients with mild or moderate glaucoma an option that can treat their disease without exposing them to the risks associated with more invasive procedures. However, even the best-laid plans can go awry, and you sometimes have to manage MIGS complications.

In this article, surgeons detail what complications could arise during MIGS procedures and offer advice on how to manage them. We'll

start by discussing general complications that can occur across many of the MIGS procedures, regardless of which outflow or inflow source the doctor is tackling. Then we'll discuss the specific procedures, what each accomplishes, their most common complications and how to manage them.

General MIGS Complications

While MIGS is an effective way to manage glaucoma in some patients,



Steven Vold, MD

Figure 1. Locating the trabecular meshwork is a crucial step in many MIGS procedures. Fort Worth, Texas' Brian Flowers, MD, says learning the anatomy of the angle is important since many MIGS procedures require you to place something in a particular location.

Slit Lamps

Brilliant Observation

there are complications associated with each procedure. However, as Robert Noecker, MD, MBA, the director of glaucoma at Ophthalmic Consultants of Connecticut says, “MIGS procedures aren’t problem-free, but they have fewer problems than standard procedures, and these problems are quite manageable. You just have to be aware of the potential issues. If you address them during the procedure or immediately after, then you should be successful.”

Common issues associated with MIGS include challenges using a gonioscope, locating the trabecular meshwork, and preventing and managing excess blood reflux.

Since many procedures require the use of a goniolens, Reay Brown, MD, a glaucoma specialist practicing at Atlanta Ophthalmology Associates, says, “Perhaps the most important thing is to absolutely insist that you achieve a good view before you perform one of these procedures.” Dr. Noecker says manipulating a goniolens can be one of the toughest aspects of an angle procedure. “Using the goniolens with your non-dominant hand with the tool in your dominant hand takes getting used to,” he adds. He urges users not to apply too much pressure on the cornea when using the gonioscope, explaining, “Wrinkling is possible, which will further obstruct your view of the angle.”

Dr. Brown remarks that the goniolens is not ideal, and says he’s working to achieve a better and wider view. To accomplish this, Dr. Brown uses a disposable goniolens that’s like a contact lens. “You don’t have to hold it in place, which is very helpful,” Dr. Brown says. While he acknowledges gonioscopy technology’s need to improve, he is adamant that it can and will improve.

Locating the trabecular meshwork is another crucial step in performing many MIGS procedures. “It’s very

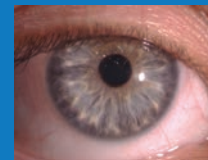
important to learn the anatomy, as all of these procedures require you to place something in a particular location,” says Brian Flowers, MD, a glaucoma specialist and managing partner of Ophthalmology Associates in Fort Worth, Texas. “You can practice viewing the angle in your office by doing a lot of gonioscopy,” he says. Dr. Brown suggests staining the meshwork with Vision Blue, saying that he’s found that to be a big help.

Another potential issue to be aware of is blood reflux. Since the main goal of MIGS is to lower IOP, this makes it easier for blood to reflux back into the canal, Dr. Noecker points out. While experiencing some blood reflux can serve as a confirmation that you’re in the right area, Dr. Noecker adds, “It’s like tapping oil, it’s a good thing...however it can become excessive.” In order to prevent or reduce blood reflux, Dr. Noecker says that viscoelastic is helpful. “I like to keep the pressure a little bit on the high side to push back on the blood. Doing this makes it harder for the blood to enter the eye. That usually works quite well. You may have some blood cells floating around, but not a frank hyphema, which would obscure the vision a lot.”

Another more intuitive way to limit blood flow is to minimize trauma to the iris or ciliary body, which can bleed more readily than an area like the trabecular meshwork. “When you do these canal-based procedures you should get a little blood,” says Dr. Noecker. “But if you’re getting a lot of blood, you may have traumatized the ciliary body or the iris.” To combat this, he suggests inflating the entry chamber very wide. “This can help to push the vascular tissues away. Also, keeping the pressure a little on the higher side is helpful in getting a good view and confirming that you’re entering the canal and not getting posterior, where the ciliary body is.”



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Trabecular Outflow Techniques

Moving on to techniques that increase trabecular outflow, these MIGS procedures deal with removing or bypassing part of the trabecular meshwork or Schlemm’s canal in order to increase flow through the conventional outflow path.

- **iStent and Hydrus.** Glaukos’ iStent and iStent Inject can be inserted into Schlemm’s canal, effectively bypassing the trabecular meshwork and creating a path for aqueous humor to move from the anterior chamber into the canal to restore natural outflow. Similarly, Ivantis’ Hydrus can be inserted into Schlemm’s canal; it aims to open the channel so blocked fluid can flow more freely. The two procedures have similar challenges: implanting the device fully and managing hyphemas.

For both the iStent and the Hydrus, it’s possible to inject the device into the wrong location, such as the sclera or the posterior wall. “The issue is making sure it’s placed in the

right location,” says Dr. Flowers referring to the Hydrus. However, Dr. Brown notes, “You can tell when it’s stuck because you can’t move it along the canal.”

“In the case of a superficial implantation, the iStent doesn’t sit properly and the rings are too visible.” Dr. Brown continues, “The fix is to simply pull back, flatten the approach and then it will slide freely along the canal.” Rotating the head farther can help to position the meshwork into an almost vertical position, creating an easy, flat target, surgeons say. “It’s an intraoperative issue; you simply adjust your positioning,” Dr. Flowers says.

When it comes to managing a hyphema or a microhyphema, it’s important to remember that, because you’re performing a pressure-lowering procedure, blood will flow more readily and you should expect to have to deal with at least some blood reflux, remarks Dr. Noecker. “Rinse out the blood that refluxes when you tap in but at the same time, prevent

it from accumulating overnight,” he says. Blood reflux can be common in these procedures, which is why understanding how to manage it is crucial. “You just keep washing it out and eventually it stops,” says Dr. Brown. “I haven’t had a problem with blood postop.”

Another issue to be aware of is reimbursement. If an insurance company deems a patient’s glaucoma case too advanced, it may deny reimbursement for the iStent or iStent Inject and be more in favor of a procedure that more significantly lowers IOP. “Insurance companies are very strict about denying coverage for patients who have more serious disease,” Dr. Brown says. This is where it can be beneficial to know how to perform multiple MIGS procedures and interpret which will work best for a given patient, depending on the severity of her glaucoma versus how much IOP you are looking to lower, surgeons say.

- **Trabectome.** The Trabectome aims to improve outflow by using electrocautery to ablate a portion of the trabecular meshwork. Complications here sometimes arise as a result of difficulty in maneuvering the device, which might mean less angle access, issues with coordination and potential thermal injury.

“[The Trabectome] is somewhat cumbersome to use because it’s a little bit big,” says Dr. Noecker. “Since you rely on electrocautery and are therefore using a thermal effect, you have to have some fluid flowing to keep the temperature down. The worst-case scenario is you can burn something you don’t want to burn.” As far as avoiding that, Dr. Noecker says technique is important, “The main thing is to have a gentle touch with the gonioscens,” he says. “You can get a wrinkly view, which makes it hard to keep the Trabectome just in that trabecular space. Don’t press down on the cornea to try to get all

Glaukos

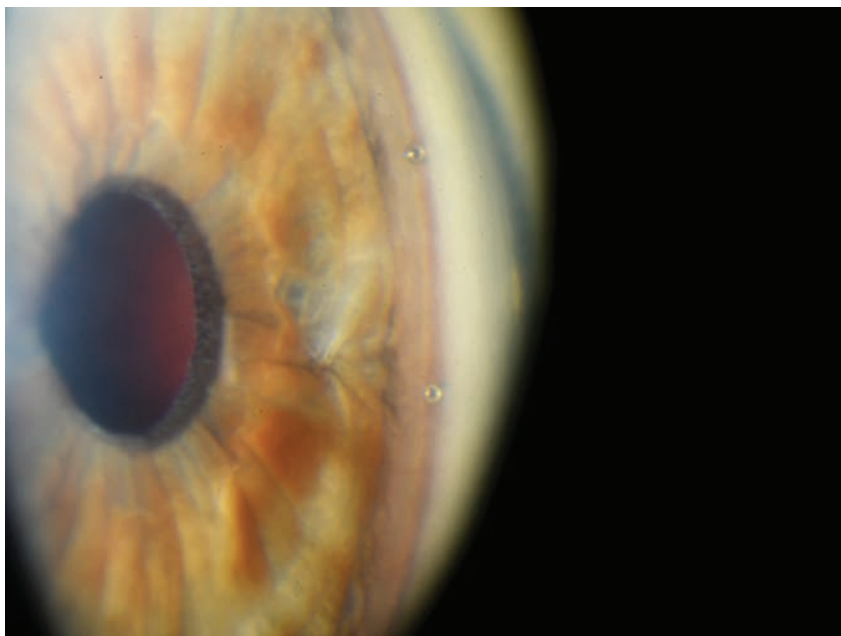


Figure 2. Surgeons say rotating the patient’s head can position the trabecular meshwork into an almost vertical position which creates an easy, flat target for the iStent or iStent Inject, helping the surgeon properly insert it into Schlemm’s canal.

