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TAMING TUBE SHUNTS

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When it’s in, it’s on
Sustained release that doesn’t power down for several months.

The DURYSTA® Difference:

- Reliable, non-incisional IOP control
- Studied in patients with mild OAG and OHT
- Bypasses the ocular surface to directly deliver medication

DURYSTA® (bimatoprost intracameral implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

Indications and Usage
DURYSTA® (bimatoprost intracameral implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

Important Safety Information
Contraindications
DURYSTA® is contraindicated in patients with: active or suspected ocular or periocular infections; corneal endothelial cell dystrophy (e.g., Fuchs’ Dystrophy); prior corneal transplantation or endothelial cell transplants (e.g., Descemet’s Stripping Automated Endothelial Keratoplasty [DSEA]) or absent or ruptured posterior lens capsule due to the risk of implant migration into the posterior segment; hypersensitivity to bimatoprost or to any other components of the product.

Warnings and Precautions
The presence of DURYSTA® implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA® should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA® in patients with limited corneal endothelial cell reserve.

DURYSTA® should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA® intracameral implant. DURYSTA® should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Proliferative diabetic retinopathy, including DURYSTA®, has been reported to cause intraocular inflammation. DURYSTA® should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated..

Ophthalmic bimatoprost, including DURYSTA® intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. While treatment with DURYSTA® can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA®, and patients should be monitored following the administration.

Adverse Reactions
In controlled studies, the most common ocular adverse reaction reported by 27% of patients was conjunctival hyperemia. Other common adverse reactions reported in 6%–10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, and headache.

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


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US-DUR-230229/12-2023-004109
INDICATIONS AND USAGE

DURYSTA® (bimatoprost intracameral implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHG).

CONTRAINDICATIONS

- Hypersensitivity to bimatoprost or any component of DURYSTA®
- Pregnancy
- Nursing women (See Warnings and Precautions and Nursing Mothers)
- Hyperpigmentation

ADVERSE REACTIONS

- Ocular reactions: Iritis, iridocyclitis, periocular infections (intraocular pressure elevations occurred in less than 1% of patients, not limited to the treatment eye)
- Local tissue reactions: Hypersensitivity reactions, foreign body sensation, conjunctival hyperemia, dry eye, eye irritation, ocular pressure increase, increased corneal pigmentation
- Other adverse reactions: Conjunctival hyperemia (intraocular pressure elevations occurred in less than 1% of patients, not limited to the treatment eye), foreign body sensation, conjunctival hyperemia, dry eye, eye irritation, ocular pressure increase, increased corneal pigmentation
- Use in Specific Populations: Geriatric Use
- Safety and effectiveness of DURYSTA® in pediatric patients have not been established.

PATIENT COUNSELING INFORMATION

- Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent (see Warnings and Precautions and Potential for Pigmentation).

Potential for Pigmentation

Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent (see Warnings and Precautions and Potential for Pigmentation).

When to Seek Physician Advice

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist (see Warnings and Precautions).

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Government Eyes Consolidation And Private Equity in Medicine

The Federal Trade Commission, the Department of Justice’s Antitrust Division and the U.S. Department of Health and Human Services have begun a cross-government public inquiry into “private-equity and other corporations’ increasing control over health care.”1 As part of the announcement, the government has opened a public comment period, where it’s invited people to notify them of their experiences with consolidation and/or private equity’s presence in medicine. The agencies are also interested in public comment regarding “transactions that would not be reported to the Justice Department or FTC for antitrust review under the Hart-Scott-Rodino Antitrust Improvements Act.”1

In an official statement, the joint task force notes, “Private equity firms and other corporate owners are increasingly involved in health-care system transactions, and, at times, those transactions may lead to a maximizing of profits at the expense of quality care. The cross-government inquiry seeks to understand how certain health care market transactions may increase consolidation and generate profits for firms while threatening patients’ health, workers’ safety, quality of care and affordable health care for patients and taxpayers.”1

The FTC Chair Lina Khan was quoted as saying, “When private equity firms buy out health-care facilities only to slash staffing and cut quality, patients lose out. Through this inquiry the FTC will continue scrutinizing private equity roll-ups, strip-and-flip tactics and other financial plays that can enrich executives but leave the American public worse off.”1

Jane Zhu, MD, a primary care physician and associate professor of medicine in the Division of General Internal Medicine at Oregon Health & Science University, has co-authored several studies into health-care access and quality, and the effects of consolidation in health care. Her research includes ophthalmology practices purchased by private equity.

She and her group take an objective view and she says they just go “where the data leads,” but she’s also able to provide some perspective on why the government has chosen to target consolidation and private equity.

“Obviously, consolidation is happening everywhere, and it’s not just private equity driving this consolidation,” she says. “It’s insurers, large retailers and large hospitals and health systems. I need to stress that private equity is a subset of that. It’s sometimes seen as ‘consolidation on steroids’ because they have so much capital, and their incentives are so precise. It’s not just PE that’s driving corporate consolidation.”

As to why there are theoretical concerns over private equity as a subset of corporate consolidation, Dr. Zhu says it has to do with the nature of the deals. “The unique part of private equity is they’re acting like house-flippers in health care in a way,” she says. “Unlike other corporate owners, private equity is buying up undervalued assets, keeping them for a very short period of time, and then selling them for a large profit. So, the incentives at play are sort of heightened, and private equity’s duty to investors may fundamentally conflict with its duty to patients.”

The attraction of getting involved with a private equity firm if you’re an ophthalmology practice or other specialty practice relates to one of PE’s biggest positives: The infusion of capital.

“As physicians, we know that the practice environment is increasingly complex,” says Dr. Zhu. “It’s much harder to keep up with practice costs these days. There’s a lot of uncertainty around Medicare payments, reimbursement rates which haven’t kept up with the cost of inflation, and the costs of maintaining a practice. And, then you have the additional burdens of electronic health records, the need for billing and coding expertise, value-based payments, population health management, quality improvements and metrics;
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and performance measurements. All of those take time and money and it’s much harder for smaller, independent practices to engage in that. So private equity for a lot of practices may represent an infusion of capital, an infusion of institutional knowledge, and the ability to roll up as a bigger organization and take advantage of the benefits of size. So, you have better negotiating power with insurers and you can potentially get better rates because of that. You can have more market power to get higher volumes of patients and achieve standardization in care. All those things can be beneficial.

“But there are some perverse incentives that can arise from private equity investment,” Dr. Zhu continues. “That comes from the short timeline, and because a lot of these acquisitions are highly leveraged by debt. So, private equity is borrowing money to finance these acquisitions and that [debt] is then placed on the acquired company to pay back. What we’d expect from that are heightened incentives to make as much profit as possible, and a heightened incentive to pay this back as quickly as possible. What we end up seeing in the evidence are increased prices most consistently. And some studies suggest that there are changes in care delivery, both in terms of work-force composition, the types of services and the types of patients. There’s not a lot of strong evidence that quality is improved.”

Along those lines, Dr. Zhu cites a study of private equity in nursing homes. The study found that being in a private equity-owned nursing home increased the chance of death by 11 percent, either during your stay or for the 90-day period after discharge. “In the context of the health economics literature, this is a very large effect,” the authors noted.

“So, this empirical evidence and the news reports about Steward Health Care and the like have caught the attention of policymakers,” Dr. Zhu says. “Those are the loudest, most negative consequences that we can think of with this [PE] involvement and that’s what’s really captured regulators’ attention.”

For her part, Dr. Zhu points to a recent study she co-authored that looked at the effects of private equity ownership in ophthalmology, gastroenterology and dermatology practices. “Our study did find an increase in turnover in pre-acquired practices versus independently owned controls,” she says. “We also saw an increase in the hiring of advanced practice providers [e.g., physician’s assistants]. So, there’s the possibility that there’s not only changes in the composition of the work-force, but also changes in the satisfaction and career trajectory for physicians.”

Ultimately, Dr. Zhu thinks that, even if no concrete regulations come of this inquiry into consolidation, just the existence of the inquiry will have an impact. “The very fact that the FTC and DOJ are looking into this issue is having a chilling effect on private equity,” she says. “Through this assessment and gathering of public comments, they’re basically telling private equity that its activity is on notice and [the government] is paying attention. There’s a lot of ‘dry capital,’ and private equity is still very interested in health-care acquisitions. However, I think these legal and regulatory guardrails are going to have some downstream impacts.”


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New OCTA Metric Could Predict Visual Field Loss

Although it’s not yet precise, a newer OCTA metric gives clinicians and researchers a glimpse of future functional progression in glaucoma patients. Researchers believe that rapid initial optic nerve head capillary density loss may be used to assess the risk of glaucoma visual field progression. Their recent study, published in *JAMA Ophthalmology*, found that rapid initial optic nerve head capillary density loss from OCTA was associated with a faster rate of VF progression and a doubling of the risk of developing event progression. They believe that their method could potentially help identify patients who demonstrate a high risk for fast glaucoma progression, resulting in more severe functional impairment and potentially in blindness, which is paramount for optimizing management strategies.¹

The retrospective study of a longitudinal cohort at a glaucoma referral center included 167 eyes (96 with primary open-angle glaucoma and 71 glaucoma suspects) of 109 patients (mean age: 69; 51.4 percent female) who were monitored for a mean of 5.7 years. The rates of initial capillary density and average retinal nerve fiber layer loss were calculated from the first three optic nerve head OCTA and OCT scans, respectively, during the initial follow-up (mean: two years).

Based on the median rate, eyes were categorized into fast- and slow-progessor groups.

Early OCTA progression rate was found to be a slightly better predictor of future VF loss than early change rates in OCT RNFL or ganglion cell complex thickness. Early OCTA progression rate was found to be a slightly better predictor of future VF loss than early change rates in OCT RNFL or ganglion cell complex thickness. In this cohort, OCTA imaging showed 83 eyes to be slow progressors and 84 eyes to be fast, with

(Continued on p. 12)
XEN® Gel Stent is a proven pathway to IOP control for refractory glaucoma patients.¹

- From a wide range of baseline pressures,* XEN® Gel Stent achieved a mean IOP of 15.9 (± 5.2) mm Hg through 12 months (n = 52)¹,²
- 76% of XEN® Gel Stent patients achieved a ≥ 20% IOP reduction in the ITT group (N = 65)¹
- 81% of XEN® Gel Stent patients achieved a ≥ 25% IOP reduction among those completing the 12-month visit (n = 52)²
- Pivotal safety data included 0% intraoperative complications (0/65) and 0% persistent hypotony (0/65); transient hypotony† occurred in 24.6% of patients (16/65)¹

IOP = Intraocular pressure; ITT = intent to treat.

* In the XEN® Gel Stent clinical study, baseline medicated IOP ranged from 20.0 to 33.7 mm Hg.²

† No clinically significant consequences were associated with hypotony, such as choroidal effusions, suprachoroidal hemorrhage, or hypotony maculopathy. IOP < 6 mm Hg was defined as an adverse event, regardless of whether there were any associated complications or sequelae related to the low pressure. Thirteen cases occurred at the 1-day visit; there were no cases of persistent hypotony, and no surgical intervention was required for any case of hypotony.¹

CONSIDER XEN® FOR THE NEXT STOP ON YOUR PATIENT’S TREATMENT JOURNEY.

INDICATIONS
The XEN® Glaucoma Treatment System (XEN® 45 Gel Stent preloaded into a XEN® Injector) is indicated for the management of refractory glaucomas, including cases where previous surgical treatment has failed, cases of primary open-angle glaucoma, and pseudoxfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
XEN® Gel Stent is contraindicated in angle-closure glaucoma where angle has not been surgically opened, previous glaucoma shunt/valve or conjunctival scarring/pathologies in the target quadrant, active inflammation, active iris neovascularization, anterior chamber intraocular lens, intracranial silicone oil, and vitreous in the anterior chamber.

WARNINGS
XEN® Gel Stent complications may include choroidal effusion, hyphema, hypotony, implant migration, implant exposure, wound leak, need for secondary surgical intervention, and intracranial surgery complications. Safety and effectiveness in neovascular congenital, and infantile glaucoma has not been established. Avoid digital pressure following implantation of the XEN® Gel Stent to avoid the potential for implant damage.

ADVERSE EVENTS
The most common postoperative adverse events included best-corrected visual acuity loss of ≥ 2 lines (≤ 30 days 15.4%, > 30 days 10.8%, 12 months 6.2%), hypotony IOP < 6 mm Hg at any time (24.6%; no clinically significant consequences were associated, no cases of persistent hypotony, and no surgical intervention was required), IOP increase > 10 mm Hg from baseline (21.5%), and needling procedure (32.3%).

Caution: Federal law restricts this device to sale by or on the order of a licensed physician. For the full Directions for Use, please visit www.allergan.com/xen/usa.htm or call 1-800-678-1605. Please call 1-800-433-8871 to report an adverse event.

Please see full Directions for Use at https://www.rxabbvie.com/pdf/xen_dfu.pdf
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INDICATIONS AND USAGE
XDEMVY (lotilaner ophthalmic solution) 0.25% is indicated for the treatment of Demodex blepharitis.

IMPORTANT SAFETY INFORMATION:
WARNINGS AND PRECAUTIONS
Risk of Contamination: Do not allow the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to minimize contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use with Contact Lenses: XDEMVY contains potassium sorbate, which may discolor soft contact lenses. Contact lenses should be removed prior to instillation of XDEMVY and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS: The most common adverse reaction with XDEMVY was instillation site stinging and burning which was reported in 10% of patients. Other ocular adverse reactions reported in less than 2% of patients were chalazion/hordeolum and punctate keratitis.


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ADVERSE REACTIONS:

Lotilaner, the active ingredient in XDEMVY1,3,4:
- Is a lipophilic agent in an aqueous drop that...
- Acts specifically via mite GABA-gated chloride channels to...
- Target, paralyze, and kill Demodex mites

GABA=gamma-aminobutyric acid.

XDEMVY gives you might over mites to eradicate Demodex blepharitis.1,2

Real results

44% and 55% of patients taking XDEMVY in SATURN-1 (N=209) and SATURN-2 (N=183), respectively, achieved a significant improvement in their eyelids (reduction of collarettes to no more than 2 collarettes per upper lid) at Day 43 vs 7% (N=204) and 12% (N=200) of patients taking vehicle (P<0.01 in each trial).1,*

All images are of actual patients who participated in clinical trials for Tarsus Pharmaceuticals.
**ADVERSE REACTIONS**

Because clinical studies 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.

**XDEMVY** was evaluated in 833 patients with Demodex blepharitis in two randomized, double-masked, vehicle-controlled studies (Saturn-1 and Saturn-2) with 42 days of treatment.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

**Risk of Contamination**

Do not allow the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to minimize contamination of the solution. Serious damage to the eyes and subsequent loss of vision may result from using contaminated solutions.

**Use with Contact Lenses**

Contact lenses should be removed prior to instillation of XDEMVY and may be reinstated 15 minutes following its administration.

**ADVERSE REACTIONS**

Because clinical studies 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.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Risk Summary: There are no available data on the use of XDEMVY in pregnant women to inform any drug-associated systemic exposure to lotilaner from ophthalmic use in pregnant women to inform any drug-associated systemic exposure to lotilaner from ophthalmic use in pregnant women to inform any drug-associated systemic exposure to lotilaner from ophthalmic use in pregnant women to inform any drug-associated systemic exposure to lotilaner from ophthalmic use in pregnant women to inform any drug-associated systemic exposure to lotilaner from ophthalmic use in pregnant women to inform any drug-associated systemic exposure to lotilaner from ophthalmic use in pregnant women to inform any drug-associated systemic exposure to lotilaner from ophthalmic use in pregnant women to inform any drug-associated systemic exposure to lotilaner from ophthalmic use in pregnant women to inform any drug-associated systemic exposure to lotilaner from ophthalmic use in pregnant women to inform any 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It's on top of the situation surrounding Steward Health Care, which apparently incurred so much debt acquiring more hospitals that the care at existing facilities may have suffered (and it’s now facing possible bankruptcy and the shuttering of hospitals), as well as the numerous physician horror stories on the open comments section of the FTC’s website regarding consolidation.

I’m sure we all hope that this apparent movement toward added scrutiny of consolidation will nudge these business entities back toward the straight-and-narrow path, where they can make a profit but physicians and patients can also feel good about the care they give and receive.

Sorry, Gordon, it turns out greed is not always good.

— Walter Bethke
Editor in Chief


iStent infinite® IMPORTANT SAFETY INFORMATION

INDICATION FOR USE. The iStent infinite® Trabecular Micro-Bypass System Model iS3 is an implantable device intended to reduce the intraocular pressure (IOP) of the eye. It is indicated for use in adult patients with primary open-angle glaucoma in whom previous medical and surgical treatment has failed.

CONTRAINDICATIONS. The iStent infinite is contraindicated in eyes with angle-closure glaucoma where the angle has not been surgically opened, acute traumatic, malignant, active uveitic, or active neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure.

WARNINGS. Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization that could lead to improper placement of the stent and pose a hazard. MRI INFORMATION. The iStent infinite is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. PRECAUTIONS. The surgeon should monitor the patient postoperatively for proper maintenance of IOP. Three out of 61 participants (4.9%) in the pivotal clinical trial were phakic. Therefore, there is insufficient evidence to determine whether the clinical performance of the device may be different in those who are phakic versus in those who are pseudophakic. ADVERSE EVENTS. The most common postoperative adverse events reported in the iStent infinite pivotal trial included IOP increase ≥ 10 mmHg vs. baseline IOP (8.2%), loss of BCVA ≥ 2 lines (11.5%), ocular surface disease (11.5%), perioperative inflammation (6.6%) and visual field loss ≥ 2.5 dB (6.6%). CAUTION: Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.

REFERENCE
Something For Nothing
Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER, MD
CHIEF MEDICAL EDITOR

It’s always nice to get something for nothing. There’s usually a catch, however, or at least a trade-off, a quid pro quo. So, it’s not really free. It’s a transaction with both sides realizing something of value. Perhaps not equal value, but value. It’s a situation where no one feels taken advantage of, or used. Because if they do end up feeling used, that might be the last transaction. It wouldn’t encourage an ongoing relationship.

If you’re in a business where there needs to be repeat customers, you might want to be careful not to push your customer/partner too far. They might leave, despite any perceived leverage or higher obligation that exists, which would likely be bad for both of you.

This entire line of thought came up as I struggled yet again, and on an almost daily basis, with the challenges of providing consulting services to our medical center affiliate. They expect almost instantaneous response to all requests—from patient consults, trauma and the ER to emergent surgery. They pay for nothing. No retainer, no click fees, no on-call payments. We can bill the patient for the services but in an inner-city location the percent of patients paying nothing is significant.

We’re certainly not covering the costs to provide 24/7 response across all subspecialties. They assume we will have or will engage the clinical staff to respond to their needs, even when those needs grow with no consideration or consultation with us.

When I’ve asked about funding to help support the necessary resources, I’m told we have to do this because we are on the medical staff, and it’s an obligation. Historically, that’s the way it worked. You needed to be on the hospital staff to practice medicine even if you didn’t use their facilities. The insurance companies demanded it. And, the ability to be part of a larger medical staff led to relationships that resulted in referrals that kept your practice alive.

If this is starting to sound like a page out of the history books, it’s because it is. Medical care has moved largely outside of the medical center and into offices and surgicenters, all encouraged by patients and insurers.

So out we went, to fend for ourselves in many ways. What benefit remained by staying affiliated? The ‘prestige’ of belonging to a famous hospital? No one believes that anymore. It’s the remnant of an obligation most of us felt when we became doctors. We wanted to help those in need, no matter their circumstances. The Hippocratic oath. Everyone chipping in together. Conceptually we still believe that, but others in the health-care system take advantage of it.

Individual physicians have taken a huge beating in reimbursement over the years. The ‘gravy’ is gone, and every minute we spend doing something unpaid is more painful. The ability to be gracious about our time and resources has been stripped away. Still, someone needs to attend to those in need of care. But who? And with what monies?

To be fair, health systems are also very strained. Many have gone out of business, merged, been bought, sold and/or have been traded like a commodity. They’re on the brink as well. And this has led to a more predatory attitude from larger players. Anyone not fully inside their walled garden is a resource to be used, not supported. Not that those inside are protected either. It’s harsh either way.

So we’re back to trying to find a relationship that is equitable enough that no one walks away, that no one is fatally hurt. It’s not really a negotiation these days. It’s a game of chicken. Or rather a contest between David and Goliath. Goliath expects something for nothing, and David is out of ammunition.
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Discontinued Surgical Procedures

How to code for situations in which you begin a procedure but aren’t able to complete it.

In recent years, as the use of MIGS surgery in combination with cataract procedures has increased, the instances where the planned procedures can’t be completed have also risen. Correct billing depends on when and why the procedure was stopped. This can occur, for example, in cases where the cataract procedure can be completed without any difficulty but the placement of the aqueous drainage device can’t be done successfully and has to be removed from the eye.

Here, we’ll discuss the coding implications for such occurrences.

Q How should the incomplete procedure be billed?
A The CPT manual includes a modifier appendix with this provision for procedures discontinued “...due to extenuating circumstances or those that threaten the well-being of the patient.” Novitas, a Medicare Administrative Contractor for several states, wrote in its fact sheet for surgical modifiers that, “discontinued due to elevated blood pressure” is a credible justification. This is described by modifier -53 for the surgeon’s claim, and either modifier -73 or -74 for the claim from the ambulatory surgery center.

In this case, the operative report describes that the cataract portion of the operation was successful, but that the MIGS procedure wasn’t performed successfully. There are many potential reasons why the surgeon didn’t succeed in placing the ADD, including difficulty with visualization, equipment malfunction, a defective implant, surgeon inexperience, poor patient selection or intraoperative misadventure.

While billing the planned procedure (66991) with modifier -53 is plausible, the use of modifier -53 should be reserved for a case that’s terminated for risk of sight-threatening reasons rather than failure to complete it.

Q When is modifier -53 used?
A Consider an inadvertent incision in an artery within the iris root resulting in a significant hemorrhage in the anterior chamber, obscuring the surgeon’s view of the anterior chamber angle, and additional viscoelastic can’t stop the bleeding. In this case, there’s an acute threat to the patient’s well-being that warrants discontinuation of the procedure. Such a situation necessitates a longer, more detailed operative report that explains what went wrong, why and how it was handled. This could support 66991-53.

Q How do you document support for discontinued procedures?
A The Centers for Medicare & Medicaid Services (CMS) instruct that, “the operative report should specify the following:

- Reason for termination of the surgery;
- Services actually performed;
- Supplies actually provided;
- Services not performed that would have been performed if surgery had not been terminated;
- Time actually spent in each stage, e.g., preoperative, operative, and postoperative;
- Time that would have been spent in each of these stages if the surgery had not been terminated; and
- HCPCS (or CPT) code for procedure had the surgery been performed.”

Q How are surgeon’s claims processed with modifier -53?
A As a practical matter, the resolution of a claim for a discontinued procedure will rely on the payer’s assessment of the portion of the procedure completed. Was it half? A quarter? Operative notes may be requested by the payer to make this decision. In this example, none of the MIGS procedure was completed, so very

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This article has no commercial sponsorship.
little value would likely be ascribed to it.

**Q How are ASC claims for discontinued procedures handled by Medicare?**

A The Medicare Claims Processing Manual instructs payers how to handle claims based on when the case is terminated:

- **A.** Contractors deny payment when an ASC submits a claim for a procedure that is terminated before the patient is taken into the treatment or operating room.
- **B.** Contractors pay 50 percent of the rate if a surgical procedure is terminated due to the onset of medical complications after the patient has been prepared for surgery and taken to the operating room but before anesthesia has been induced or the procedure initiated (use modifier -73).

**Q What is the billing alternative?**

A Frequently when one procedure is discontinued, another procedure is completed instead. If the reason the ADD implant isn’t implanted successfully doesn’t support modifier -53 (e.g., poor patient selection or inadequate surgeon skill), it’s reasonable to bill only for the cataract surgery (66984)—the completed procedure.

**Q What happens to the ASC payment?**

A If the ADD procedure can’t be supported but cataract surgery can, then reimbursement to the ASC is for 66984 only. There’s no reimbursement for the ADD device. It may be possible for the ASC to obtain a refund or a replacement product from the manufacturer for the unused device.

In conclusion, not all surgical procedures go as planned. Accurate, detailed documentation in the operative note provides the necessary information for payment, whether a discontinued surgery is billed or the surgeon completes and bills for an alternate procedure. 1

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1. Medicare Claims Processing Manual (Chapter 14, §40.40).

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Cell Therapy Clinical Trials: An Update

Insight into the next generation of potential therapies entering our field of view.

KRISHNA PRADEEP NAYAR, MD, LUIS A. ACABA-BERROCAL, MD, YOSHIHiro YONEKAWA, MD, ALLEN C. HO, MD
PHILADELPHIA

They say that time heals all, but perhaps a more accurate argument would be that time gives us the data to heal all. Twenty years ago, patients diagnosed with age-related macular degeneration would have few treatment options. With AREDS studies just taking off, treatment for neovascular AMD would have been limited to photodynamic therapy or laser photocoagulation. Over time, new players entered the game, quickly changing the paradigm of the field of retina and our understanding of AMD. Success in clinical trials helped anti-VEGF drugs such as bevacizumab, ranibizumab and aflibercept become the mainstays of neovascular AMD treatment.1-3 Today, we even have options for patients with advanced dry AMD, with pegetacoplan and avacincaptad pegol entering the market following the market following positive trial results.4 However, current treatments require adherence to strict treatment windows, are associated with potential complications such as endophthalmitis and retinal vasculitis, and don’t have the potential to restore the cellular damage already caused by the disease. This is the gap that regenerative therapies aim to fill.

Cell therapy, if proven to be a viable form of treatment, could help alleviate some of the limitations associated with our current standard of care in ophthalmology. In this article, we’ll describe the pipeline for stem cell trials hoping to make some headway not only for AMD, but also for retinal dystrophies, including retinitis pigmentosa and Stargardt disease. Unlike gene replacement therapy where specific genes are replaced for specific genetic conditions, cell therapy is disease-agnostic. This means that one cell therapy may be able to provide treatment for multiple diseases, regardless of genetic makeup or even disease entity.

Astellas/ACT Trials for Stargardt Macular Dystrophy

Stargardt macular dystrophy (SMD) is the most common form of juvenile macular dystrophy and has no current FDA-approved treatments on the market. It may be associated with mutations of the ABCA4 gene, causing dysregulation of the photoreceptor retinoid cycle ultimately leading to gradual RPE and photoreceptor cell death.5 Eyes with advanced SMD often have limited vision due to macular atrophy.

Embryonic stem cells, given their ability to differentiate into various cell types, have theoretical potential to repair and replace degenerated tissues.6 In 2010, the FDA approved the second ever U.S. clinical trial to test human embryonic stem cells (hESCs), and the first to use them in patients with SMD.7 Now acquired by Astellas Pharma, the 7316-CL-0001 study was initiated by Advanced Cell Technology (ACT) as a Phase I/II safety and tolerability assessment for the use of hESC-derived RPE cells (named ASP7316 or MA09-hRPE) in patients with SMD.8

An identical design was used in simultaneous U.K.-based SMD trials, under the protocol 7316-CL-0003.9 The U.S. study enrolled 13 patients, divided into four “worse vision” cohorts and one “better vision” cohort based on visual acuity at presentation. Each cohort was assigned a dose ranging from 50,000 to 200,000 hESC RPE cells, with the same design replicated for the U.K. protocol, 7316-CL-0003, in which a total of 12 patients were enrolled. Each patient underwent a pars plana vitrectomy in the worse-seeing eye, followed by subretinal injection of viable hESC-RPEs in suspension form. A regimen of tacrolimus and mycophenolate mofetil was introduced a few days before surgery to prevent rejection. Patients were followed over the course of 52 weeks following cell transplant in the initial U.S. and U.K. protocols, and all continued onto respective five-year long-term follow-up studies.