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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

- Prolonged use of corticosteroids, including DEXYCU, 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

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 corticosteroids

Exacerbation of Infection

- The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of 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

- Use of a corticosteroid in the treatment of patients with a history of herpes simplex requires caution and may prolong the course and may exacerbate the severity of many viral infections
- Fungal infections of the cornea are particularly prone to coincidentally develop with long-term local steroid application and 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
- 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

Cataract Progression

- The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts

ADVERSE REACTIONS

- The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis

Please see brief summary of full Prescribing Information on adjacent page.

References: 1. DEXYCU[™] (dexamethasone intraocular suspension) 9% full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. December 2018. 2. Donnenfeld E, Holland E. Dexamethasone intracameral drug-delivery suspension for inflammation associated with cataract surgery: a randomized, placebo-controlled, phase III trial. *Ophthalmology*. 2018;125(6):799-806. 3. Data on file. EyePoint Pharmaceuticals, Inc.



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**DEXYCU (dexamethasone intraocular suspension) 9%,
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1 INDICATIONS AND USAGE

DEXYCU (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure

Prolonged use of corticosteroids including DEXYCU 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.

5.2 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 corticosteroids.

5.3 Exacerbation of Infection

The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of 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.

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires 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 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.

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.

5.4 Cataract Progression

The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Increase in Intraocular Pressure [see *Warning and Precautions (5.1)*]
- Delayed Healing [see *Warnings and Precautions (5.2)*]
- Infection Exacerbation [see *Warnings and Precautions (5.3)*]
- Cataract Progression [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

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

The following adverse events rates are derived from three clinical trials in which 339 patients received the 517 microgram dose of DEXYCU. The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis. Other ocular adverse reactions occurring in 1-5% of subjects included, corneal endothelial cell loss, blepharitis, eye pain, cystoid macular edema, dry eye, ocular inflammation, posterior capsule opacification, blurred vision, reduced visual acuity, vitreous floaters, foreign body sensation, photophobia, and vitreous detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of DEXYCU (dexamethasone intraocular suspension) in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice and malformations of abdominal wall/intestines and kidneys in rabbits at doses 7 and 5 times higher than the injected recommended human ophthalmic dose (RHOD) of DEXYCU (517 micrograms dexamethasone), respectively [see *Data in the full prescribing information*].

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. There is no information regarding the presence of injected DEXYCU in human milk, the effects on breastfed infants, or the effects on milk production to inform risk of DEXYCU to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DEXYCU and any potential adverse effects on the breastfed child from DEXYCU.

8.4 Pediatric Use

Safety and effectiveness of DEXYCU in pediatric patients have not been established.

8.5 Geriatric Use

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

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of the air out and get a good view. Pressing the cornea can deflate it. I put viscoelastic on the cornea so that the gonioscopes can kind of float on that and give you a good view.”

Surgeons say that they can only treat between 90 and 120 degrees using the Trabectome, which, again, makes it important to understand the patient, his specific glaucoma case and IOP-lowering needs. “[The Trabectome] is sometimes not enough to have an impact,” remarks Dr. Brown. “The makers of the Trabectome are trying to make a comeback with some newer designs which may have a role in the future.”

- **Kahook Dual Blade.** This procedure completely removes a strip of the trabecular meshwork in order to increase outflow. “It’s kind of like [the Trabectome],” Dr. Noecker says, “but without the cautery part. It’s very straightforward and it’s a relatively inexpensive device, but you’re limited in how much of the trabecular meshwork you can open in one sitting.” It can involve complications that have already been discussed, such as problems using the gonioscope, accessing more than 120 degrees of the meshwork and dealing with blood reflux.

- **Circumferential trabeculotomy procedures.** This MIGS method lowers IOP by inserting a suture (GATT), or device (Trab360) into Schlemm’s canal, navigating 180 or 360 degrees around the canal, and then performing a trabeculotomy. Complications involve the suture or device getting stuck (which we’ll discuss in the next section), accidentally pulling it out of the canal and dealing with more blood reflux than usual as you remove the meshwork tissue.

Dr. Brown discusses what to do in the case of a device accidentally being pulled out. “Regarding the portion of the catheter that’s outside of the eye, it’s easy for that to get caught on something, or be pulled out. You

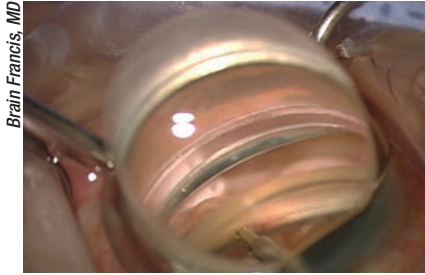


Figure 3. Ablation of the trabecular meshwork is seen through the white appearance of the outer wall of Schlemm’s canal to the right of the Trabectome tip. Dr. Noecker suggests using viscoelastic on the cornea to avoid wrinkling when using the gonioscopes. This can help provide a good view and aid in keeping the Trabectome in the trabecular space.

have to know how to deal with that portion of the catheter,” he says. “In that event you just start over. As you get more experienced, that shouldn’t happen.”

When it comes to blood reflux, Dr. Flowers says, “Each time you do a trabeculotomy you’ll get bleeding. [To manage this], it’s always important when you pierce the eye that you keep it pressurized afterwards. If you have the eye full of viscoelastic, you have to leave it in there for a while to tamp on the blood. Once you rinse the viscoelastic out, immediately make sure that the balanced salt solution goes right in so that the pressure stays above 20 mmHg while the viscoelastic discourages bleeding right afterwards. It’s transient; blood usually goes away within a few days.”

Dr. Brown agrees, saying, “It’s usually managed just by waiting. I’ve never had to re-operate on a patient.”

ABiC Procedures

An *ab interno* canaloplasty procedure seeks to improve outflow by catheterizing the canal and dilating the natural outflow pathways, including Schlemm’s canal, the trabecular meshwork and the distal outflow system. Complications as-

sociated with an ABiC procedure include overinflation of Schlemm’s canal and the device getting stuck. “I think the main complication could be overinflation of Schlemm’s canal with the Healon,” notes Dr. Flowers. “When you’re doing *ab interno* there are two ways to do it; you can do it with Sight Sciences’ device (the OMNI) which determines for you how much viscoelastic is going to be injected, or you can do it with the Ellexprobe (iTrack) where you control how much gets injected.” In regard to Ellex’s iTrack, Dr. Flowers continues, “When you’re doing *ab interno*, you don’t have to worry about a scleral window rupturing because you’ve injected too much viscoelastic, so you can inject a little more than you would in an *ab externo* procedure. It’s nice to be able to be a little bit more aggressive, but if you get carried away and overdo it with the injecting, you can create a Descemet’s detachment, which can be an issue.”

Dr. Flowers says that how you manage these complications depends on their location. “If you have a Descemet’s detachment and it’s superior, you can leave a little bit of air in the eye, which will tend to flatten it out,” he says. “Sometimes you can hit it, pop it with a YAG laser and the fluid will leak out. [However] I’ve never had a Descemet’s detachment that ultimately compromised the vision.”

When discussing the propensity for the device to get stuck, Dr. Flowers estimates it happens about 10 percent of the time; however he goes on to explain how to remedy this issue. “If you can’t advance it all the way around, you can do various maneuvers to try to advance it as far as possible,” he says. “A typical maneuver would be to pull back and then advance it again—a back-and-forth motion that breaks through the blockage.” Dr. Flowers offers additional management techniques: “You can put a little external pres-

sure on the eye where the iTrack is,” he says. “You can pull it out one way then turn around and go the other direction. If that doesn’t work, you inject and treat the areas that you can. Think about a circle; if you get a quarter of the way around one way, then halfway around going the other way, at least you can inject those areas and treat three quarters of the eye.”

More specifically, with regard to the OMNI, Dr. Flowers says, “It’s really a combination of canaloplasty and GATT, so it has similar complications.” The OMNI device first catheterizes and viscodilates, then performs a trabeculotomy. In terms of bleeding, Dr. Brown says that since viscodilation is done first, that reduces the blood reflux, both at the time of surgery and postop. “There’s more direct control of what you’re doing in this procedure as it’s less likely for the catheter to get caught on something or to have the tech inadvertently pull it out,” he says. While issues may not be as pronounced as those with GATT or an ABiC procedure, Dr. Noecker says there are things to be aware of. “Don’t do the procedure until the view is great. Pressurize the eye as much as possible during the procedure, which can help enhance the view so that the cornea is not wrinkling and you have a nice clear view of the trabecular meshwork. This also keeps the other structures away from the trabecular meshwork so you don’t traumatize them inadvertently. And the most important thing to prevent bleeding is to make sure the pressure is on the higher side.”

Subconjunctival Outflow

Using this technique, IOP is lowered by bypassing the conventional outflow pathway altogether. Here, aqueous humor moves from the anterior chamber into the subconjunc-

The Promise of MIGS

Many doctors choose to treat glaucoma using medication because trabeculotomies and tube shunts are seen as more aggressive approaches that carry inherent risks despite IOP-lowering efficacy. However, many patients don’t need a dramatic reduction in pressure. Wills Eye Hospital’s Marlene Moster, MD, presented an overview of minimally-invasive glaucoma surgery at the 2014 FDA Workshop in Washington, D.C., “Supporting Innovation for Safe and Effective MIGS.” She estimated that 75 to 80 percent of patients have the ability to control glaucoma symptoms using medication. By undergoing MIGS, patients can decrease their dependency on medication and therefore minimize risks associated with prolonged medicinal use, which include drug side effects, the medications’ financial burden and problems with adherence.