At six months follow-up in the U.S. trial, three patients had a gain of ≥15 ETDRS best-corrected visual acuity letters, four had maintenance of baseline acuity, and one patient had a decrease of ≥10 letters.10 At one year, four patients experienced an improvement of ≥10 letters while no fellow untreated eyes experienced a gain of...
≥10 letters. Overall, transplantation was successful without failure or rejection in all 13 patients through the one year follow-up period. The most prevalent postoperative complication was significant cataract progression, as seen in three out of 13 patients in the U.S. trial (two of which required cataract surgery). Two cases of vitreous inflammation were also noted in this trial: One was attributed to endophthalmitis, and the other remained stable until spontaneous resolution by month six.10,11

Data from the U.S. LTFU study, protocol 7317-CL-0004, showed that the treatment was safe and well-tolerated at all doses, with no major safety events supporting dose-dependent trends. No immune responses or adverse events pointing to cell graft rejection or failure were noted, and visual acuity data demonstrated a sharper decline in the BCVA letter score for untreated eyes as opposed to treated eyes through the end of the study. At one year post-transplant, eyes treated on the initial study had an average BCVA letter decline of 6.7 letters, compared to a mean decrease of 1.3 letters in the untreated eyes. However, at five years post-transplant, treated eyes experienced an average BCVA letter score decrease of eight letters, compared to 20.7 in eyes that weren’t treated.12,13

LTFU data from U.K. protocol 7316-CL-0006 similarly reported no evidence of graft failure or rejection in any of the patients. Notably, there was also no remarkable difference in BCVA between treated and untreated eyes. Among the 12 patients enrolled, the mean change in BCVA letter score for treated eyes between the baseline visit and the month 60 post-transplant assessment was 2.8 letters, compared to an average change of two letters in untreated eyes. Epiretinal membrane formation was observed more frequently in treated eyes, although the number of cases seen for each hasn’t yet been published.14,15 While data regarding the rate of retinal detachments has yet to be disclosed for these trials, it should be noted that this is an additional risk factor to be considered with many invasive transvitreal procedures including PPVs and delivery of subretinal therapies.

Astellas Trials for GA Secondary to AMD
Photoreceptor and RPE degeneration with central vision loss is the hallmark of geographic atrophy in AMD. In the early 2010s, a cell therapy protocol for this subset of patients was initiated to determine whether the Astellas ASP7316 line of hESC-RPEs could be a safe and tolerable treatment consideration for the future. The ASP7316 cell line’s Phase I/II safety and tolerability trial for U.S. patients with advanced dry age-related macular degeneration was conducted under the protocol 7316-CL-0002.16 A total of 13 patients were treated in this study, which followed a dose-escalation design starting at a 50,000-cell transplant, increasing in sequences of 50,000 cells-per-cohort until a maximum of 200,000 cells was reached. As with the SMD studies, the cells were transplanted in the subretinal space following PPV in the eye presenting with worse vision. Upon completion of the initial trial, 11 subjects were enrolled into the corresponding five-year LTFU protocol, 7316-CL-0005, for further review.17

Although data analysis of the follow-up study remains unpublished, a summary report released by Astellas stated that it was overall well-tolerated, with no signs of graft failure, immune response or rejection. As with the initial SMD studies, data indicating the frequency of common postoperative complications such as RDs and ERM formation have yet to be published, but should still be noted as a potential risk for any patient. Vision data demonstrated that between months 12 and 24 postop, the average BCVA score increased by 10.4 letters in the treated eye, and 3.8 letters in the untreated eye. However, by month 30 post-transplant BCVA letter scores decreased by 1.6 and 0.7 letters in the treated and untreated eyes, respectively.18 A follow-up report analyzed these BCVA trends and reported better averages for subjects that didn’t experience postoperative cataract formation.10

Given the success in safety and tolerability of these previous trials, the Astellas pipeline now includes an
updated product of hESC-RPE cells (ASP7317), which will continue to be investigated as a potential treatment for GA and SMD. The Phase Ib 7317-CL-0003 trial is actively enrolling, gathering safety and tolerability data, as well as efficacy results related to potential impacts to vision and GA lesion size.19 The trial is expected to conclude in late 2025, with its design following that of the earlier, dose-escalation method of treating patients with 50,000 to 200,000 cells. As with previous Astellas protocols, this surgical procedure includes a PPV, followed by subretinal injection of the cell dosage designated to each patient based on cohort selection.

Roche/Genentech (Previously CellCure/Lineage) Trials for GA

In 2015, Lineage Cell Therapeutics began a Phase I/IIa dose-escalation trial testing a cell suspension of directly differentiated hESC-RPE cells (RG6501) in patients with GA in both eyes secondary to dry AMD. Similar to the cell therapy used throughout the Astellas pipeline, the Lineage trial investigated hESC-RPE cells for safety and tolerability delivered in two forms. The first form was a standard subretinal implantation following PPV, and the second consisted of an FDA-approved suprachoroidal to subretinal delivery (Orbit Subretinal Delivery System) of the cells, performed in seven out of 24 enrolled patients. A total of 12 patients were treated with RG6501 doses between 50,000 and 150,000 cells, while the remaining 12 patients received 200,000 cell units.20,21

The first phase of the trial followed subjects until a year post-transplant, and 21 subjects have continued into the second phase: A period of routine observation lasting up to five years. This study is still actively collecting data as part of its follow-up segment. Endpoints include safety and tolerability analyses as well as changes to the rate of GA progression. Subjects were assigned tacrolimus and mycophenolate therapy for six and 12 weeks post-transplant, respectively.22

Overall, data demonstrated that the hESC-RPEs were well-tolerated in most patients, although two of 17 patients in the PPV group experienced RDs post-transplant, and 15 out of 17 patients in the group experienced mild to moderate ERM formation. Both retinal detachments observed were subsequently treated and resolved, and out of the 15 ERM cases, three required surgical peeling. Among the seven patients treated with RG6501 via suprachoroidal delivery, choroidal neovascularization was noted in three cases, one of which resolved completely following a single treatment with anti-VEGF. The remaining two CNV patients required regular anti-VEGF administration following AE onset.23

In terms of visual changes and disease progression over time, lower-dose cohorts followed a relatively typical course of GA progression from surgery to long-term follow-up, with no remarkable results being disclosed in interim results. The 200,000-cell group, however, showed more promising results, particularly in the smaller GA lesion and better baseline VA cohort and when the subretinal bleb showed extensive coverage of the GA lesion. Out of 12 patients enrolled in that cohort, three (25 percent) had a BCVA improvement ≥15 letters in the treated eye at year one post-transplant. The average BCVA change by year one post-transplant was a gain of 7.6 letters. Untreated eyes, however, declined in BCVA letter score on average.

Similarly, fundus autofluorescence imaging showed that treated eyes across all cohorts demonstrated reduced rates of RPE loss at the border of GA lesions.23,24 Subjects with extensive bleb coverage demonstrated improvements in outer retinal structure on qualitative OCT analysis by a masked grader. The Phase I/IIa trial, currently in the observational phase, is expected to conclude in mid-2025.

Another Phase IIa RG6501 GA study from Roche and Genentech, protocol GR44251, is currently active and enrolling close to 60 patients in California, Ohio and Pennsylvania.25,26 Unlike the initial dose-escalating study, this trial is focusing only on safety and efficacy results of the 200,000 hESC-RPE cell dosage, with hopes to provide more statistical power to the data in the Phase I/II line trial’s high-dose cohort results.

Regenerative Patch Technologies Trials for GA

A 2016 study conducted by Regenerative Patch Technologies (RPT) explored the use of a bioengineered retinal “patch” implant for GA, consisting of a monolayer of hESC-derived mature RPE cells adhered to a perylene scaffold.27

The cell product (CPCB-RPE1) was delivered subretinally to 16 patients enrolled in this Phase I/IIa trial, completely covering the atrophic lesion in each study eye. Tacrolimus and intravenous steroids were provided to all subjects.

The surgical method for this study was published in 2020 by Amir Kashani, MD, PhD, and colleagues at the University of Southern California (Continued on p. 62)
HOW TO COMBINE MIGS FOR THE GREATEST EFFECT

Glaucoma surgeons share their tips and techniques for maximizing the results of minimally invasive glaucoma surgery using combined techniques.

Combining MIGS: Why and When

Although MIGS are combined in standalone procedures, the classic definition of combination MIGS includes the use of phacoemulsification and two or more MIGS procedures, according to David Solá-Del Valle, MD, a glaucoma and cataract specialist, chief medical officer at Chittick Eye Care, and associate professor at the Carle Illinois College of Medicine in Champaign, Illinois.

Dr. Solá-Del Valle recently led a comprehensive review of studies on MIGS combinations.1 When selecting a patient, he first determines if one MIGS modality alone is appropriate. “If we can agree on that, then we can explore who would be good candidates for combined MIGS,” explains Dr. Solá-Del Valle, who also conducts part-time research at Massachusetts Eye and Ear as a former assistant professor at Harvard Medical School.

And when does he combine MIGS? “Let’s say the patient’s goal pressure is 17 mmHg, and the pressure is above 20 mmHg—at 23 mmHg or 24 mmHg, for instance,” he explains. “The patient is on two or three medications and wants to end or significantly decrease his medication burden. I find that single MIGS would have difficulty achieving this goal, which would enable the patient to stop using all agents, for example. So combination MIGS will be a great option for that patient, who...”
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may have mild-to-moderate disease.”

**Last Ditch Effort?**

Although MIGS combinations are usually used early in disease, Derek Mai, MD, a glaucoma specialist at Madigan Army Medical Center in Tacoma, Washington, sometimes uses them in advanced glaucoma cases. Many patients in his military-based practice have had surgeries 20 to 30 years before he even sees them. “Some are still progressing,” he says. “I will have a pretty in-depth discussion with these patients about what they can expect, including limitations. If they have an open angle, and they don’t have any contraindications for an endocyclophotocoagulation procedure, I discuss combining different MIGS. Combined MIGS in these patients entails long-term inflammatory risks and an immediate risk of hyphema developing right after surgery. But I’ve had some very good successes, in terms of improving a patient’s quality of life, reducing medication burden and lowering IOP into the low to mid-teens.

“The literature may indicate there is minimal evidence to support combined procedures for these advanced patients,” he continues. “But when there are no other options left, I find myself using these combinations as a last-ditch effort to get their glaucoma under control.”

Dr. Solá-Del Valle also uses combined MIGS in patients with moderate-to-severe disease, defined by the ICD-10 codes. “I’m thinking of a patient with small nasal steps such as a superonasal step with an early inferonasal step that may not always be repeatable,” he notes. “Combined MIGS can be a stepping stone before moving on to more invasive procedures.”

After combined-MIGS, some patients can still experience glaucoma progression and a need for multiple medications. But without the option of combined MIGS, Dr. Solá-Del Valle adds, “that patient may have otherwise undergone a trabeculectomy or a tube shunt earlier on. Nonetheless, I still avoid combined MIGS in extremely advanced disease, such as patients with central islands of vision or those who need single-digit IOPs.”

**Only the Beginning?**

Matt Porter, MD, a cataract and glaucoma surgeon and an assistant professor at Texas Tech University Health Sciences Center School of Medicine, is also bullish on combining MIGS, an approach that he believes will become more prevalent in the future. “This is a subject that is somewhat under-explored in the literature,” he says. “It has a lot of potential to help patients, and it’s important to talk about it and get people thinking about it.”

Dr. Porter has tried varied combinations of MIGS but he’s most comfortable using the Hydrus (Alcon)—an eyelash-sized stent for mild and moderate glaucoma—in conjunction with the iTrack Advance (Nova Eye Medical), which provides 360 degrees of catheterization and pressurized viscodilation in the conventional outflow pathway.

“It’s not the only combination that I use,” he explains. “But it’s the most common one. My colleagues, Mark Gallardo, MD, Brandon Wood, MD, and I collected our own data on this, and we’ve been very pleased with
strong results several years out. When you see your patients are still doing well, it’s hard to argue with the results, especially in the absence of randomized controlled trials.”

Their retrospective evaluation of first-year results was based on 51 patients, 41 of whom were uncontrolled—defined as any patient with an average baseline IOP of 19 mmHg who was taking a mean of 2.2 medications.

“A lot of these patients were very sick,” he notes. “That’s significant when you consider that most patients in typical MIGS trials have mild to moderate glaucoma. Three-quarters of our patients were actually either moderate or severe. At one year, their IOP was down to an average of 13 mmHg, while they were taking only one medication. That’s a significant reduction in pressure and medication burden.”

Findings in the study’s uncontrolled patients, whom he would have otherwise treated with a tube shunt or a trabeculectomy, have also continued to be strong. “In fact, the uncontrolled patients did just as well or better than more controlled patients in the study,” he points out. “They had a higher starting IOP of 19.9 mm Hg and were using an average of 2.4 medications with similar results as was experienced by the total group. If we can combine different mechanisms of action, we can potentially improve the results for these patients.”

He notes that Hydrus scaffolds the canal, providing multiple openings over a quarter of the canal’s circumference. “When combining Hydrus with canaloplasty, the result is use of two procedures that are complementary, attacking both the proximal and distal conventional outflow systems,” he says. “Bypassing the trabecular meshwork and treating the distal canal and collector channels might increase chances of success without having to excise the trabecular meshwork. Adding stents to canaloplasty can perhaps make it work longer and more effectively. In my experience, a moderate open-angle patient with an IOP in the mid 20s, on three or four medications, could benefit from these combination procedures.”

Dr. Porter also hopes to try a standalone combination by using stents and ab interno canaloplasty in uncontrolled patients who don’t require cataract surgery. He plans on combining ab interno canaloplasty with iStent Infinite (Glaukos) stents as his choice of a standalone combination approach.

Combining the Right MIGS

Many surgeons develop favored lists of MIGS procedures to combine, including the use of Xen (Allergan), a subconjunctival-based intervention. Like Dr. Porter, Dr. Solá-Del Valle mixes his preferred options to take advantage of different mechanisms of action for moderate-to-severe patients. “I’m a big fan of doing phaco with ECP and goniotomy, using the Kahook Dual Blade, the SION device, or gonioscopy-assisted transliminal trabeculotomy (GATT), Omni, or a similar procedure,” he says. “I find that these are amazing combinations because you’re opening the drainage system via the trabecular meshwork with the goniotomy, for example. But you’re also using the ECP laser to decrease fluid production.”

As an alternative to ECP, Dr. Solá-Del Valle says micropulse transscleral cyclophotocoagulation can be helpful. He notes that he participated in a study at his institution that compared the micropulse laser combined with phaco to ECP combined with phaco.

“We found that the transscleral group did just as well as the group in which phaco and ECP were used—if not just as well, even a little better than the ECP group, depending on which factors we considered,” recalls Dr. Solá-Del Valle. “Keep in mind that you can combine either of these procedures with any number of trabecular meshwork procedures (such as iStent, or the ICE procedure, which combines iStent, phaco and ECP), as well as with iAccess, Hydrus, and other stents. The possible MIGS combinations can seem endless, especially with all the new MIGS in the pipeline.”

He points out that two trabecular meshwork-based procedures can also be combined, especially for patients with less severe glaucoma. “I’m thinking of Streamline canaloplasty with iStent Infinite or iStent Infinite with iAccess,” he explains. “Success depends on individualizing patient care by considering patient characteristics, goals of care and surgeon experience.”

Dr. Solá-Del Valle and his colleagues presented the findings of an ongoing study at the 2024 American Society of Cataract and Refractive Surgeons in Boston that showed how adding iAccess to the ICE-2 procedure (iStent Inject, cataract extraction and
Tyrvaya® is not another drop
It’s an ocular surface-sparing nasal spray.2

Activates real, basal tears
Tyrvaya® is believed to work by activating the trigeminal parasympathetic pathway resulting in basal tear production.2*

Real tears, real fast
In 2 clinical trials with mild, moderate, and severe dry eye disease patients, Tyrvaya increased tear production from baseline by ≥10 mm in Schirmer’s Test Score (STS) in nearly 50% of patients at week 4, with increased tears seen as early as the first dose and over 12 weeks.2-8†

*The exact mechanism of action is unknown.
†Tyrvaya was evaluated across 3 randomized, vehicle-controlled, double-masked studies in which adults aged ≥22 years diagnosed with dry eye disease received 1 spray of either active drug or vehicle in each nostril twice daily. Primary endpoint: % of patients with mean change from baseline in STS of ≥10 mm at week 4 in ONSET-1: 52% with Tyrvaya (n=48) vs 14% with vehicle (n=43) and in ONSET-2: 47% with Tyrvaya (n=260) vs 28% with vehicle (n=252). Onset of action: mean change from baseline in STS ~5 minutes after first dose (not a prespecified endpoint) in ONSET-1 was 17.2 mm with Tyrvaya (n=48) vs 4.0 mm with vehicle (n=43) and in ONSET-2 was 16.5 mm with Tyrvaya (n=260) vs 6.9 mm with vehicle (n=251). Observed data. On Day 1 in clinical studies, a baseline anesthetized Schirmer’s test was performed. Tyrvaya was then administered concurrently with Schirmer’s test. Schirmer’s test results were measured at ~5 minutes. Mean change from baseline in STS at week 12 in the MYSTIC study was 10.8 mm with Tyrvaya vs 6.0 mm with vehicle. Limitations: Ex-US, single-center study. All subjects were Hispanic or Latino. Tyrvaya group mean baseline STS 5.5 mm (n=41); vehicle group mean baseline STS 5.3 mm (n=41). All randomized and treated patients were included in the analysis and missing data were imputed using last-available data.2-8

See references on next page.

Indication
Tyrvaya® (varenicline solution) nasal spray is indicated for the treatment of the signs and symptoms of dry eye disease.

Important Safety Information
The most common adverse reaction reported in 82% of patients was sneezing. Events that were reported in 5-16% of patients were cough, throat irritation, and instillation-site (nose) irritation.

Please see Brief Summary of Prescribing Information on the next page and the full Prescribing Information at Tyrvaya-pro.com.
TYRVAYA® (varenicline solution) nasal spray 0.03 mg

BRIEF SUMMARY: Consult the full Prescribing Information for complete product information available at www.tyrvaya-pro.com.

INDICATIONS AND USAGE
TYRVAYA® (varenicline solution) nasal spray is a cholinergic agonist indicated for the treatment of the signs and symptoms of dry eye disease.

ADVERSE REACTIONS
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.

In three clinical trials of dry eye disease conducted with varenicline solution nasal spray, 349 patients received at least 1 dose of TYRVAYA. The majority of patients had 31 days of treatment exposure, with a maximum exposure of 105 days.

The most common adverse reactions reported in 82% of TYRVAYA treated patients was sneezing. Other common adverse reactions that were reported in >5% of patients include cough (16%), throat irritation (13%), and instillation-site (nose) irritation (8%).

USE IN SPECIFIC POPULATIONS
Pregnancy: Risk Summary: There are no available data on TYRVAYA use in pregnant women to inform any drug associated risks. In animal reproduction studies, varenicline did not produce malformations at clinically relevant doses.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. 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.

Data: Animal Data: Pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. While no fetal structural abnormalities occurred in either species, maternal toxicity, characterized by reduced body weight gain, and reduced fetal weights occurred in rabbits at the highest dose (4864 times the MRHD on a mg/m² basis).

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day (1216 times the MRHD on a mg/m² basis). Decreased fertility and increased auditory startle response occurred in offspring at the highest maternal dose of 15 mg/kg/day.

Lactation: Risk summary: There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies varenicline was present in milk of lactating rats. However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk.

The lack of clinical data during lactation precludes a clear determination of the risk of TYRVAYA to an infant during lactation; however, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for TYRVAYA and any potential adverse effects on the breastfed child from TYRVAYA.

Pediatric Use: Safety and efficacy of TYRVAYA in pediatric patients have not been established.

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


Manufactured for Oyster Point Pharma, Inc. in the United States and certain jurisdictions. OPP-TYR-002308 7/23
or formal studies regarding the
treatments and surgeries, combinations
Like all combinations of glaucoma
burden at six months.
ECP) seemed to reduce the medication
burden at six months.

Reality Check
Like all combinations of glaucoma
treatments and surgeries, combinations
of MIGS are far from perfect.
“There’s currently a lack of evidence
or formal studies regarding the
combination of MIGS procedures,”

“However, in most glaucoma patients,
the primary resistance appears to be
beyond Schlemm’s canal rather than
at the trabecular meshwork. If we
perform MIGS in a quadrant with
functioning aqueous veins, then we
can reasonably expect a fair reduction
in IOP.” The challenge, however,
is achieving this type of success
predictably, Dr. Razeghinejad adds.

Coding and Billing for Combination MIGS
Coding and billing for combined micro-invasive glaucoma sur-
gery procedures may require as much planning as performing
the procedures themselves. “MIGS policies in general have been
a little bit challenging recently,” says Joy Woodke, COE, OCS,
director, Coding and Reimbursement, at the American Academy
of Ophthalmology. Fortunately, draft Medicare policies that once
challenged the medical necessity of some MIGS procedures have
been retired. But, she notes that existing CPT codes still require
careful consideration before you proceed with your surgical plan.

“You have to look at the documentation to see if your performance
of the procedure matches the definition that’s listed in the CPT
code,” she says. “You also have to consider what is required by your
payor policies. For the CPT codes, for example, a commercial plan
may say that it won’t cover canaloplasty. That exclusion may be spe-
cific to that payor only.”

Varying reimbursements and requirements are dictated by
Medicare, Medicaid, Advantage Medicare plans, and, as always,
regional reimbursement and coding differences. Before proceed-
ing with combined MIGS procedures, Woodke urges surgeons to
seek guidance from aao.org/migs, where CPT codes, definitions,
and requirements for procedures are clearly spelled out in guide-
lines and fact sheets.

“There may be some procedures that are considered bundled
when completed during the same session,” she notes. “For example,
when a canaloplasty and goniotomy are performed together,
only the canaloplasty should be billed the majority of the time.
That’s because ‘CPT Assistant’ guidance says that canaloplasty
represents the procedure performed, not goniotomy. Also, when,
goniotomy is performed with the insertion of a stent, the goni-
otomy can be considered incidental to the stent insertion. In addi-
tion, some micro-goniotomies may also not meet the definition of
the CPT code.”

Above all, Woodke advises surgeons and their billing staffs to
make a continuing study of the regularly updated aao.org/migs
website. “We do expect Medicare to come forward with additional
policies that take a closer look at coverage of different types of
MIGS procedures,” she adds.
Combining suprachoroidal and angle-based MIGs appears promising if suprachoroidal implants become available.

Complications to Consider
One of the more common complications of combining MIGS is hyphema, which is typically microscopic but can occasionally be macroscopic and associated with elevated IOP, according to Dr. Razeghinejad. “While most patients will experience reabsorption of the hyphema, there are cases where anterior chamber washout, with or without filtering surgery, may be necessary,” explains. “To reduce the risk of hyphema, I remove viscoelastic material several minutes after completing the MIGS procedure, allowing it to have a tamponading effect on the refluxing blood. Additionally, I maintain the IOP within the range of 20-25 mmHg at the end of surgery to further decrease the chance of hyphema. It’s important to note that patients undergoing MIGS typically have an optic nerve capable of handling this IOP.”

Cyclodialysis clefts are increasingly observed as a complication following MIGS, says Dr. Razeghinejad. “The attachment of the iris to the sclera is not firm,” he notes. “Any trauma to the iris could lead to cleft formation. To decrease the chance of this complication, the anterior chamber may be filled with cohesive OVD (viscoelastic) during surgery. This helps maintain the depth of the anterior chamber and avoid forward movement of the iris,” he says.

Looking Ahead
Complications aside, many surgeons remain optimistic about combining MIGS. “The beauty of glaucoma in 2024 is that there are so many groups all over the world trying to come up with better treatments for our patients,” says Dr. Solá-Del Valle. “It’s now our job to match the best treatments to the best patient. That’ll be the challenge for all of us in the future. Hopefully, more research will help guide us in this endeavor.”


U.S. Military Disclaimer
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Taming Tube Shunts

Cutting-edge techniques and surgical pearls for combating hypotony and achieving success.

THOUGH A MORE STRAIGHTFORWARD SURGERY IN MANY RESPECTS THAN TRABECULECTOMY, TUBE SHUNT PROCEDURES STILL HAVE THEIR FAIR SHARE OF INTRAOPERATIVE AND POSTOPERATIVE CHALLENGES. NON-VALVED TUBES IN PARTICULAR, REQUIRE CRITICAL MODIFICATIONS TO FUNCTION AT THEIR BEST. BUT, WITH THE RIGHT TECHNIQUES, SURGEONS CAN ENSURE THEIR PATIENTS RECEIVE ALL THE PRESSURE-LOWERING BENEFITS.

Here, glaucoma surgeons share pearls and the latest techniques for getting the most out of these glaucoma drainage devices while reducing complications.

Valved or Non-Valved?

When considering the choice between a valved or non-valved tube for glaucoma surgery, surgeons weigh several key factors to tailor their approach to each patient’s needs. Eileen C. Bowden, MD, of the University of Texas at Austin, says the tube selection often comes down to the target IOP and the urgency of that pressure reduction. “Non-valved implants tend to give patients lower pressures than valved implants, so if I have a patient with more advanced disease who needs lower pressures, I generally choose a non-valved tube,” she says. “When I need the pressure down immediately, such as in cases of neovascular glaucoma, I’d be more likely to choose a valved implant.”

Surgeons say they also consider the patient’s age and natural scarring response. The likelihood of scarring is higher in a younger patient than an older patient, and younger patients may do better with non-valved tubes’ extended efficacy.

“I’ve actually moved away from implanting valved tubes because they have a lower long-term success rate compared to non-valved tubes, as shown by the ABC and AVB studies,” says Mary Qiu, MD, of the Cole Eye Institute at the Cleveland Clinic. “I try as much as possible to offer patients non-valved tubes because of this higher success rate. The trade-off is that non-valved tubes have a higher risk of hypotony.”

Ligating Tubes

“If we were to implant a non-valved tube and let it start functioning right away, there’d be very little resistance in the beginning and the eye pressure would drop right down to zero in most cases, leading to a host of problems,” Dr. Bowden explains. “Most surgeons have some technique of ligating the tube in the first several weeks of surgery to allow for the eye to heal and form some scar tissue at the end plate, so that when the tube does eventually start functioning when the ligature dissolves or is removed, there’s some natural resistance to outflow from the scar tissue. This allows for the eye pressure to come down gradually.”

A typical ligation consists of closing off the tube with a 7-0 Vicryl suture that’s expected to dissolve within five to six weeks. Here are some additional strategies surgeons employ to gain more control over pressure reduction:

- **Irrigate the tube to ensure 100-percent ligation.** “After I ligate it with a 7-0 Vicryl, I always put a 30-gauge cannula up the tube and try to irrigate it to ensure that it’s completely ligated,” says Jonathan Eisengart, MD, of the Cole Eye Institute.
INDICATIONS AND USAGE: ROCKLATAN® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION:

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS:

Increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes can occur. Iris pigmentation likely to be permanent. Gradual change to eyelashes may include increased length, thickness, number, and misdirected growth of lashes. Usually reversible upon discontinuation of treatment.

Use with caution in patients with a history of intraocular inflammation (iritis uveitis). Should generally not be used in patients with active intraocular inflammation.