MIGS aims to lower IOP by improving outflow or reducing inflow from an *ab interno* approach. This can be achieved through bypassing or eliminating the trabecular meshwork, shunting aqueous humor into the suprachoidal or subconjunctival space or reducing aqueous humor production. MIGS differs from traditional procedures in patient head position, microscopic or gonioscopic view, as well as placement of the surgeon’s hands. There’s minimal trauma associated with MIGS because there’s less disruption to the normal anatomy of the eye, surgeons say. In most instances, this can lead to a quicker postop recovery, possibly allowing patients to resume day-to-day activities after only a short period of time.

MIGS procedures can also be combined in order to achieve higher efficacy. Since there are various ways in which MIGS seeks to lower pressure, should an initial procedure fail or not achieve desired results, a doctor can try another MIGS method. This is why it’s suggested to know how to perform more than one procedure, preferably ones that seek to lower pressure through different paths. Brian Flowers, MD, a glaucoma specialist and managing partner of Ophthalmology Associates in Fort Worth, Texas, suggests learning how to do a Schlemm’s canal procedure and also learning to do some form of gonioscopy-assisted transluminal trabeculotomy, or GATT. Learning procedures that lower IOP through different methods, he reasons, can allow you to analyze a patient and decide which MIGS would best suit her specific glaucoma case.

While MIGS isn’t as efficient in lowering IOP as a traditional surgical approach, these procedures can provide modest reduction in pressure, and they continue to show increases in efficacy as MIGS methods and devices advance. MIGS can decrease and, in some cases, completely eliminate the risks associated with traditional surgery, which is why it continues to gain popularity. Reay Brown, MD, a glaucoma specialist practicing at Atlanta Ophthalmology Associates discusses the aims of the procedures. “The goal is to lower the pressure, that’s number one, and number two is to get patients off medication as much as possible,” he says. “That’s also very important and is a great benefit to the patient. Reducing the medication burden is a gain financially, but it also helps with side effects.” Robert Noecker, MD, MBA, the director of glaucoma at Ophthalmic Consultants of Connecticut, says, “It’s a whole new era with these procedures and they’re certainly, as a group, safer than traditional glaucoma surgery.”

—A.S.

tival space, effectively creating a new drainage canal.

• **Allergan’s XEN gel stent.** Complications associated with inserting this device involve issues with patient facial anatomy, ensuring flow is es-

tablished and monitoring the patient postop.

“The biggest challenge is the injector itself,” Dr. Brown acknowledges. “Especially in the left eye, it can be hard to work over a high

cheekbone.” Similarly, Dr. Noecker notes, “It can be difficult depending on patient anatomy, as you ideally want to get the stent to inject between 11 and 1 o’clock superiorly underneath the eyelid.” In order to manage facial-anatomy complications, Dr. Noecker says, “You can use a second instrument to twist the eye in order to kind of move it away from the bad anatomy site. It takes a little practice, but you can rotate the eye a few clock hours, and then you have space to do the injection.”

For a successful procedure, flow from the anterior chamber into an internal bleb must be established. “You confirm this by increasing the pressure in the eye and washing the viscoelastic out,” Dr. Noecker says. “That’s an important step. Once the device is placed, you want to rinse the eye out and remove all the viscoelastic so that it doesn’t clog the tube. You want to establish that fluid is going through the tube and puffing up the conjunctiva to make a bleb. Then you can be confident in the function of the stent. If you don’t do that, the flow may not start and it’s easier for subconjunctival scarring to begin.”


Since this is a bleb procedure, albeit an *ab interno* one, there can be cases of leakage and scarring of the bleb in addition to exposure of the tube. For these reasons, Dr. Noecker says that you have to follow patients fairly closely postop. “You need to manage the bleb,” Dr. Brown adds. “It’s important to be able to needle these blebs, which is something not necessary with other internal procedures.” Dr. Noecker points out that, in terms of postop monitoring and intervention, “The good thing is that you can do something. The bad thing is that you have to do it.”

Aqueous Humor Reduction

Here, the ciliary body is treated in an effort to lessen the production

of aqueous humor and, ultimately, lower IOP.

• **Endoscopic cyclophotocoagulation.** Complications that can occur when performing an ECP procedure include inflammation and problems working with the probe.



“It’s a whole new era with these procedures and they’re certainly, as a group, safer than traditional glaucoma surgery.”

—*Robert Noecker, MD*



Dr. Flowers says that the biggest complication to be aware of with ECP is inflammation. Dr. Noecker agrees, saying, “You tend to get more inflammation because you’re treating the ciliary body. [To manage this] the patient has to be on steroids a little bit more.” Dr. Flowers says intracameral steroids have been a great help. “We used to get fibrin—a protein buildup—in the eye after the surgery,” he says. “But years ago we started using intracameral steroids and it virtually eliminated fibrin. A very robust anti-inflammatory treatment will minimize inflammation complications.”

To avoid further inflammation, Dr. Noecker says, “You have to be careful with the endo probe in the eye so as not to traumatize the iris by either lasering or bumping the iris, because that will lead to a fair amount of inflammation.”

Dr. Flowers has some final tips.

“Make sure that the lens [at the tip of the probe] is clean before it is autoclaved,” he says. “If you leave any debris on the lens of the camera then it’ll get baked on and mess up your view. The lens is very durable so you can wipe it with some force to make sure the tip is clean. Also, when you insert the camera into the eye, make sure you’re in a blood-free zone so you don’t get blood on the tip of it, which would obscure your view.”

The Future

MIGS is at the cutting edge of glaucoma surgery; and Dr. Flowers says, “MIGS is here to stay.” Dr. Brown calls it “the greatest breakthrough in glaucoma to come about in [my] 30 years within the industry. The goal now is to increase efficacy so that we’re able to lower pressure in patients who have more advanced disease and higher pressure.”

MIGS is still a relatively new category in glaucoma treatment and while each procedure has its complications, doctors continue to explore management practices as MIGS provides an alternative to medical therapy and more invasive surgery. “We appreciate having these procedures,” Dr. Noecker says. “They aren’t perfect, however, and anything we do involves a little bit of a risk or a downside. However, by knowing the downsides, we can make these surgeries safe and give people good vision quickly while, at the same time, addressing IOP.” **REVIEW**

Dr. Noecker reports financial ties to Glaukos, Ellex, Sight Sciences, BVI and Allergan. Dr. Brown is the chief medical officer for Sight Sciences. Dr. Flowers is a consultant for and does research with Glaukos, Ivantis, Alcon, iStar, InnFocus and Sight Sciences.

Cutting-Edge Retinal Therapies

Michelle Stephenson, Contributing Editor

New drugs and gene therapies look promising for sight-threatening retinal conditions.

A number of exciting, cutting-edge retinal treatments are being investigated against the backdrop of Spark's Luxturna being approved by the Food and Drug Administration last year. Here's a sampling of some promising new drugs and gene therapies.

Next-Generation Anti-VEGF

According to Pravin Dugel, MD, who is in practice in Phoenix, one of the most exciting drugs in this category is brolocizumab (Novartis), which is a single-strand antibody fragment. "The Phase III trials, HAWK and HARRIER, have shown anatomic superiority over aflibercept. This is the next drug in the pipeline that will change our management," he says.

The HAWK study included neovascular AMD patients randomized 1:1:1 into three treatment groups: 358 patients received 3 mg of brolocizumab, 360 patients received 6 mg of brolocizumab, and 360 patients received 2 mg of aflibercept (Eylea, Regeneron).¹

The HARRIER study included neovascular AMD patients randomized 1:1 into two treatment groups: 370 patients received 6 mg of brolocizumab and 369 patients received 2 mg of aflibercept.¹

In both studies, patients in the brolu-

cizumab group received three loading doses and then were treated every 12 weeks during the maintenance phase. Patients in the aflibercept group were treated every eight weeks.

In HAWK and HARRIER, the mean change in best-corrected visual acuity from baseline to week 48 was noninferior for brolocizumab compared with aflibercept. In the HAWK study, brolocizumab patients who received 3 mg experienced a mean BCVA gain of 6.1 letters, and those who received 6 mg improved by 6.6 letters, compared with 6.8 letters for the patients who received 2 mg of aflibercept.

In the HARRIER study, patients who received 6 mg of brolocizumab experienced a mean gain in BCVA of 6.9 letters compared with 7.6 letters in the aflibercept group. Additionally, 57 percent of HAWK patients and 52 percent of HARRIER patients who received 6 mg of brolocizumab were maintained on a 12-week interval after the loading phase until the final end point of week 48.

Another exciting anti-VEGF drug is conbercept, which is made by Kang Hong Biotech from China. "It may be the first drug that's FDA-approved from China," Dr. Dugel explains. "It's a fusion protein with a change in domain IV that will potentially allow it

to bind better to the target than we've seen before."

A study was conducted to compare the efficacy and safety of conbercept and ranibizumab (Lucentis, Genentech) when administered according to a treat-and-extend (TREX) protocol for the treatment of neovascular AMD in China.² The study concluded that both drugs had equivalent effects in visual and anatomic gains at one year. Longer treatment intervals were achieved in more patients in the conbercept group.