Macular edema, including cystoid macular edema, has been reported with latanoprost. Use with caution in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or patients with known risk factors for macular edema.

Use with caution in patients with a history of herpetic keratitis. Avoid use in cases of active herpes simplex keratitis.

Bacterial keratitis has been reported with multiple-dose containers of topical ophthalmic products inadvertently contaminated by patients.

ADVERSE REACTIONS: The most common ocular adverse reactions were conjunctival hyperemia (59%), with 5% of patients discontinuing therapy for this reason, instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

DOSAGE AND ADMINISTRATION:

The recommended dosage is one drop in the affected eye(s) once daily in the evening. If one dose is missed, treatment should continue with the next dose in the evening. The dosage of ROCKLATAN® should not exceed once daily.

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

Please see Brief Summary for ROCKLATAN® Solution on the following page.

To report Suspected Adverse Reactions, contact Aerie Pharmaceuticals, Inc. at 1-855-740-1924 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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ROCKLATAN®
(netasudil and latanoprost ophthalmic solution) 0.02%/0.005%, for topical ophthalmic use

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE. ROCKLATAN (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is a fixed dose combination of a Rho kinase inhibitor and a prostaglandin F2α analogue indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS. None.

WARNINGS AND PRECAUTIONS. Pigmentation—ROCKLATAN contains latanoprost which has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of latanoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. Beyond 5 years the effects of increased pigmentation are not known. Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become brownish. Neither new nor freckles of the iris appear to be affected by treatment. While treatment with ROCKLATAN can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly (see Patient Counseling Information in the Full Prescribing Information). Eye Pruritus—ROCKLATAN contains latanoprost which may gradually change eyelashes and veilius hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment (see Patient Counseling Information in the Full Prescribing Information). Intraocular Inflammation—ROCKLATAN contains latanoprost which should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation because it may exacerbate inflammation. Macular Edema—Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. ROCKLATAN should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. Herpetic Keratitis—Reactivation of Herpes Simplex keratitis has been reported during treatment with latanoprost. ROCKLATAN should be used with caution in patients with a history of herpetic keratitis. ROCKLATAN should be avoided in cases of active herpes simplex keratitis because it may exacerbate inflammation. Bacterial Keratitis—There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Patient Counseling Information in the Full Prescribing Information). Use with Contact Lenses—Contact lenses should be removed prior to the administration of ROCKLATAN and may be reinserted 15 minutes after administration.

ADVERSE REACTIONS

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 clinical practice. The most common ocular adverse reaction observed in controlled clinical studies with ROCKLATAN was conjunctival hyperemia which was reported in 59% of patients. Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions reported were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients. Other adverse reactions that have been reported with the individual components and not listed above include: Netarsudil 0.02%: Irritation of the eye, burning or stinging, photophobia, conjunctival hyperemia, eyelid margin crusting, eyelid edema, mydriasis, and periorbital edema. Latanoprost 0.005%: Dryness of the eye, conjunctival hyperemia, conjunctival hyperemia, photophobia, foreign body sensation, punctate keratitis, burning and stinging, itching, increased pigmentation of the iris, excessive tearing, eyelid discomfort, dry eye, eye pain, eyelid margin crusting, erythema of the eyelid, upper respiratory tract infection/nasopharyngitis/influenza, photophobia, eyelid edema, myalgia/arthralgia/back pain, and rash/allergic reactions.

DRUG INTERACTIONS

In vitro drug interaction studies have shown that precipitation can occur when eye drops containing thimerosal are mixed with ROCKLATAN. If such drugs are used, they should be administered at least five (5) minutes apart. The combined use of two or more prostaglandins or prostaglandin analogs including latanoprost ophthalmic solution 0.005% is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

USE IN SPECIFIC POPULATIONS

Pregnancy—Risk Summary: There are no adequate and well-controlled studies of ROCKLATAN ophthalmic solution or its pharmacologically active ingredients (netarsudil and latanoprost) in pregnant women to inform any drug associated risk. However, systemic exposure to netarsudil from ophthalmic administration is low (see Clinical Pharmacology in the Full Prescribing Information). Reproduction studies of latanoprost showed embryofetal lethality in rabbits. No embryofetal lethality was observed at a dose approximately 15 times higher than the recommended human ophthalmic dose (RHOD). Intraocular administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures. ROCKLATAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Data: Animal Data. Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the RHOD, based on Cmax). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on Cmax). Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on Cmax). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on Cmax), including throracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on Cmax). Reproduction studies have been performed with latanoprost in rats and rabbits. In 16 pregnant rabbits, no viable fetuses were present at a dose that was approximately 80 times higher than the RHOD. Latanoprost did not produce embryofetal lethality in rabbits at a dose approximately 15 times higher than the RHOD. Lactation—Risk Summary: There are no data on the presence of netarsudil or latanoprost in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ROCKLATAN and any potential adverse effects on the breast-fed child from ROCKLATAN. Pediatric Use—Safety and effectiveness in pediatric patients have not been established. Geriatric Use—No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenesis: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the RHOD) for up to 20 and 24 months, respectively. Mutagenesis: Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the in vivo rat micronucleus test. Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed in vitro with human lymphocytes. Additional in vitro and in vivo studies on unscheduled DNA synthesis in rats were negative. Impairment of Fertility: Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed. Latanoprost has not been found to have effects on male or female fertility in animal studies.

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

U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043; 9,911,336; 9,993,470; 10,174,017; 10,532,993; 10,588,991 ROCKLATAN is a trademark of Aerie Pharmaceuticals, Inc. Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

PI Version Date: 6/2020
Institute at the Cleveland Clinic. “I’ve found especially with Ahmed ClearPath tubes, it can sometimes be difficult to get to a full ligation. You really do want to make sure that it’s completely and totally ligated so that you don’t have hypotony on postoperative day one.”

- **Laser the Vicryl suture to open it earlier.** If pressures are too high for too long, “using a laser can help to augment the tube function postoperatively,” says Michele C. Lim, MD, of the University of California, Davis.

- **Consider using a Prolene ligature in certain cases.** Dr. Bowden says she ligates with a Prolene suture instead of a Vicryl suture for certain patients, such as those who’ve had a vitrectomy in the past or who are highly myopic, who could be at risk for hypotony and subsequent suprachoroidal hemorrhage if their tube were to open before there was enough resistance to flow. “I’ll place the ligature in a location where I can see it in the clinic at the slit lamp,” she explains. “This gives me a bit more control over when the tube opens, because I can use a YAG laser to open the Prolene suture ligature, and I can do it in a more controlled fashion. I’ll do this in patients who I’m worried are at high risk of hypotony as their tube opens. Some surgeons use a Prolene ripcord suture in a similar fashion.”

- **Place a ripcord suture for earlier tube functionality.** When removed, a smaller diameter ripcord, such as 4-0 Prolene, can promote flow before the ligature dissolves. “You just have to be careful because if you remove the ripcord too early, before that capsule is formed enough, then you’ll get hypotony,” Dr. Eisengart cautions. “Four weeks is pushing it. Five weeks, I would say is usually pretty safe to remove a rip cord.

  “Some surgeons have found that the larger 3-0 Prolene will cause some resistance to flow or some incomplete obstruction of the tube,” he continues. “The advantage of this partial obstruction is that when the ligature releases after five or six weeks, if the 3-0 Prolene is still in place it can provide some protection against hypotony. Mary Qiu, MD, does this often. I’ve used this approach occasionally in patients whom I really want that low pressure from a non-valved tube, but I’m worried about hypotony, especially early after surgery.

  “Once the pressure is stabilized and you’re happy with it, you can go ahead and remove it,” he says. “In most cases, you’ll end up removing the ripcord suture eventually, but Dr. Qiu recently published an article describing cases where she’s left the ripcord in long-term with no apparent ill effects from it.”

  The 3-0 Prolene ripcord placed at the time of surgery partially occludes the tube lumen, so when the ligature dissolves on its own as expected at postop week six, the lumen is partly blocked by the 3-0 Prolene,” Dr. Qiu says. “This gives us a chance to titrate the pressure before removing the ripcord at a time of our choosing, if needed. For example, when the ligature dissolves, if the pressure drops too low and you have a shallow anterior chamber or choroidal effusions, then you wouldn’t want to remove the ripcord to fully open the tube. If the ligature opens and the pressure is in the mid- to high teens, and the patient is still on some baseline pressure-lowering drops, then you can remove the ripcord and stop some of the glaucoma drops.

  “If the eye is inflamed when the ligature dissolves—ligature dissolution is an inherently inflammatory process—or the patient isn’t using as much steroid as instructed, then having the ripcord in place also gives you a chance to increase your steroids before choosing when to remove the ripcord,” she continues. “So, this ripcord is useful because it helps reduce or minimize hypotony-associated complications at the time of ligature dissolution, which can be a problem with non-valved tubes done without a ripcord.”

  Dr. Qiu’s group published a series of patients who underwent tube shunt surgery with non-valved implants with a ripcord. “In two-thirds of patients, when the ligature dissolved, the pressure was good and the eye wasn’t inflamed. We were able to remove the ripcord at the next visit after the tube opened and stop some glaucoma drops. Those eyes did great. In the remaining one-third of patients, some patients’ pressures were already quite low and we were able to stop some drops before removing the ripcord later; some eyes were inflamed, and we were able to increase steroids and remove the ripcord later; and one eye with persistent single-digit IOP had the ripcord trimmed and left in place permanently. There were no hypotony-associated or infectious complications.

  “For patients [such as the latter] at high risk for hypotony (e.g., from uveitis, neovascular glaucoma or prior cyclodestructive laser procedures), you...
could plan to leave the ripcord in for longer than you would otherwise, or indefinitely," she adds. “The ripcord can be trimmed so it’s entirely under the conjunctiva with nothing exposed, and you can always cut down and retrieve it later.”

While waiting for non-valved tubes to become functional, surgeons say they’ll usually continue the patient’s glaucoma medications. Additionally, some may “start or continue oral acetazolamide, a carbonic anhydrase inhibitor that helps make a big impact in lowering the eye pressure during the period the tube is ligated,” Dr. Bowden says.

Fenestrations
The use of fenestrations is surgeon- and patient-dependent, says Dr. Bowden. “If you have a patient who can’t tolerate oral acetazolamide as we wait for the tube to open, for example, I might make two fenestrations in the implant so there’s some flow,” she says. “In most cases, however, just because I find fenestrations can be unpredictable sometimes depending on the needle you use or where you place your fenestrations, I try to reserve fenestrations for when I really need them and usually in patients who can’t tolerate their glaucoma medications.”

Using the needle of the 7-0 Vicryl to pierce the tube a few times distal to the ligature is a common way of making fenestrations. Dr. Eisengart says he used to make his fenestrations this way but was finding the pressures still higher than he wanted them to be. “So, for a while I switched to using a 15-degree blade and making a larger fenestration in the tube. I did that for a couple years, and I found I was getting lower pressures but also that there was no way to standardize the size of these [fenestrations]. The fenestration you make with a 15-degree blade varies depending on how far through the tube you stick the triangular blade.”

Now, when implanting non-valved tubes, he’s using a single 10-0 nylon wick suture. “It seems to work really well for giving me good pressure control early in the postoperative period without causing too much hypotony,” he says. “I take a 10-0 nylon on the needle and pass it straight through the tube, and then cut the needle off. I leave about a five- or six-millimeter piece of nylon right through the tube. In my hands, that seems to produce just enough flow to control the pressure.”

Wick sutures or the “vent and stent” technique, Dr. Lim says, “allows aqueous humor to trickle out. It has a much more profound effect on fluid exit than doing a fenestration where you don’t leave a length of suture in passing through the tube. So, this can give you some good control for several weeks after surgery until the tube opens on its own.”

Adding Goniotomy
“A couple of years ago, I started doing a technique where I add a goniotomy to my non-valved tubes in eyes that have an open angle; that aren’t on aspirin or blood thinners; that haven’t had prior angle surgery; and don’t have PAS in the angle,” Dr. Qiu says. “This way, the goniotomy can help provide some early pressure lowering and the aqueous can flow out the goniotomy site. You don’t get as much hypotony because of the episcleral venous pressure. This way, the pressure can be lowered immediately, even with a non-valved tube, and without the same risk of hypotony-associated complications that can occur if fenestrations or the wick are too big.

“We recently published our series of non-valved tubes combined with goniotomy,” she continues. “My early results show that patients achieve good pressure before the ligature dissolves, and no one had any hypotony-associated complications. We presented our one-year outcomes in a poster at the American Glaucoma Society meeting earlier this year.”

Supramid to the Rescue
Despite surgeons’ best efforts to prevent hypotony early on and when the ligature dissolves, late hypotony with non-valved tubes can strike. “If the eye’s outflow is greater than the aqueous production, the pressure is going to be too low,” Dr. Qiu says. “In eyes that have a non-valved tube, down the line, they may end up with too-low pressures and the potential for hypotony-associated complications such as hypotony maculopathy or choroidal effusions that don’t improve with medical management. You can always go back and revise the tube to decrease the amount of flow exiting the non-valved tube.

“Historically, this has been done by adding a ligature onto the tube either by opening the conjunctiva or by ligating the tube inside the anterior chamber,” she continues. “More
INDICATION AND USAGE: VEVYE® (cyclosporine ophthalmic solution) 0.1% is indicated for the treatment of the signs and symptoms of dry eye disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

• Potential for Eye Injury and Contamination – To avoid the potential for eye injury and/or contamination, patients should not touch the bottle tip to the eye or other surfaces.

• Use with Contact Lenses – VEVYE should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following the administration of VEVYE.

Adverse Reactions

In clinical trials with 738 subjects receiving at least 1 dose of VEVYE, the most common adverse reactions were instillation site reactions (8%) and temporary decreases in visual acuity (3%).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

For additional information about VEVYE, please see Brief Summary on adjacent page and Full Prescribing Information at vevye.com.

References: 1. Vevye (cyclosporine ophthalmic solution) 0.1% [package insert], Harrow IP, LLC; 2023. 2. Cequa (cyclosporine ophthalmic solution) 0.09% [package insert], Sun Ophthalmics, LLC; 2023. 3. Restasis (cyclosporine ophthalmic emulsion) 0.05% [package insert], Allergan, LLC; 2023. 4. Data on file.

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BRIEF SUMMARY – PLEASE SEE THE VEVYE® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE:
VEVYE® (cyclosporine ophthalmic solution) 0.1% is indicated for the treatment of the signs and symptoms of dry eye disease.

DOSAGE AND ADMINISTRATION:
Instill one drop of VEVYE® twice a day in each eye approximately 12 hours apart.

WARNINGS AND PRECAUTIONS
- Potential for Eye Injury and Contamination – To avoid the potential for eye injury and/or contamination, patients should not touch the bottle tip to the eye or other surfaces.
- Use with Contact Lenses – VEVYE® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following the administration of VEVYE®.

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 practice.

In clinical trials with 738 subjects receiving at least 1 dose of VEVYE®, the most common adverse reactions were instillation site reactions (8%) and temporary decreases in visual acuity (3%).

USE IN SPECIFIC POPULATIONS

PREGNANCY

Risk Summary
There are no adequate and well-controlled studies of VEVYE® administration in pregnant women to inform a drug-associated risk. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses. VEVYE® doses are approximately 4,700 times lower than recommended oral doses, with blood concentrations being undetectable after topical administration.

Data
Animal Data: Oral administration of cyclosporine oral solution to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body weight) were approximately 7,250 and 48,000 times higher than the daily maximum recommended human ophthalmic dose (MRHOD) of 0.67 mcg/kg/day, respectively.

No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 4,100 and 14,500 times higher than the MRHOD, respectively).

An oral dose of 45 mg/kg/day cyclosporine (approximately 10,900 times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in mothers or offspring were observed at oral doses of up to 15 mg/kg/day (3,600 times greater than MRHOD).

LACTATION
Risk Summary
Cyclosporine is known to be excreted in human milk following systemic administration but excretion in human milk after topical treatment has not been investigated. VEVYE® doses are approximately 4,700 times lower than recommended oral doses of cyclosporine, with blood concentrations being undetectable after topical administration. However, caution should be exercised when VEVYE® is administered to a nursing woman.

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

GERIATIC USE
No overall difference in safety or effectiveness has been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility

In genetic toxicity tests, cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. Cyclosporine was positive in an in vitro sister chromatid exchange (SCE) assay using human lymphocytes.

Impairment of Fertility
Oral administration of cyclosporine to rats for 12 weeks (male) and 2 weeks (female) prior to mating produced no adverse effects on fertility at doses up to 15 mg/kg/day (approximately 3,600 times higher than the maximum recommended human ophthalmic dose). In a 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats were approximately 120 times higher than the maximum recommended human ophthalmic dose (0.67 mcg/kg/day), normalized to body surface area.

Mutagenesis
In a 52-week oral study in male rats, the incidence of lymphocytic lymphomas increased in a dose-related manner. In a 2-year oral study in female rats, the incidence of lymphocytic lymphomas remained at the control level, even at the high dose level (approximately 3,600 times higher than the maximum recommended human ophthalmic dose).

Risk Summary
In a 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats were approximately 120 times higher than the maximum recommended human ophthalmic dose.

PATIENT COUNSELING INFORMATION
Risk of Contamination
Advise patients to wash their hands well before each use. Advise patients not to allow the dropper tip to touch the eye or any other surface, as this may contaminate the solution.

Contact Lens Wear
Advise patients not to touch the dropper tip to any surface to avoid contaminating the contents.

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recently, there have been techniques describing the insertions of a stent suture into the lumen of the tube ab interno through multiple paracenteses. My latest strategy to address late hypotony in a non-valved tube is to insert a segment of 3-0 Supramid suture into the tube lumen through a single paracentesis in an ab interno approach. If the ripcord has been removed, you can put a very long piece of 3-0 Supramid up the tube, and it will go all the way up into the capsule. This will block flow—3-0 Supramid is a twisted suture, so it expands a bit when hydrated, providing some occlusion of the tube lumen. Even if the original ripcord hasn’t been removed, you can still put a shorter piece of 3-0 Supramid up the tube, just up until it reaches the position of the ripcord.

Obstruction & Fibrosis
 Tube shunts can become blocked by materials such as iris pigment or heme. “Much of the time, if you wait a few days, [the blockage] will flush through and clear out,” Dr. Bowden says. “I’ve tried using a YAG laser to dissolve the blockage if I’m able to easily visualize it. But, if it’s been several days and the blockage is still in place, I’ll take the patient back to the operating room, remove the tube from the anterior chamber and flush it with saline to clear the blockage manually.”

According to Dr. Lim, tube blockage is less of an issue than when the bleb over the end plate becomes thickened due to fibrosis. “In the hypertensive phase, about two to three months after surgery, patients tend to experience a pressure rise, which we think is the bleb remodeling over the implant plate,” she explains. “Some surgeons will inject more anti-metabolite medication around the tube area in the postop period if they think there’s a lot of scarring. Right now, there’s not a lot of good evidence on the outcomes of doing that. Some studies are coming out of University of California in San Francisco, looking at the outcomes of injecting mitomycin-C at the time of surgery. Their studies are showing that it can augment the outcome of these implants.”

“Even after revision, there’s a chance the fibrosis may form again,” Dr. Bowden says. “It’s more common in the valved implants but can occur in non-valved implants as well. Some surgeons advocate for using anti-fibrotic materials like mitomycin-C or 5-flurouracil but there haven’t been any large studies or randomized controlled trials showing the best ways to do this. Some advocate injecting mitomycin-C or 5-FU when you place the tube and others advocate for injecting that into the subconjunctival space the week after the tube is placed, while the eye is still inflamed.

“Others use a needle several months after a tube is placed if there’s significant fibrosis,” she continues. “Using a needle as well as an anti-fibrotic to manually break up the scar tissue over the plate can be done either at the slit lamp in the office or back in the operating room. I’ve found that whenever there’s a lot of fibrosis over the plate, it’s best to take the patient to the operating room and take down the conjunctiva and sub-Tenon’s and then remove the capsule manually, cut it out and close the conjunctiva again.”

Sulcus Placement
 “One of the downsides of tube shunts versus trabeculectomies is that there’s a foreign body in the eye,” Dr. Qiu says. “Anterior chamber placement in particular can increase the risk of corneal decompensation, and then these eyes may require corneal transplants such as endothelial keratoplasty.”

To reduce the risk of corneal decompensation, Dr. Qiu preferentially places tubes in the ciliary sulcus whenever possible when the eye is pseudophakic. “I have a relatively low threshold to do cataract surgery concurrently in eyes that need tubes if they qualify for cataract surgery, so that I can make the eyes pseudophakic and place my tube in the sulcus instead of in the anterior chamber. We need more long-term data on this, but right now, the data show that there’s less endothelial cell loss with sulcus tubes compared to anterior chamber tubes.”

Sulcus placement can be challenging, for a number of reasons. “You’re inserting the needle behind the iris,
and you can’t always see exactly where it’s going to come out,” Dr. Qiu says. “Sometimes the needle enters the vitreous instead inadvertently or pokes into the iris root instead of the sulcus. Sometimes the needle does successfully enter the sulcus where you want it, but when you try to insert the tube into the needle track, it doesn’t want to go, because unlike the rigid, metal needle, the tube is floppy. The trade-off with sulcus placement is that sometimes the sclerotomy is quite posterior and the tubes may end up behind the IOL.

“To place tubes in the sulcus more predictably, we’ve recently been using a guidewire,” Dr. Qiu continues. “There are multiple ways to do this, and we recently presented three different approaches at AGS. Videos demonstrating how to do this are also published in AJO Case Reports. My approach of doing guidewire-assisted sulcus tube entry is to first inflate the eye with viscoelastic. I prefer Healon. Make a paracentesis 180 degrees across the eye from where the tube entry site is going to be. Have a segment of 3-0 Prolene suture cut and ready. (This is the same 3-0 Prolene suture I use for my ripcord, so it’s already open and on the field.) Once the needle entry is made into the sulcus, the guidewire can be inserted into the paracentesis with the other hand and docked into the bevel of the needle and then pulled through the sclerotomy site. Now there’s a segment of 3-0 Prolene in the sulcus for the tube to follow. Put the tube onto the guidewire and push it into the sulcus. The tube will follow the guidewire into the sulcus, and it can’t end up behind the IOL. I like my sulcus tubes to sit as posteriorly as possible, so they’re far away from the iris.”

**Tube Erosions**

Another potential challenge of tube shunts is that they may erode or become exposed, opening pathways for infection such as tube-associated endophthalmitis. Tube erosions occur in two main places: 1) over the tube path and 2) over the plate. “It’s far less common for the conjunctival tissue to break down over the plate of the tube itself, but when it happens these types of erosions are very hard to fix,” Dr. Lim says. “In fact, when we see these erosions, we often think that we won’t be able to fix it and get it to work long-term.”

In a poster presentation at AGS this year, Dr. Lim shared retrospective data on outcomes of tube erosion repair. “We were interested in the rate of re-erosion based on where the initial erosion occurred,” she says. “Our study showed that the recurrence rate of erosion, when the erosion happened over the tube, was much lower than when it happened over the plate. The overall sample size was small, however, so you have to take this study with a grain of salt.”

Dr. Bowden says that many of the tube erosions that she’s seen over time have been due to an anteriorly placed tube. “I try to place the tube at least eight millimeters posterior to the limbus to minimize the risk of erosions,” she says. “I also like to use a patch graft of some sort, whether that’s sclera or cornea, to cover the tube adjacent to the limbus.”

“For cases where you’re placing a tube in the anterior chamber, which is probably where a majority of tubes still go, that means creating a two- to three-, but ideally three-millimeter scleral tunnel,” Dr. Eisengart adds (Figure 1). “So rather than just putting the tube directly into the anterior chamber at the limbus, you want to start more posteriorly, about three millimeters back, and tunnel the tube through sclera. In my experience this really reduces your erosion rate. The downside of tunneling is that it’s a little more challenging to get the angle right and to try to get the entry parallel to the iris and posterior enough.”

To reduce the risk of erosion due to eyelid rubbing, he recommends positioning the tube entry site close to the 12 o’clock position. “I find that a lot of erosions happen where the lid margin rubs over the tube. Generally, that’s going to be where the lid margin crosses the limbus super-temporally and superonasally, at roughly the 10:30 and 1:30 positions. So, when I’m putting a tube in the anterior chamber, I try to make the entry site closer to the 12 o’clock position. I think we have fewer erosions if we can get the tube to enter around 12 o’clock rather than entering super-temporally or, much less commonly, superonasally.
If an erosion occurs, there are two key things to consider:

1. **Change the location of the tube.** “You may want to think about repositioning the tube,” Dr. Eisengart says. “The easiest thing to do is to simply re-cover the tube where it is, but if it eroded in that area once, there may be a risk of recurrent erosion if you just recover it.”

2. **Switch graft materials.** In the same vein, experts recommend using a different patch graft material for the repair. “Donor sclera is the most common way we [cover when] we put in tubes, so the surgeon might use donor cornea instead because it tends to be more durable than sclera,” Dr. Eisengart says.

    “Tutoplast, which is preserved human pericardial tissue, is another good option,” Dr. Lim adds. “I haven’t seen any good studies comparing different patch graft materials but there’s some thinking that corneal tissue would have greater coverage longevity because the collagen fibers of the cornea are a lot tougher, perhaps, than what you’d find in an engineered Tutoplast or a scleral patch graft.

### Using the Capsule

When faced with a tube erosion, it can sometimes be difficult to mobilize enough tissue to cover the tube. If that’s the case, or the surgeon isn’t sure which type of patch graft material they may want to use, Dr. Qiu suggests using some of the capsule itself as graft material.

“For Ahmed erosions (a valved tube), you can harvest a piece of the capsule that’s grown around the Ahmed end plate and use that autograft to patch up the tube erosion (Figures 2 and 3). This autograft is autologous and vascularized, so it may have some advantages over other patch graft materials such as irradiated donor sclera, donor pericardium or donor cornea that’s not autologous to the patient. We think that this capsule autograft may integrate into the body’s tissues a little better.

“As with other types of patch grafts, you can leave the autograft uncovered by conjunctiva because conjunctiva will grow over it,” she continues. “So, if you’re able to harvest a piece of the Ahmed capsule and put that over the part of the tube that’s eroded, you can then cover it up with conjunctiva as best as you can. But even if it’s not fully covered, conjunctiva will grow over it. This autograft material is perhaps because it’s already very spongy and vascular.”

When attempting this capsule autograft approach with a non-valved tube, Dr. Qiu cautions that “you can’t simply cut off a piece of the capsule, use it as a patch graft and walk away.” She explains, “If you violate the capsule [of a non-valved tube] you’ll get hypotony. So, when doing this with a non-valved tube, you have to re-ligate the tube so that the body has time to regrow the capsule around the end plate. You can still harvest the capsule autograft; you just have to re-ligate the tube.”

“Dr. Kahook has published a case series using this technique for Ahmed erosions, specifically, and my subsequent case series demonstrates the use of this capsule autograft for a variety of indications,” she says, noting that it’s useful when placing a second tube or performing a tube exchange in addition to tube erosion. “I’ve now done this technique in more than 20 eyes, and we’re working on publishing an updated case series with photos of everyone’s outcomes. The capsule autograft has a more cosmetic result compared to other types of patch grafts (Figure 4). Scleral patch grafts, for example, look like little white rectangles sitting on the surface of the eye, whereas the autologous capsule patch graft just looks like the body’s own tissue. I’ve only been doing this technique for the last four years, so we don’t have long-term data about how well these patch grafts hold up in terms of erosion rates. I’m looking forward to longer term outcomes on these patients.”

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CORRECTING CATARACT OUTCOMES

When post-cataract patients are left with a residual refractive error, surgeons must take several factors into consideration before proceeding.