Allergan's abicipar pegol is also showing promise. "It's a very small drug that theoretically has great potential and may have greater durability than any of the drugs that we've had so far," says Dr. Dugel. "However, the challenge for this drug is that the inflammation rate is very high, 15 percent, so we're hoping to get more clarity on that."

In the Phase II trial, abicipar demonstrated durability of effect.³ Best-corrected acuity and central retinal thickness (CRT) improvements were similar between abicipar and ranibizumab at weeks 16 and 20 (eight and 12 weeks after the last abicipar injection and four weeks after the last ranibizumab injection). No serious adverse events were reported.

This multicenter, randomized, double-masked comparison included 64 patients who received intravitreal injections of abicipar 1 mg or 2 mg at baseline, week four, and week eight (three injections) or ranibizumab 0.5 mg at baseline and monthly for five months.

Twenty-five patients received 1 mg of abicipar, 23 patients received 2 mg of abicipar, and 16 patients received ranibizumab. Least-squares mean BCVA change from baseline was +6.2, +8.3 and +5.6 letters at week 16 and +8.2, +10 and +5.3 letters at week 20. Least-squares mean CRT reduction from baseline was 134, 113, and 131 μm at week 16, and 116, 103 and 138 μm , respectively, at week 20. Five of 48 pa-

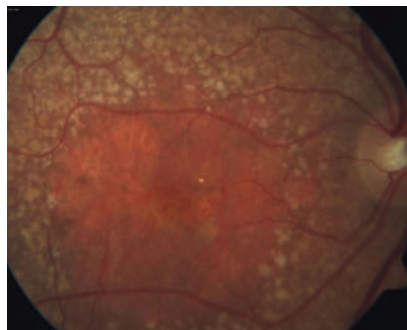


Figure 1. New drugs may slow the progression of geographic atrophy.

tients who were treated with abicipar experienced intraocular inflammation, which resolved without sustained vision loss.

Combination Drugs

Several combination drugs are under development. Topping the list is faricimab, which used to be known as RG7716, from Genentech/Roche. "This is a bispecific antibody, so it will simultaneously bind to Ang-2 and VEGF-A," Dr. Dugel says. "The studies that have been done in neovascular AMD and DME have been very encouraging."

"This dual mechanism of action is attractive in that it provides inhibition of the neovascular AMD process via two separate pathways," says Chicago's Jennifer Lim, MD.

The Phase II STAIRWAY study explored the extended durability of faricimab in the treatment of wet AMD.⁴ At 52 weeks, faricimab patients dosed either every 16 weeks or every 12 weeks demonstrated sustained vision outcomes comparable to ranibizumab dosed every four weeks.

This study assessed two extended-dosing regimens of faricimab 6 mg given every 16 weeks or every 12 weeks, compared to ranibizumab 0.5 mg every four weeks. At week 24, which was three months after the last loading dose, patients who received faricimab every 16 weeks were switched to 12-week dosing if they were shown

to have active disease, per predefined criteria. At week 24, 65 percent of patients treated with faricimab had no active disease, demonstrating the potential of 16-week dosing in nearly two-thirds of patients. Initial gains in BCVA were fully maintained through week 52 with 16- and 12-week dosing regimens.

Patients treated with faricimab dosed every 16 weeks experienced a mean improvement of 11.4 letters from baseline, compared to 10.1 letters in patients treated with faricimab dosed every 12 weeks and 9.6 letters in patients treated with ranibizumab 0.5 mg dosed every four weeks. Comparable reductions in CRT were also noted in patients treated with both dosing intervals of faricimab and those treated with ranibizumab. In STAIRWAY, the rates of ocular and systemic adverse events observed with faricimab were similar to those with ranibizumab. "These results are very encouraging given the less frequent dosing interval of faricimab," Dr. Lim says.

Based on these data, Genentech/Roche will be initiating a global Phase III program for faricimab in wet AMD. "The LUCERNE Study (Phase III faricimab versus aflibercept) is unique in its design in that it will explore different dosing intervals in the first year and then a 'personalized treatment interval' from week 60 onward," Dr. Lim says. "This will be of great value for the day-to-day care of patients if the drug is approved."

Another promising drug is OPT-302 from Opthea, an Australian company. "It suppresses VEGF-C and D," Dr. Dugel explains. "It would allow for a pan-VEGF inhibition in combination with any of the VEGF-A inhibitors currently available. The early studies have been very encouraging, and the Phase III studies are being done in neovascular AMD and DME."

There is also the drug previously known as Luminate. It's now called risuteganib from Allegro. "The results

All images: Jennifer Lim, MD

have been encouraging for diabetic macular edema,” Dr. Dugel says.

Last is a topical agent from Oculus that contains a cycloheximide platform. It’s currently being studied in Scandinavia and Eastern Europe, according to Dr. Dugel.

Dry AMD/Geographic Atrophy

Apellis has developed a drug to treat geographic atrophy called APL-2, which is a complement inhibitor. “It inhibits the transformation of C3, and the preliminary results have been very encouraging in slowing down the progression of geographic atrophy,” Dr. Dugel says. “However, the downside is that there seems to be an increased risk of developing neovascular macular degeneration. We don’t know why yet, but Phase III studies are under way. This is the first time that we’ve seen something that shows an encouraging result in geographic atrophy.”

Dr. Lim emphasizes that more data will be necessary to make a decision about it. “This increased risk of CNV may prove to be the limiting factor in the use of this drug,” she says.

According to Apellis, APL-2 is designed to inhibit the complement cascade centrally at C3, and it may have the potential to treat a wide range of complement-mediated diseases more effectively than is possible with partial inhibitors of complement.⁵ APL-2 is a synthetic cyclic peptide conjugated to a polyethylene glycol (PEG) polymer that binds specifically to C3 and C3b, effectively blocking all three pathways of complement activation. Interim data from three trials have demonstrated meaningful improvements in lactate dehydrogenase and hemoglobin levels in previously untreated patients and in patients who are suboptimal responders to eculizumab.

Another interesting drug is AKB-9778 from Aerieo. “It is currently being studied for diabetic retinopathy,” Dr. Dugel says. “It’s delivered subcu-

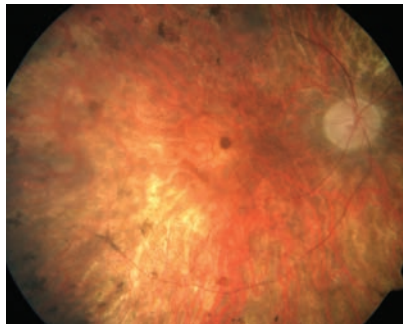


Figure 2. Gene therapy has finally provided a treatment for a form of retinitis pigmentosa.

taneously, so it goes to both eyes systemically. In previous studies it was associated with a decrease in progression of diabetic retinopathy, as well as improvement in renal function. If any of these results are duplicated in this study, I think it will have an enormous impact, not just because it’s a different mechanism of action but also because of its subcutaneous delivery.”

The Phase IIa clinical trial found that activation of Tie2 by subcutaneous injections of AKB-9778 combined with suppression of vascular endothelial growth factor caused a significantly greater reduction in DME than that seen with suppression of VEGF alone, and similar reductions in the two-step progression of diabetic retinopathy were seen compared to ranibizumab in both eyes.⁶

Gene Therapy

Luxturna (voretigene neparvovec) from Spark is the first gene therapy in ophthalmology to be FDA-approved. It’s a gene replacement for RPE65 for patients with retinitis pigmentosa, as well as Leber’s. “It’s a groundbreaking, unique treatment that gets to the heart of the cause of the problem for this type of retinitis pigmentosa,” says Dr. Lim. “I think it gives patients hope where there wasn’t any hope before. Because these children can now be cured, they won’t be relegated to a lifetime of blindness.”

Phase I studies showed potential benefit of gene replacement in RPE65-mediated inherited retinal dystrophy. The Phase III study found that voretigene neparvovec gene replacement improved functional vision in RPE65-mediated inherited retinal dystrophy, previously medically untreatable.⁷

The open-label, randomized, controlled Phase III trial was conducted at two sites in the United States in patients aged 3 years or older with BCVA of 20/60 or worse and/or visual field less than 20 degrees in any meridian, or both, in both eyes, with confirmed genetic diagnosis of biallelic RPE65 mutations, sufficient viable retina, and the ability to perform standardized multi-luminance mobility testing (MLMT) within the luminance range evaluated. Participants were randomly assigned (2:1) to intervention or control. Intervention was bilateral, subretinal injection of 1.5×10^{11} vector genomes of voretigene neparvovec, 0.3 mL total volume. The primary efficacy endpoint was the one-year change in MLMT performance, measuring functional vision at specified light levels. The intention-to-treat and modified ITT populations were included in primary and safety analyses.

The study included 29 patients who were randomly assigned to intervention (n=20) or control (n=9). At one year, mean bilateral MLMT change score was 1.8 light levels in the intervention group versus 0.2 in the control group. Thirteen (65 percent) of 20 intervention participants, but no control participants, passed MLMT at the lowest luminance level tested (1 lux), demonstrating maximum possible improvement.

For treating chronic disease, RegenXBio has developed RGX-314, which is being developed as a one-time subretinal treatment for wet AMD. It includes the NAV AAV8 vector encoding an antibody fragment, which inhibits VEGF, modifying the pathway for formation of new leaky blood ves-



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*Comparison based on results from individual pivotal trials and not head to head comparative studies.



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REVIEW

Feature Retinal Therapies

sels that lead to retinal fluid accumulation and vision loss. In preclinical animal models with conditions similar to macular degeneration, significant and dose-dependent reduction of blood vessel growth and prevention of disease progression was observed after a single subretinal dose of RGX-314.⁸

“This is an actual anti-VEGF Fab gene put in a specialized virus vector, which is technologically very difficult,” Dr. Dugel explains. “In other words, it’s not just a generic virus vector, which is usually AAV2; it’s AAV8, which is specialized to go specifically to the retina. And they’ve been able to show, for the first time, that there is a dose relationship with expression of the protein, which is extraordinarily important. It’s the first time we’ve ever seen that, and the early phase study has been very encouraging. With a higher dose, there’s a dose relationship, and there’s a decrease in the number of injections and an increase in the visual acuity. But to me, the most important thing is that there is an objective dose relationship in terms of the protein that’s produced. I look forward to further results, but also to the next phase in study. If that finding is duplicated in a larger study, it will transition gene therapy from a rare disease treatment into a chronic disease treatment. That will really change everything we do.”

The Phase I clinical trial has enrolled 24 previously treated wet AMD patients who are responsive to anti-VEGF therapy and are 50 years of age or older in four cohorts.⁸ The study is designed to evaluate four doses of RGX-314: 3 x 109 GC/eye; 1 x 1010 GC/eye; 6 x 1010 GC/eye; and 1.6 x 1011 GC/eye. The study will evaluate the safety and tolerability of RGX-314 at 24 weeks after a single dose administered subretinally. Primary endpoints include safety and tolerability. Following completion of the primary study period, patients will continue to be assessed until week 106 for long-term safety and durability of effect.

Dr. Lim is optimistic about the future of retinal therapies. “The future is bright for patients with neovascular AMD and even rarer genetic diseases such as RPE65 RP,” she says. “New drugs with longer duration of action, different molecular targets, combination therapies and even extended drug delivery may be on the horizon. For non-neovascular AMD and geographic atrophy, advances are also occurring. Innovation and scientific discovery will hopefully alleviate the suffering of many of our patients in the near future.” **REVIEW**

Dr. Dugel is on the scientific advisory board of Novartis, Genentech, Aerpio and Opthea. He is a consultant to Genentech, Novartis, Allergan, Aerpio, Opthea, Spark, Regeneron and Chendu Kang Hong Biotechnology, and he is a minor stockholder in Aerpio. Dr. Lim has a financial interest in Genentech, Regeneron and Aerpio.

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Tech Trends in Vitreoretinal Surgery

A look at retinal surgery innovations, from visualization to instrumentation.

Müller Urias, MD, Felipe Pereira, MD, Rodrigo Brant, MD, Rafael Caiado, MD, Antonio Brant Fernandes, MD, Rubens Belfort Jr., MD, PhD, and Mauricio Maia, MD, PhD, São Paulo, Brazil

Over the past five years, our specialty has witnessed several significant changes in the technologies available to us in the operating room. Though these innovations come from different parts of the technology realm, they each aim to improve surgeons' performance and outcomes. Such innovations include new models of surgical microscopes and smaller, more efficient vitrectomy devices. Looking ahead, robotics will be present in the operating room sooner than we expect and may allow the surgeon to perform delicate tasks without injuring adjacent tissues. Here, we'll discuss some of the latest inventions.

Visualization

One area that's made strides in recent years is our ability to visualize retinal procedures. This new point-of-view includes 3-D systems like that from Alcon/TrueVision and real-time, intraoperative optical coherence tomography.

The Ngenuity 3-D system uses a high-dynamic-range camera and a high-resolution 4K monitor. It provides the surgeon with very good im-

age depth and magnification power, while maintaining a wide field of view and comfortable ergonomics for long surgeries.¹ The digital image system and regulation in the aperture of the camera can display a usable image while using lower light intensity, which could mean less retinal phototoxicity for patients. The manipulation of the digital image with the use of different image filters to improve the color and contrast at specific moments during the surgery is another possibility that will be explored in the near future.

One significant benefit of a 3-D viewing system is that it allows the surgeon to teach residents and fellows surgical techniques, since it allows the operating team to see what the surgeon sees (*Figure 1*). Also, an assistant can help by designating targets and defining paths using a computer mouse.

Many retinal surgeons around the world seem interested in the

technology; the latest Preferences and Trends Survey of the American Society of Retinal Specialists in 2018 reported that 15 to 20 percent of surgeons have used the 3-D system and found it useful. Furthermore, 35 to 50 percent said that they plan to purchase the equipment in the future.

Also in the imaging arena, intraoperative OCT has made strides.⁶ Systems such as the iOCT (Haag-Streit), EnFocus (Leica) and the Rescan 700 (Carl Zeiss Meditec) can make internal limiting membrane peeling, management of adhesions and visualization of a tractional detachment easier, as well as give a better view of the subretinal space (*Figures 2 and 3*).



Figure 1. Heads-up surgery may help improve documentation as well as assist in the training of other surgeons.

Rodrigo Brant, MD

The advent of swept-source OCT, with its longer wavelength compared to SD-OCT, improved the study of pre- and postoperative retinal status.^{7,8} This characteristic of SS-OCT allows it to visualize through some media opacities and to reduce RPE laser scattering. After macular hole surgery, SS-OCT appears to be a novel way to assess retinal status in a gas-filled vitreous cavity, and provides a high-quality image. Therefore, with an early assessment of macular hole closure, patients may need to be in a face-down position for less time.⁷ Certainly, image quality and acquisition latency from devices such as the intraoperative OCT have much to improve. However, there wouldn't be any innovation without any initial effort.

Instruments

Alongside a new view of the procedure are new ways to manipulate the posterior segment's structures.

- **27-ga. vitrectomy cutters.** The 27-ga. vitrectomy system was introduced in 2010, but, to date, has not been adopted by most retinal surgeons.² This is shown by the 2017 ASRS PAT Survey in which about 70 percent of surgeons reported not using it, and 20 percent say they use it for only 5 percent of their cases.

Despite creating self-sealing incisions and the promise of lower frequency of hypotonia, vitreous prolapse and endophthalmitis, disadvantages such as reduced luminance from a smaller-gauge light probe and worse vitreous aspiration rates may have delayed the widespread adoption of this technology.

With technological improvements, different light sources such as xenon, mercury vapor or LEDs were introduced. These light sources decreased the risk of phototoxicity while still yielding good illumination. This efficient lighting allows better visualiza-

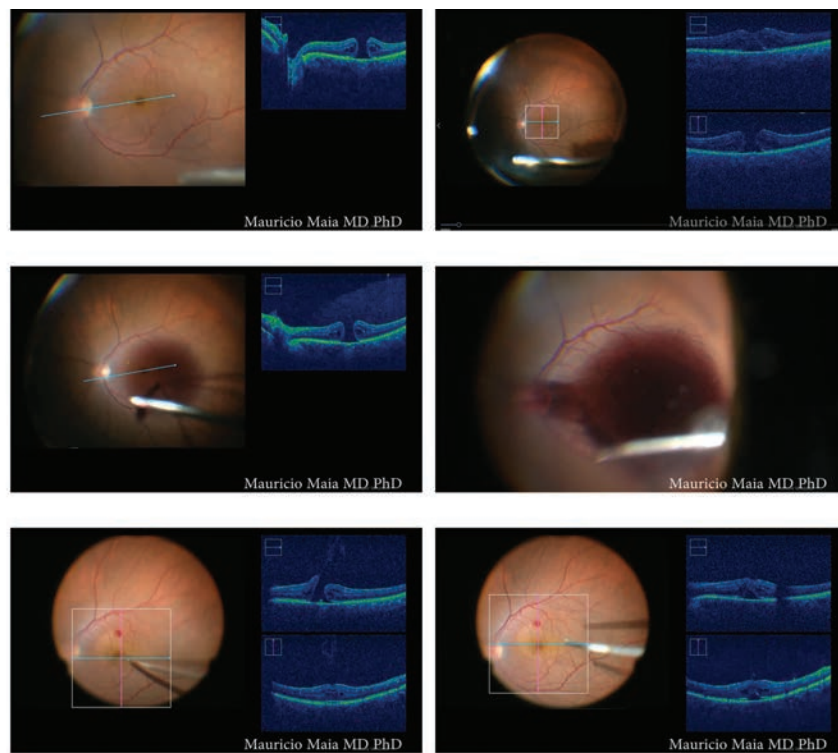


Figure 2. Intraoperative optical coherence tomography during macular hole surgery imaged during an açai dye protocol. Upper left: One line raster. Upper right: Macular cube. Middle left and middle right: Injection of açai dye. Bottom left: OCT during peeling. Bottom right: OCT during fluid-air exchange, with intraoperative verification of macular hole closure.