Cataract-refractive surgery has become increasingly demanding as patient expectations have risen. Technology has responded with improved preoperative assessment and testing, and the advent of new-generation IOL power formulas has also contributed to better accuracy. Surgeons are getting closer to hitting their targets consistently, as evidenced by several studies. For instance, 44.6 to 58.4 percent of patients achieved a ±0.5 D deviation between 1996 and 2005, a proportion that increased to between 61.2 and 88 percent between 2007 and 2017.1

“I think the impetus to improve our refractive results has been stimulated by the increased use of premium lens implants that has occurred over time,” says Jonathan B. Rubenstein, MD, chairman of the department of ophthalmology at Rush University Medical Center in Chicago. “Now that patients have options for paying out of pocket for a more premium type of lens implant product, the bar goes up to achieve satisfaction. If they’re paying something out of pocket, they want to be satisfied with the outcome. There’s greater pressure on making sure that we get accurate preoperative results when assessing and measuring these patients so that we get accurate postoperative refractions afterwards.”

Despite this progress, a percentage of post-cataract patients will experience some postoperative glare, halos and starburst symptoms.1 This could be due to a number of factors, including inaccurate preoperative biometry, ocular comorbidities, a history of laser vision correction and dry-eye disease, among others. We spoke with cataract-refractive surgeons about how they approach these patients, their strategies for determining the root cause of the issue(s) and what influences their treatment decision.

Getting to the Cause

One of the best strategies for dealing with unhappy patients is to address their expectations in advance, says surgeons. Premium lenses have made this preoperative conversation even more important.

Alice T. Epitropoulos, MD, FACS, who practices in Ohio and is a clinical assistant professor at The Ohio State University, says she tells patients there’s no perfect lens. “I emphasize that there isn’t a one-size-fits-all solution; some compromises may be necessary,” she says. “For instance, while extended depth of focus lenses provide a broad range of vision, these implants prioritize distance and intermediate vision, however, near vision may not be as sharp as with a multifocal or trifocal implant. Trifocal implants provide clear vision at near, intermediate and distance ranges, but may be associated with glare or halos at night.”

The ocular surface must also be pristine, she continues. “Premium lenses require more intensive treatment for dry-eye disease, just to ensure accurate biometry and to minimize the higher order aberrations. These patients really do have a greater sensitivity to ocular surface irregularities, especially when it comes to multifocal technology. A dysfunctional ocular surface is a very frequent cause of patient dissatisfaction post-
Patient Considerations

DR. AKPEK: What types of patients would benefit from autologous serum tears?

DR. MASSARO-GIORDANO: Most patients with varying degrees (mild to severe) of ocular surface disease can benefit. These are patients with conditions that range from dry eye due to autoimmune conditions such as Sjögren’s syndrome, rheumatoid arthritis, and thyroid eye disease, etc., in addition to those with graft-versus-host disease (GVHD), neurotrophic keratitis (NK), recurrent erosions, neuropathic pain, chemical burns, and Stevens-Johnson syndrome.

DR. LANG: Autologous serum eye drops (ASEDs) have very broad anti-inflammatory and regenerative properties, which give them a widespread application profile in eye care. I tend to reach for ASEDs in patients who have an inability to supplement their own cornea and ocular surface with the proper nutrients and growth factors found in healthy, natural tears. This includes many autoimmune patients, aqueous deficient dry eye patients, anyone with neurologic abnormalities (neurotrophic and neuropathic) of their cornea that may affect the supply of nerve growth factors and neurotrophins, as well as patients with other inflammatory corneal conditions including corneal erosions, and even poor wound healing after injury or surgery.

DR. KARPECKI: The great thing about autologous serum is that it can be utilized for many patient conditions. The obvious is dry eye disease, especially keratoconjunctivitis sicca (KCS) and Sjögren’s syndrome KCS. But other conditions also benefit significantly, such as NK, limbal stem cell deficiency, neuropathic corneal pain, GVHD, and superior limbal keratoconjunctivitis (SLK), to name a few.

DR. AKPEK: Autologous serum eye drops are particularly beneficial in healing punctate erosions or non-healing epithelial defects in the cornea and for maintenance treatment for patients who make no tears, among other uses.

DR. MASSARO-GIORDANO: Often my patients report their eyes feel more comfortable after using autologous serum tears. The eyes look less irritated, and my patients are not using their artificial tears as often.

DR. KARPECKI: Most patients prefer serum tears over artificial tears for comfort. They like the fact that they are natural and derived from their own blood serum. And while patients experience the comfort of the drops upon instillation, the therapeutic benefits continue to help treat the disease.

DR. LANG: Patients benefit from a natural, biological therapeutic that is preservative-free and delivers the nutrients and biochemical support that their eye is unable to produce, or adequately produce. The
CASE: Sjögren’s Disease-Related DED
By Esen Karamursel Akpek, MD

A 63-year-old female patient with Sjögren’s disease-related dry eye presented for cataract surgery evaluation. Slit-lamp examination demonstrated significant corneal punctate erosions highlighted with topical fluorescein.

The patient, who had been on topical cyclosporine drops and over-the-counter preserved artificial tears for several years prior to presentation, was advised to switch to preservative-free artificial tears, and increase the topical cyclosporine drops from 2 to 4x daily. In addition, inferior permanent tear duct plugs were inserted and autologous serum tears at 50% concentration 4x daily were added to the regimen.

Eight weeks into the new treatment using autologous serum tears, slit-lamp appearance of the corneal fluorescein staining demonstrated significant improvement.

Slit-lamp examination demonstrated significant corneal punctate erosions highlighted with topical fluorescein (top). Eight weeks into the new treatment using autologous serum tears, slit-lamp appearance of the corneal fluorescein staining demonstrated significant improvement (bottom).

dosing schedule is also somewhat beneficial as the frequent instillation promotes hydrating effects as well.

DR. AKPEK: Autologous serum tears help optimally heal the patient’s ocular surface and restore the homeostasis of the corneal epithelialization process in this important segment of patients.

Prescribing Insights

DR. AKPEK: When prescribing autologous serum tears for dry eye, where do they fit into your treatment protocol?

DR. MASSARO-GIORDANO: They are the second step after the patient has tried artificial tears, immunomodulators, steroids, and more viscous tears and or ointments.

DR. KARPECKI: With some conditions, such as Sjögren’s syndrome, autologous serum tears are my initial or primary treatment. For other forms of dry eye, they become an option when corneal staining is not resolved with other drops. In these cases, I might begin with topical corticosteroids but if after one month I am seeing minimal resolution, I immediately start to add autologous serum tears.

DR. LANG: I find ASEDs lend themselves well when chronic and ongoing therapy is needed. This is not typically a pulsed or flare treatment, but an ongoing supplement and supportive therapy for the ocular surface. Many ocular conditions are chronic, and “cure” is not a common word in my clinics (unfortunately). In these cases, ongoing therapy with ASEDs makes a lot of sense. I also find myself discussing ASEDs more once the initial presentation is stabilizing but not resolving. It’s a good option to keep the healing going.

DR. AKPEK: I follow the TFOS DEWS II guidelines in that we use a sliding scale to first address environmental factors, followed by preservative-free over-the-counter drugs, then prescription drugs, and treatments specifically for meibomian gland dysfunction. If the patient continues to exhibit corneal epithelial fluorescein staining despite the previous interventions, I find that autologous serum tears are often highly effective at this stage in alleviating symptoms and promoting healing of the ocular surface.

DR. AKPEK: How do you determine what concentration to order? How many times per day are your patients using autologous serum tears?

DR. MASSARO-GIORDANO: Studies vary. I do 50% 4x daily, although some other practitioners do 20% 6-8x daily, based on the significant effect that 50% concentration has had in several studies.

DR. KARPECKI: It depends on the condition. For most dry eye patients, I typically begin with 20% or 25% concentration. However, if I’m dealing with NK or GVHD, I typically begin at 40% or 50%. I recommend 6 drops per day spaced out about every 2 hours while awake. Once the condition is showing improvement, patients may taper down to QID. However, many patients tell me that 6 times per day works best for them and continue with that dosing long-term. The 20% concentration, when the condition allows for it, enables the patient to obtain an ample amount of autologous serum drops.

DR. LANG: In general, much of the clinical research around ASEDs utilizes 20% serum, although concentrations up to 100% have been used. Twenty percent tends to be the starting point as it mimics the concentrations of biologically active components in natural tears. I start with 30%, 6-8x per day, every 2 hours during waking hours, for most conditions.

DR. AKPEK: There’s no evidence-based answer to these questions. It’s based on experience. I believe that putting too many drops on the eye surface is detrimental, especially to meibum- or mucin-deficient dry eye patients. I would rather deliver the same amount of nutrients using a less frequent regimen, so I use 50% concentration and have patients use it only 4x a day. Usually, these patients also wear some kind of therapeutic contact lens. If that is the case, I ask them to place a couple of drops into the reservoir of the contact lens as well, so they use even less, maybe 2 or 3x a day.

Management of the Patient Using Serum Tears

DR. AKPEK: How long do you keep your patients on autologous serum tears?
DR. KARPECKI: For most patients, especially those with KCS, GVHD, neuropathic pain, etc., autologous serum tears are a lifetime medication, unless their lacrimal glands somehow can improve on their own. When treating conditions like NK, mild/moderate LSCD, or SLK, patients can discontinue use once the condition has improved or resolved.

DR. LANG: This is definitely a marathon, not a sprint. I suggest patients take ASEDs for 6 months before deciding to continue therapy. I hope for some improvements around 3 months but typically stay the course for 6 months. If we are seeing improvements, I usually continue therapy with ASEDs for the foreseeable future.

DR. MASSARO-GIORDANO: I keep them on for 3-6 months depending on severity and response. I may repeat the cycle 1-2x a year. Cost is an issue so I will usually give patients prescription drops in the winter months when dryness may be worse.

DR. AKPEK: What do you look for at follow up to determine whether autologous serum tears are an effective therapy?

DR. MASSARO-GIORDANO: I look for subjective improvements on questionnaires, in addition to objective signs, i.e., corneal stain with fluorescein and conjunctival stain with lissamine green, as well as overall conjunctival hyperemia.

DR. KARPECKI: I look at corneal and conjunctival staining, and also monitor osmolarity. An improvement in either indicates they are working. I don’t expect symptoms to improve until I’ve improved the ocular surface and provided a homeostatic tear environment. At that point the nerves begin to normalize and symptom improvement follows. Most patients are encouraged by the improvement in signs knowing that symptom resolution may lag. Fortunately, autologous serum tears are very comfortable as a drop, which helps the patient while their dry eye disease continues to improve.

DR. LANG: I evaluate symptoms by using a symptom survey (typically SPEED) although other surveys, such as the Ocular Pain Assessment Survey (OPAS), may have more merit when treating neuropathic eye pain. Regarding clinical signs, corneal and conjunctival staining, tear break-up time, conjunctival erythema, and visual acuity are all measures I lean on.

DR. MASSARO-GIORDANO: I simply state that I feel that they will benefit from this treatment and, unlike artificial tears, serum tears contain growth factors and proteins that may indirectly help with inflammation and promote healing. I explain that the serum facilitates the repopulation of epithelial cells on the surface of the eye.

DR. KARPECKI: It is an easy recommendation in dry eye and other advanced ocular surface disease conditions because I explain how, for example, this autoimmune disease has damaged the patient’s lacrimal glands. These glands once served to take the serum from their blood to make tears but they can no longer do that, so we will have their blood drawn and use the serum within it to make their own personalized tears. I then discuss how this will typically lessen or eliminate the need for artificial tears, which is a cost savings, and how autologous serum tears are typically more comfortable than artificial tears, are a natural biologic, and are far more effective. From there I discuss how tears and medications can cost over $100 per month and patients often nod in agreement. I then state that this option will offset much of that and although the cost is similar, autologous serum tears are far more effective and biocompatible having come from their own serum.

DR. LANG: I usually review how patients’ eyes are unable to produce the necessary nutrients that their ocular surface needs to stay healthy.

Vital Tears are prepared in a medical laboratory using validated safety procedures and delivered throughout the US. Vital Tears autologous serum eye drops can be obtained in as little as 48 hours from the patient’s blood draw.
because of their disease state and explain that many of the healing components of tears are the same as blood. By utilizing this natural therapy, we can harness the power of the patient’s own blood in a drop form to help the eye and rehabilitate the ocular surface.

Even though autologous serum tears have been around for many years and proven to be safe and effective, insurance companies do not pay for them. This doesn’t surprise most patients because many are used to getting denial letters and prior authorization forms for everything from antibiotics to cold medicine. Compared with some of the other therapeutic options in this space, cost is usually not too much of a shock to the patient.

**DR. AKPEK:** If patients still have significant corneal, or central corneal, staining after having tried environmental modulations, over-the-counter eyedrops, and prescription medications, then I will bring it up to them. Most of my patients are referrals and have talked to people who are on serum tears; they usually come in asking for them. Or when I bring it up, they usually say, “Oh okay. I heard about them.” So it’s not very difficult for me to explain that they are going to take eye drops made out of their own blood. In general, dry eye patients are pretty educated, and they understand how autologous serum tears can help heal the surface vs. just artificial tears.

**DR. AKPEK:** How does your practice order/source autologous serum tears for your patients?

**DR. MASSARO-GIORDANO:** I have used various compounding companies in the past but now use Vital Tears, a national company with numerous labs and a mobile phlebotomy service to aid in collection.

**DR. KARPECKI:** Vital Tears is a national outfit that provides incredible customer service and uses trained phlebotomists, the highest level of care and safety, and a sterile environment to process the serum tears. They are experts at this. They can also do the blood draw from the patient’s home or office, offering convenience for busy people. And they have renewal plans, which makes it easy to follow and maintain your supply of serum tears.