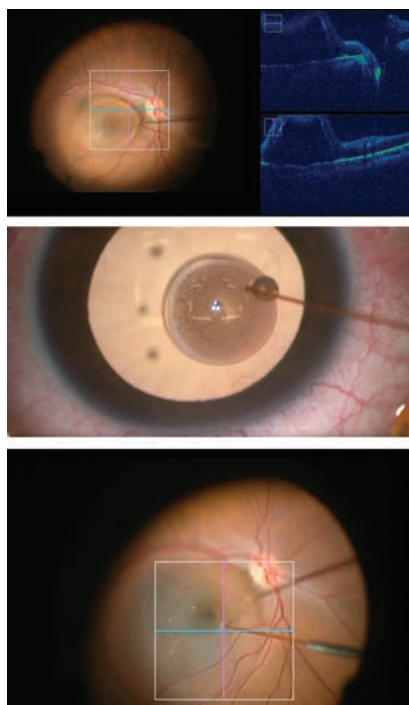
tion in 27-ga. surgeries, making the option more attractive to surgeons. What's more, a 3-D surgical viewing system can optimize the illumination of the lower-gauge cutting devices, thanks to the aperture control of the camera and its ability to use less light. Another critical step toward improved efficiency with the 27-ga. system is the use of high-cut-rate technology. With a higher cutting rate, the aspirated vitreous has a lower viscosity, allowing a better rate of aspiration.

Another recent innovation is two-dimensional cutting. TDC is a technology developed by Dutch Ophthalmic Research Center that features two cutter openings inside the guillotine shaft. This design allows a vitreous cutting action in both the forward and backward movements. The main benefits of this technology include cutting rates of up to 16,000 cpm, increased flow rate and reduced retinal traction. Other

companies also use techniques to increase duty cycle and improve system efficiencies, such as the Bi-Blade Dual Port (Bausch + Lomb) and the Hypervit Dual-Blade (Alcon) that can generate up to 20,000 cpm.

Due to the improvements in the features and safety of the 27-ga. system, the indications for its use have expanded. Today, it can be used in nearly all cases of retinal surgery and it's especially useful in cases of diabetic retinopathy with multiple areas of fibrovascular proliferation and retinal traction. Thanks to its size, the 27-ga. probe can easily enter small spaces for membrane dissection, reducing the need for bimanual techniques.³ Despite the companies' and surgeons' best efforts, though, the 27-ga system still has limitations, with reduced stiffness of the instruments and fragile tools for longer complex surgeries.

Some patients who are receiving



Rodrigo Brant, MD

Figure 3. Intraoperative optical coherence tomography to assist with surgery in the subretinal space in UNIFESP Stem Cell protocol, Sao Paulo, Brazil. Top: iOCT during the creation of a subretinal space. Middle: 40-ga. needle with stem cells. Bottom: Injection of stem cells into subretinal space.

multifocal IOLs, and who have symptomatic floaters, find their floaters to be more bothersome, and some surgeons feel that vitrectomy is a possible option for these patients. For those cases of floaters in patients with excellent visual acuity, a 27-ga vitrectomy could be a suitable procedure due to the smaller scleral wound and the possibility for reduced leakage. This sutureless procedure may decrease the risk for refractive errors postop and also may reduce the risk of endophthalmitis (Figure 4), though more data on this is required.^{4,5}

• **New models of instruments and vitrectomy cutters.** The latest technology in the field of vitrectomy cutters is the hypersonic probe developed for the Stellaris Elite (Bausch + Lomb), which is available for the company's 23-ga. system. During vitrectomy, this

probe uses hypersonic vibrations that reach about 1.7 million per minute to liquify adjacent vitreous. With this technology, the aspiration port is open at all times, allowing constant aspiration flow and, consequently, greater stability in vitreous removal, even in severe cases such as pediatric vitrectomies.

Technique Assistance

In addition to visualization, implementation of technologies in different areas—such as robotics and pharmacology—has enhanced our surgical techniques and could improve surgical outcomes.

Experimental models of robotic instruments have demonstrated that it may be possible to reduce surgeon hand tremor in order to access specific retinal depths precisely—including intravascular spaces. Robotics may also be able to prevent inadvertent retinal touch.⁹ In addition, a procedure performed by a surgeon-controlled robot—already a reality in surgical specialties such as gastrointestinal surgery and urology—is in a human trial, and has already performed 12 surgeries.¹⁰

Currently, one of the possible limitations of this technology lies in the massive number of variables and patterns during surgery that a human can identify and react to faster than the algorithm. There's also the constant fear of software failure during the operation.

In the realm of pharmacology, research into novel anti-vascular endothelial growth factor agents that could be used before surgery to reduce bleeding; new dyes, such as an açai-fruit extract (Figure 2),^{11,12} that could be used during the operation to improve the identification of ocular structures; and the development of sustained-release drug implants all show potential to enhance both our techniques as well as visual outcomes. Research is also underway on a new vitreous substitute that may decrease

the need for face-down positioning after certain retinal procedures.

Visual and Retinal Recovery

Researchers are also investigating ways to assist retinal and/or visual recovery and regeneration. Due to the level of difficulty of these projects, however, their results and numbers are still not statistically robust. However, they're still very important, since they're encouraging more studies in their areas. Embryological, genetic and technological projects stand out in the search for retinal and visual recovery.

Embryology has been an exciting tool in retinal recovery, mainly with the use of stem cells (recently covered in the June 2018 Retinal Insider by Peter Bracha, MD, and Thomas A. Ciulla, MD). Currently, however, amniotic transplantation has been questioned as a tool for recurrent macular holes (NCT03528122). The treatment using embryological therapy suffered from lack of safety data until recently, and it's important to emphasize that such studies should be ethical and conscientiously analyzed, and their results carefully published, to avoid a frenzy among the media and desperate patients.

Providing stronger evidence, at least in specific applications, are genetic therapies, exemplified by Luxturna (voretigene neparvovec-rzyl, Spark Therapeutics). Luxturna's successful trial and subsequent approval caught the world's attention and encouraged further studies. The main obstacle, however, to a greater emphasis on gene therapy is the high cost of the treatment. With a larger number of clinical trials, and a more significant number of companies supporting the research, the production cost could possibly be lowered, and the feasibility of this type of treatment could increase.

Another trend in visual rehabilitation is the use of retinal prostheses (reviewed in the June 2017 Retinal Insider by Derrick L. Cheng, MD, David

A. Borton, MD, and Paul B. Greenberg, MD). The current improved access and ability to manipulate different retinal sites (epiretinal, subretinal, suprachoroidal), as well as improved computer processing, make the implantation of these prostheses a promising area of research. With all of these strategies for vision restoration or recovery, it's essential to reiterate the need to conduct and publish this research ethically. We must remember that these studies usually involve individuals with severe vision loss, and their desperate need to believe in a "miracle" could make them jump at the nearest study or therapy.

Trends in vitreoretinal surgery go hand-in-hand with scientific evidence. The interplay between technology and techniques can start a trend or reveal a new solution to an old problem. For instance, new visualization systems could allow us to document surgery differently, and therefore improve our ability to criti-

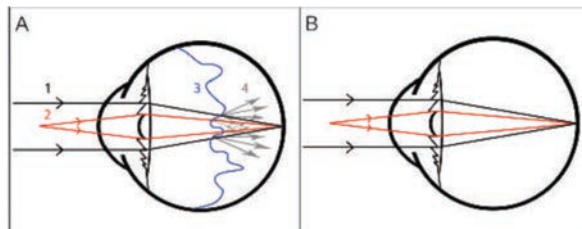


Figure 4. The benefits of small-gauge vitrectomy for floaters are minimal wound leakage, less postop inflammation and complications. (A) Drawing showing an eye with a multifocal IOL and posterior vitreous detachment. The light rays first pass through the cornea and then the IOL. The high density of the PVD causes dispersion of the light rays. (1) The light rays in black represent distance vision. (2) The light rays in red represent near vision. (3) The wavy blue line represents vitreous detachment. (4) The gray arrows show dispersion of the light rays when they pass through the dense vitreous, causing halos floaters and blurred vision. (B) The drawing shows the light rays reaching the retina without interference from the vitreous detachment after PPV, indicating the potential for good near and distance vision without glasses. (Navarro RM, Maia A, Arevalo F, et al. *J Ophthalmol.* 2015; 2015:156910.)

cally analyze each new technological trend as it works its way through the pipeline. In this way, using scientific evidence, surgeons will be able to make the best decisions regarding which new technology to use for their surgeries. **REVIEW**

Table 1. Vitrectomy for Floaters: Quality-of-Life Impact

Subscale	Before PPV (median)	After PPV (median)	p-value	No. with improved scores (%)
General health	75 (50-100)	75 (50-100)	0.157	2 (25)
General vision	60 (40-80)	80 (60-100)	0.023*	6 (75)
Ocular pain	81 (38-100)	81 (63-100)	0.180	2 (25)
Near activities	75 (42-100)	92 (58-100)	0.043*	5 (63)
Distance activities	67 (58-100)	100 (75-100)	0.041*	5 (63)
Social functioning	94 (75-100)	100 (88-100)	0.083	3 (38)
Mental health	75 (38-81)	94 (50-100)	0.011*	8 (100)
Role difficulties	88 (25-100)	100 (75-100)	0.042*	5 (63)
Dependency	100 (58-100)	100 (83-100)	0.102	3 (38)
Driving	67 (50-67)	92 (75-100)	0.016*	8 (100)
Color vision	100 (50-100)	100 (100-100)	0.317	1 (13)
Peripheral vision	75 (50-100)	100 (75-100)	0.059	4 (50%)
UCVA (LogMar)	0.17 (0.09-0.30)	0.09 (0.00-0.17)	NA	

Visual function questionnaire score results before and after vitrectomy. * indicates statistically significant result. Table data adapted from: Navarro RM, Maia A, Arevalo F, et al. *J Ophthalmol.* 2015:156910.

Dr Maia is a professor of ophthalmology at Federal University of São Paulo-UNIFESP. He can be reached at mmaia@unifesp.br. Dr. Urias and Dr. Pereira are vitreoretinal fellows and postgraduate students at UNIFESP. Dr. Brant and Dr. Caiado are also postgraduate students at UNIFESP. Dr. Belfort Jr. is the chair of the ophthalmology department of UNIFESP.

Dr. Maia is a consultant for Alcon, Allergan, Bausch + Lomb, Bayer, Kemin and Novartis. Dr. Belfort is a consultant to Abbvie, Alcon and Allergan, and has received grants from Novartis, Ophthalmos and Roche.

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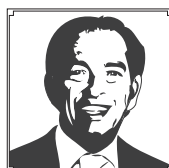
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Laser vs. Ranibizumab For PDR Patients

Scientists aimed to identify whether baseline characteristics of eyes with proliferative diabetic retinopathy were associated with better outcomes when treated with panretinal laser vs. ranibizumab in the DRCR.net Protocol S.

Participants had PDR, visual acuity of 20/320 or better, and no previous PRP. Eyes were randomized to PRP or intravitreal 0.5-mg ranibizumab. Here are some of the findings:

- Ranibizumab was superior to PRP for change in visual acuity and development of vision-impairing central-involved diabetic macular edema over two years ($p < 0.001$).

- Among 25 characteristics, none in PRP participants were associated with superior outcomes relative to ranibizumab-assigned participants.

- The relative benefit of ranibizumab over PRP in terms of change in VA appeared greater in participants with higher mean arterial pressure ($p = 0.03$); without previous focal/grid laser ($p = 0.03$); with neovascularization of the disc and elsewhere on clinical exam ($p = 0.04$); and with more advanced PDR on photographs ($p = 0.02$).

- For development of vision-impairing central-involved DME, the relative benefit of ranibizumab over PRP seemed greater among non-white participants ($p = 0.01$) and those with higher mean arterial pressure

($p = 0.01$).

Scientists wrote that no identified characteristics were associated with superior outcomes using PRP vs. ranibizumab. They added that their exploratory analyses provides additional support for the premise that ranibizumab might be a reasonable alternative to PRP for PDR over a two-year period.

Retina 2019; Feb. 18 [Epub ahead of print].

Bressler SB, Beaulieu WT, Glassman AR, et al.

The Sleep/Glaucoma Connection

Researchers from the Wilmer Eye Institute at Johns Hopkins University say that a patient's sleep characteristics may play a role in the development of glaucoma.

In this cross-sectional study, the researchers included 6,784 glaucoma patients from the 2005 to 2008 National Health and Nutrition Examination Survey who were age 40 and above and who had completed a detailed sleep questionnaire. Participants were asked such questions as, "How much sleep do you usually get at night on weekdays or work days?" and "How long does it usually take you to fall asleep?" The questionnaire was set up to look at the following predictors:

- sleep duration;
- sleep latency;
- sleep disorders;

- sleep disturbances;
- sleep medication use; and
- daytime dysfunction due to sleepiness.

The outcomes included disc-defined glaucoma (either right or left disc demonstrating glaucoma) and visual field defects (VFD) assessed by frequency-doubling perimetry.

The investigators found that the odds of disc-defined glaucoma were three times higher among subjects who slept for ≥ 10 hours per night compared with those who slept seven hours per night. The odds of disc-defined glaucoma were two times higher among subjects who fell asleep in ≤ 9 minutes or ≥ 30 minutes, compared with 10 to 29 minutes. The odds of VFD were three times higher among subjects who slept for ≤ 3 hours per night, compared with seven hours per night. The odds of VFD were two times higher among subjects who had difficulty remembering things and three times higher among subjects who had difficulty working on a hobby due to daytime sleepiness compared with those without difficulty.

The researchers say there appear to be associations between glaucoma and abnormal sleep parameters, and that these abnormal sleep patterns may be a risk for, or consequence of, glaucoma.

J Glaucoma 2019;28:97-104
Qiu M, Ramulu P, Boland M.

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A 12-year-old boy presents to the Wills Eye emergency room with unilateral blurred vision and photophobia.

Connie Wu, MD, James P. Dunn, MD, and Carol L. Shields, MD

Presentation

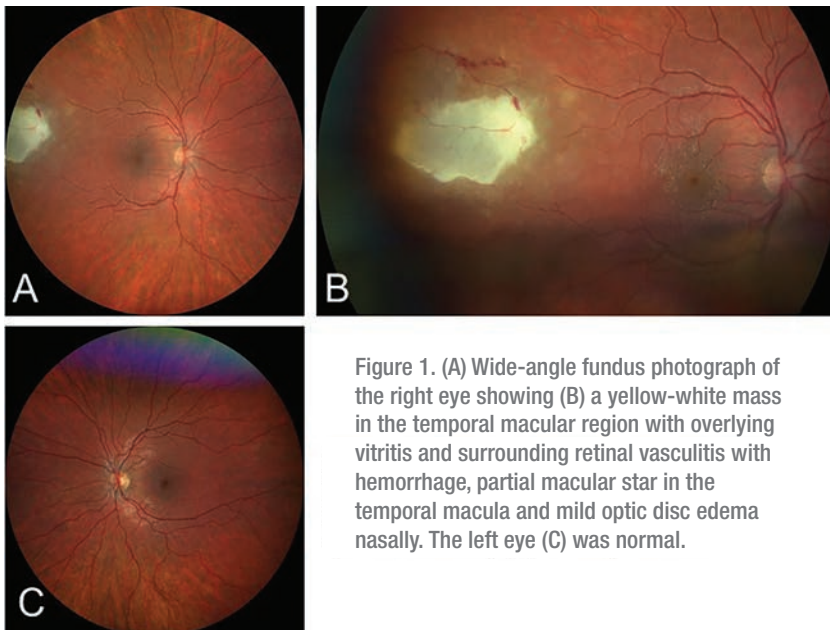
A 12-year-old Caucasian male with progressive blurred vision, photophobia and pressure-like pain in his right eye presented to the Wills Eye emergency room. Symptoms were noted two days prior when he was playing soccer and had to step off the field due to excessive photophobia of his right eye, which was also red. His left eye was asymptomatic. He didn't sustain any ocular trauma and was otherwise in his usual state of good health.

Medical History

There was no past ocular history. The past medical history revealed mild intermittent asthma. Family history included glaucoma in his grandmother and a cerebrovascular accident in his grandfather. Social history was negative for recent travel or contact with cats or dogs but included contact with a family-owned farm that raised free-range chickens. He had no known allergies and took no medications.

Examination

On ocular examination, visual acuity was 20/20 OU. Pupils were normal. Intraocular pressure was 30 mmHg OD and 14 mmHg OS. Confrontation visual fields and ocular motility were full bilaterally. The anterior segment examination of the right eye revealed mild injection of the conjunctiva temporally, stellate inferior keratic precipitates, 1+ cell and trace flare, and moderate vitreous cell. The left eye was unremarkable.



On fundus examination of the right eye there was blurring of the nasal margin of the optic disc and a partial macular star without edema. An elevated white retinal lesion with associated subretinal fluid, vitritis, vasculitis and intraretinal hemorrhage, suggestive of an inflammatory mass, was identified in the inferotemporal midperiphery (Figure 1).

Figure 1. (A) Wide-angle fundus photograph of the right eye showing (B) a yellow-white mass in the temporal macular region with overlying vitritis and surrounding retinal vasculitis with hemorrhage, partial macular star in the temporal macula and mild optic disc edema nasally. The left eye (C) was normal.

What is your diagnosis? What further workup would you pursue? The diagnosis appears on p. 72.

Workup, Diagnosis and Treatment

Imaging of the affected eye with macular OCT (Fig. 2A) revealed disruption of the inner and outer retina with subtle cystic changes and mild vitritis in the temporal macula. OCT through the inflammatory mass in the right eye revealed overlying vitritis, retinitis, choroiditis and subretinal fluid with debris (Figure 2C, D). B-scan ultrasonography (Figure 3) revealed an echodense elevated mass measuring 4.26 mm in diameter by 0.91 mm in thickness. The left macula was normal.

Based on the appearance of the retinal lesion, the patient was diagnosed with *Toxoplasma* chorioretinitis; the patient and his parents denied any risk factors for exposure including contact with cats or raw meat/unclean foods. He was treated empirically with Bactrim while awaiting serologic testing results. Unfortunately, the first collected sample was inadequate and a second sample had to be drawn after he had already undergone two weeks of treatment. Titers for *Toxoplasma* IgG were positive at 164 IU/mL, but the IgM was negative. Although it wasn't possible to confirm active *Toxoplasma* infection with this particular test, the patient was treated empirically with Bactrim, prednisolone acetate 1% and dorzolamide 2%-timolol 0.5% for intraocular pressure control during the early inflammatory phase. He improved over the course of six weeks.

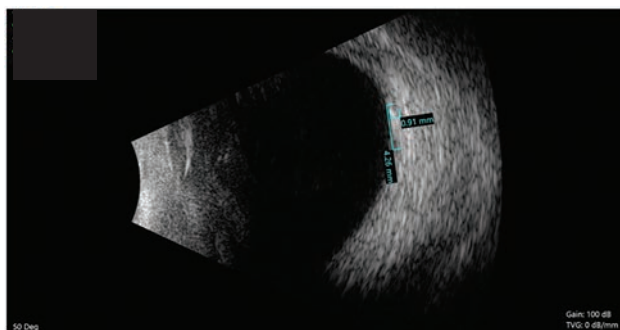


Figure 3. B-scan ultrasonography revealed an echodense elevated mass measuring 4.26 mm in diameter and 0.91 mm thick.

Discussion

The differential diagnosis in this young patient with acute onset, unilateral decreased vision and photophobia in the setting of ocular hypertension and an inflammatory retinal lesion included infectious, inflammatory and neoplastic etiologies. Infectious causes included protozoan (e.g., toxoplasmosis), bacterial (e.g., *Bartonella*, tuberculosis, syphilis, Lyme disease), viral (e.g., mumps, herpes simplex), fungal (e.g., histoplasmosis) and nematodal (e.g., *Toxocara*). Inflammatory etiologies included juvenile idio-

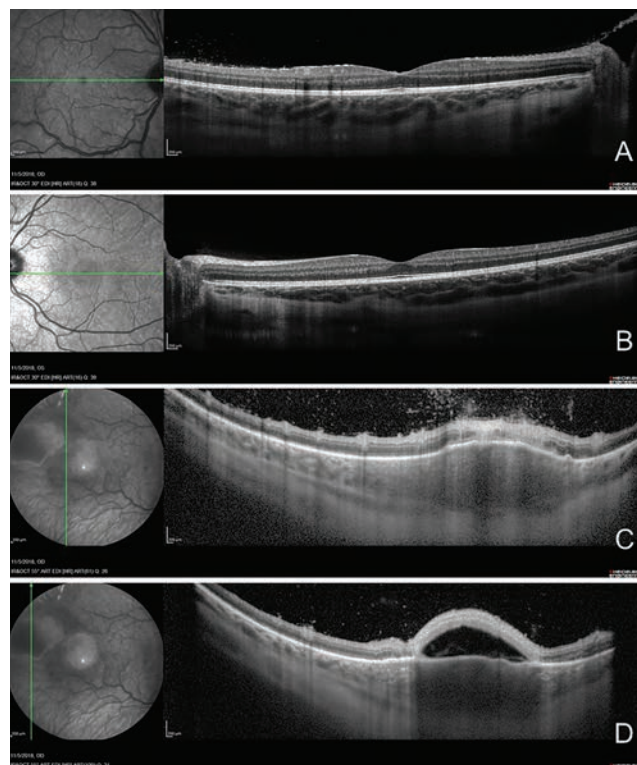


Figure 2. OCT of the right eye revealed (A) disruption of the inner and outer retina with subtle cystic changes and mild vitritis in the temporal margin. The left macula (B) was normal. OCT through the inflammatory mass in the right eye (C,D) revealed overlying vitritis, retinitis, choroiditis and subretinal fluid with debris.

pathic arthritis, sarcoidosis, tubulointerstitial nephritis and uveitis syndrome, and inflammatory bowel disease. Less likely malignant etiologies included leukemia, lymphoma and retinoblastoma.

Toxoplasma gondii is a parasitic protozoan thought to be the most common cause of infectious posterior uveitis in the world, infecting about a quarter of the U.S. population and an even greater proportion in other parts of the world.¹ Ocular involvement is estimated at 2 percent in the United

States. Following initial ocular infection with *T. gondii*, the recurrence rate is greatest within the following year. Most infections are acquired through ingestion of the oocyte from soil/water or the cyst form from infected meat; only a fraction of cases comprise transplacental transmission.²

We didn't come across a case report of *Toxoplasma* chorioretinitis from free-range chickens; however, chickens are considered one of the most important hosts in the epidemiology of *T. gondii* infection.³ Free-range chickens are a particularly efficient source of infection for cats who then excrete the environmentally resistant oocysts. Additionally, human consumption of undercooked infected chicken meat may play a role.

Toxoplasma chorioretinitis is largely a clinical diagnosis, and while a positive IgG antibody does not confirm the diagnosis, a negative IgM and IgG titer effectively rules it out. Affected individuals often present with unilateral decrease in vision with floaters. Ophthalmic examination typically reveals a posterior or panuveitis, and a subset may have associated elevated IOP.⁴ The classic retinal findings include a necrotizing chorioretinitis with yellow-white inflammatory lesions with blurred margins and focal vitritis, classically described as a "headlight in the fog." Our case was different in that there was no old chorioretinal scar. Some cases present with a characteristic lobular perivasculitis, thought to be due to vascular endothelial inflammation.

Treatment of ocular toxoplasmosis remains controversial without a clear evidence-based protocol. Left alone, most cases resolve within two months. However, treatment is typically initiated in cases of vision-threatening lesions of the macula or optic nerve and in immunocompromised patients.^{5,6} Various combinations of antibiotics and steroids have been studied. There is currently no treatment regimen that

definitively improves final visual acuity compared to placebo, but current goals of treatment include shortening the active disease course and reducing recurrence.⁶ A recent double-masked randomized clinical trial found that intermittent antibiotic treatment with Bactrim decreased the risk of *Toxoplasma* retinochoroiditis recurrence up to three years following initial infection.⁷ Additionally, intravitreal injection of clindamycin and dexamethasone may be an acceptable alternative to the classic treatment in ocular toxoplasmosis, as outcomes including visual acuity improvement and vitreous inflammation reduction were comparable to traditional oral agents.⁸

In conclusion, *Toxoplasma* chorioretinitis is a clinical diagnosis with characteristic findings, but clinical history does not always include an exposure to cats. Free-range chickens should be considered in cases of *Toxoplasma* chorioretinitis as a potential vector of disease transmission in cases without feline contact. Treatment is controversial because it hasn't been shown to alter final visual outcomes, although most clinicians opt to treat severe, vision-threatening cases to shorten the active course and possibly reduce recurrence. **REVIEW**

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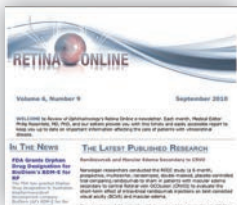
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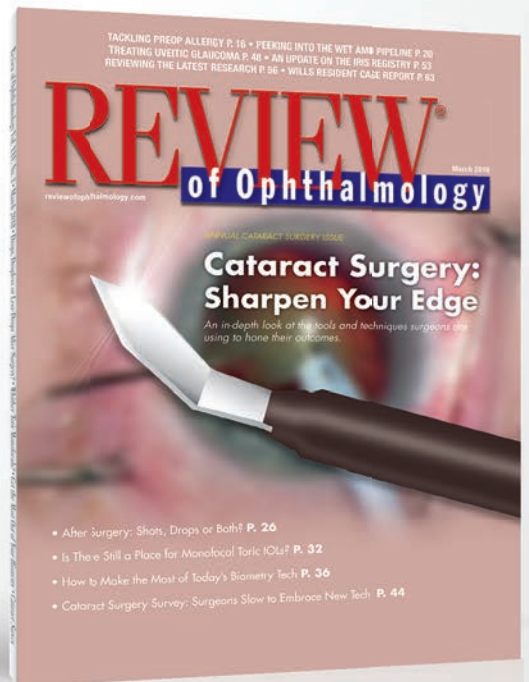


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BRIEF SUMMARY:

Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSAGE AND ADMINISTRATION

Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤ 3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose

tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data

Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg /day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.

Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.

Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.



Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421.

For more information, go to www.Xiidra.com or call 1-800-828-2088.

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XIIDRA MAY DIISRUPT THE INFLAMMATORY CYCLE^{1,2}



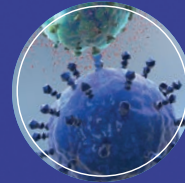
BLOCKS

Xiidra blocks the interaction of ICAM-1 and LFA-1¹



INHIBITS

Xiidra may inhibit T-cell recruitment and activation¹



REDUCES

Xiidra may reduce pro-inflammatory cytokine release¹

Xiidra is the only LFA-1 antagonist approved to treat the signs and symptoms of Dry Eye Disease (DED)^{1,3}

Xiidra is designed to target the interaction between LFA-1 on T cells and ICAM-1. ICAM-1 may be overexpressed in corneal and conjunctival tissues in DED. This interaction is a key mediator of inflammation, which may contribute to the chronic and sometimes progressive nature of DED and perpetuate the signs and symptoms.^{1,2,4,5}

In vitro studies have shown that Xiidra may inhibit the recruitment of previously activated T cells, the activation of newly recruited T cells, and the release of pro-inflammatory cytokines.¹

The exact mechanism of action of Xiidra in DED is not known.¹

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Check it out at Xiidra-ECP.com
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Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.

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