**DR. LANG:** I utilize Vital Tears for all my ASEDs orders. Their program and organization streamline my staff’s workflow and make the process easy for both doctor and, more importantly, patient.
Operatively. In fact, dry-eye disease is a common reason why patients are poor candidates for presbyopia-correcting technology initially, Dr. Epitropoulos says. “Taking that extra chair time with patients really helps to prevent surprises and disappointment in patients. This is particularly important in patients who’ve had previous laser vision correction and have expressed an interest in premium lens technology. The presence of prior refractive surgery adds complexity to IOL calculations and can induce higher-order aberrations. Despite the potential for achieving complete spectacle independence, it’s important never to guarantee this to patients.”

A refractive miss can be identified within a week after surgery, but surgeons shouldn’t jump right into fixing it. “If a patient is unhappy with their surgical outcome, it’s essential to investigate the underlying reasons,” says Dr. Epitropoulos. “Could it be due to untreated or inadequately treated dry-eye disease? If so, aggressive treatment of their dry eye (preferably preoperatively), often leads to satisfaction. However, if preoperative measurements such as IOL Master or topography were inaccurate preoperatively, this may lead to residual refractive errors, which may need to be addressed. Typically, I prefer to wait three or four months, allowing for neuroadaptation before considering invasive interventions, such as IOL exchange or laser vision correction. Oftentimes, the brain can adjust to the new optical system, avoiding additional procedures.”

Surgeons should turn to their preop diagnostic tools to accurately assess the situation, recommends John Berdahl, MD, a partner at Vance Thompson Vision in Sioux Falls, South Dakota. “The first thing that you need to do is a good refraction to determine if it is refractive error in the first place,” he says. “A second important diagnostic is topography. A third important diagnostic is an OCT of the macula, a fourth important diagnostic that’s widely underutilized is epithelial mapping. That can help show us subtle anterior basement membrane dystrophy or irregular epithelium, and then the fifth is a gas-permeable over-refraction to help us determine if the anterior surface of the cornea is the source of error for the vision. Of course, we’re looking for all of the other potential comorbidities: glaucoma; macular degeneration; epiretinal membrane; subtle cystoid macular edema; and we’d target our therapies at those approaches.”

Dr. Berdahl says surgically induced astigmatism accounts for a surprising amount of refractive misses. “The standard deviation around surgically induced astigmatism is much higher than we generally think that it is and it’s a little bit difficult to predict post-operative surgically induced astigmatism,” he explains.

He also evaluated if multifocal toric IOLs left patients worse off than monofocal toric options. “Interestingly, we looked at data from Astigmatismfix.com and the impact of residual cylinder on visual acuity and found that monofocals didn’t have worse visual acuity than multifocals for the same level of residual astigmatism,” says Dr. Berdahl. “One thing our study couldn’t assess of course is visual quality, which may or may not be decreased in patients who have residual refractive error in multifocality.”

Handling the Ocular Surface
If a contributing culprit is determined to be some form of dry-eye disease, it should be treated accordingly before even considering other interventions. Ideally, dry-eye disease would be caught preoperatively. Dr. Epitropoulos says she abides by the oft-repeated quote by Eric Donnenfeld, MD: “If you diagnose dry eye preoperatively, it’s an expectation, if you don’t diagnose until after surgery, it’s a complication.”

“Many people aren’t aware of having dry-eye disease until they start experiencing symptoms after surgery, leading them to attribute their discomfort to the procedure,” she says. “Whereas, if asymptomatic dry-eye is identified before surgery and patients are informed that they may experience dry-eye symptoms afterwards, they are more prepared for it. Prevention, in this case, is the most effective approach to managing this issue.”

“If by chance it goes undetected preoperatively, the goal is to identify the type and severity of their dry-eye conditions such as epithelial basement membrane dystrophy or punctate keratitis are missed during preoperative screening, then the patient’s biometry, topography and IOL calculations may be affected.
disease or their ocular surface disease,” continues Dr. Epitropoulos. “Is it meibomian gland dysfunction or aqueous deficient dry-eye disease? Or is it a combination? Is there a possibility of another contributing factor such as anterior basement membrane disease, that may have been overlooked preop?”

One of the first-line treatments she recommends is a high-quality, re-esterified Omega 3 as a fundamental component in managing DED. A preservative-free, artificial tear is another consideration. “Avoiding preservatives is important to prevent toxicity to the cornea,” says Dr. Epitropoulos. “When recommending an artificial tear, opting for those with added oil or lipid is beneficial, especially in addressing MGD or evaporative dry-eye disease that we commonly see. My threshold for prescribing an immunomodulator is relatively low because many patients have an underlying inflammatory component to their dry eye. Prescribing an immunomodulator helps to increase that tear production and reduces inflammation. It’s essential to allow sufficient time for these medications to take effect as they may not yield immediate results. There are several effective options available, including cyclosporines, Lifitegrast and Miebo.”

Many cataract surgeons have adopted in-office dry-eye treatments, including LipiFlow, iLux, TearCare and intense pulsed light therapy. “These can be performed preferably before surgery, but can also be considered postoperatively if patients are symptomatic and having problems with DED,” continues Dr. Epitropoulos. “Typically, I avoid performing these procedures immediately after surgery to prevent any interference with the wound or incision. Instead, I wait for several weeks before considering such interventions. Additionally, I incorporate amniotic membrane therapy into my treatment approach, particularly for patients that have moderate to severe dry-eye disease. This therapy can also be performed pre- or postoperatively.”

**Corneal-Based Refractive Procedures**

Once the ocular surface has been addressed or ruled out, patients have a few options for moving forward with correcting their error, including laser correction with LASIK or PRK, or astigmatic incisions, depending on the degree of error.

Dr. Berdahl says it’s common and helpful to give the patient glasses in the early postop period to determine if the refractive error is the problem. “We have them wear a temporary pair of glasses until they’re three months out from their surgery before considering options,” he says. “It also serves to decrease the anxiety level of the patient because they know that they can see okay, and they know the problem is fixable. Imagine you had cataract surgery, you’ve got 1 D of cylinder, you don’t like your vision and your doctor says: ‘Don’t worry, it’ll be fine. Just live with the blurry vision for three months.’ No, let’s give them a temporary pair of glasses and make them see better.”

However, if patients are adamant about not wearing glasses, then PRK or LASIK is an option. “If it’s astigmatism only and their spherical equivalent is near plano or zero, then astigmatic incisions work extremely well and allow you to correct astigmatism, without altering their spherical power,” says Dr. Rubenstein. “If they have a combination of myopia and astigmatism or hyperopia and astigmatism, then you might want to consider either PRK or LASIK. The decision of which of those two procedures to perform depends on the patient’s ocular surface and how you think they’re going to heal.”

Surgeons differ on their preferred method for the corneal refractive procedure, and take patient-specific factors into account.

“If they’re very dry, then LASIK may not be a good procedure and PRK may be better,” Dr. Rubenstein says. “If they actually have true corneal epithelial staining—I’ll stain them with either rose bengal, lissamine green, or fluorescein stain—and the epithelium is showing signs of damage or injury due to their dryness, then I would avoid LASIK. If they’re not staining, but they’re just moderately dry, then I could consider something like punctal plugs, enhancing their artificial tears preoperatively or treating their eyelid disease. If there’s no epithelial staining I would do those
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measures and consider LASIK.”

Dr. Rubenstein tends to favor LASIK when possible on these patients. “An older patient may not heal well so PRK can be a harder operation for them to recover from,” he says. “Some people tend to do PRK in all of these patients, but I think LASIK works quite well. Some physicians worry that LASIK requires suction to hold the eye in place before creating a flap and there was concern that this could move the lens implant or harm the eye. With the femtosecond creation of a laser flap, I don’t think that’s an issue as far as disturbing lenses.”

Dr. Epitropoulos favors PRK. “I personally believe that a flapless procedure is generally less invasive, however, this perspective may not be universal among all practitioners,” she says. “I hold the view that PRK potentially reduces the risk of DED compared to LASIK, as LASIK involves cutting through the corneal nerves, which may contribute to dry-eye disease. While LASIK proponents argue for faster healing due to bypassing epithelial healing, I find that when the ocular surface is optimized most PRK patients heal quite rapidly, typically within three to four days.”

“Following PRK, I employ a regimen involving a bandage contact lens, along with antibiotics (for a week) and steroids usually for a couple of months to minimize any haze or regression afterwards,” she continues. “When addressing refractive errors after cataract surgery, it’s common for patients to have minor residual refractive errors. In such cases, PRK is a suitable option. It’s worth noting that there are fewer concerns regarding corneal thickness limitations associated with LASIK in such cases.”

Dr. Berdahl was part of a study comparing post-refractive enhancements on IOL patients. A total of 822 post-cataract eyes underwent either LASIK or PRK. Sixty-seven percent of LASIK-enhanced patients achieved 20/20 or better post-enhancement UDVA, compared with 43 percent of PRK-enhanced patients. LASIK also had better outcomes when controlling for pre-enhancement UDVA, except in those with pre-enhancement vision of 20/20 or better, or those worse than 20/50.3

The biggest technique for LASIK in these patients is to be gentle. They’re more at risk for epithelial erosions. Treat the ocular surface very aggressively in the postoperative period, especially if they’re having refractive surgery.

— John Berdahl, MD

“We found that LASIK is more predictable than PRK and I think that’s likely because the epithelium is a bit more irregular by nature in patients that are older and hence, if you did a PRK instead of LASIK, you’d be removing that slightly irregular epithelium and treating the underlying stroma, but the underlying stromal refraction is different than the surface refraction,” explains Dr. Berdahl.

Considerations may also change if the patient had previous refractive surgery. These patients are more likely to need post-cataract enhancement, says Dr. Rubenstein. “Previous LASIK or PRK may take further LASIK enhancement out of the picture,” he says. “If you think their cornea is already thin or already very flat, you may not want to treat their cornea. If they’ve had LASIK that has any complications—whether it be flap complications, scarring, epithelial ingrowth or anything that could make their cornea less than perfect—I may not want to do further corneal refractive surgery on that patient. Therefore, that’s a patient on whom I may consider an IOL exchange if I don’t want to touch their cornea with refractive surgery.”

If the patient has undergone previous corneal refractive surgery, Dr. Epitropoulos says the age of a LASIK flap matters. “Having a flap makes it easy to lift it, perform ablation and then reposition the flap, resulting in slightly quicker healing for patients,” she says. “However, over time, the flap may become more challenging to lift, especially after several years. In these cases, performing surface ablation directly over the flap may be preferable.”

The surgeons we spoke with say they commonly target plano in these procedures, with some exceptions. “I try to target plano unless the patient wants mild myopia for monovision or mini-monovision,” Dr. Rubenstein says. “You try to pick the refractive target after talking to the patient and finding out what their visual needs are. If the patient wants to be plano for good distance vision then that’s really what I aim for. If possible, try to leave them with a small degree of with-the-rule astigmatism versus against-the-rule astigmatism, because there’s a progressive drift towards against-the-rule astigmatism in patients as they age.”

“In general we target for plano OU for these patients with the exception if we’re trying to do a little mini-monovision with EDOF or LAL lenses,” Dr. Berdahl says. “The biggest technique for LASIK in these patients is just to be gentle. They’re more at risk for epithelial erosions. Then treat the ocular surface very aggressively in the postoperative period, especially if they’re having refractive surgery. Although I don’t personally use AKs frequently as a treatment in the postoperative period, I think that’s a reasonable treatment if your spherical equivalent is adequate and the benefit is that it doesn’t impact the epithelium.”

Other Ways to Correct

Surgeons say there are additional approaches available to you:

• Limbal-relaxing incisions. Dr. Rubenstein says this is an underutilized skill.
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**ADVERSE REACTIONS**

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.

RYZUMVI was evaluated in 642 subjects in clinical trials across various subject populations. The most common ocular adverse reactions reported in >5% of subjects were instillation site discomfort including pain, stinging, and burning (16%) and conjunctival hyperemia (12%). The only non-ocular adverse reaction reported in >5% of subjects was dysgeusia (6%).

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** Risk Summary: There are no available data with RYZUMVI administration in pregnant women to inform a drug–associated risk. In animal toxicology studies, when phentolamine was administered orally to pregnant mice and rats during the period of organogenesis skeletal immaturity and decreased growth was observed in the offspring at doses at least 24-times the recommended clinical dose. Additionally, a lower rate of implantation was seen in pregnant rats treated with phentolamine administered at least 60-times the recommended clinical dose. No malformations or embryofetal deaths were observed in pregnant rats treated with phentolamine administered at least 60-times the recommended clinical dose. No malformations or embryofetal deaths were observed in the offspring of pregnant mice, rats, and rabbits administered phentolamine during the period of organogenesis at doses of at least 24–, 60–, and 20–times, respectively, the recommended clinical dose (see Data). RYZUMVI should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

**Data Animal Data** Oral administration of phentolamine to pregnant rats and mice at doses at least 24-times the recommended clinical dose (based on a body weight per surface area (mg/m²) comparison with a 60-kg human) resulted in slightly decreased growth and slight skeletal immaturity of the fetuses. Immaturity was manifested by increased incidence of incomplete or unossified calcanei and phalangeal nuclei of the hind limb and of incompletely ossified sternebrae. At oral phentolamine doses at least 60-times the recommended clinical dose (based on a mg/m² comparison with a 60-kg human), a slightly lower rate of implantation was found in rats. Phentolamine did not affect embryonic or fetal development in rabbits at oral doses at least 20-times the recommended dose (based on a mg/m² comparison with a 60-kg human). No malformations or embryofetal deaths were observed in the rat, mouse or rabbit studies.

**Lactation:** Risk Summary: There is no information regarding the presence of phentolamine in human milk, the effects on the breastfed infants, or the effects on milk production during lactation to inform risk of phentolamine ophthalmic solution 0.75% to an infant. The developmental and health benefits of breastfeeding should be considered alongside with the mother’s clinical need for RYZUMVI and any potential adverse effects on the breastfed child from RYZUMVI.

**Pediatric Use:** The safety and effectiveness of RYZUMVI have been established in pediatric patients aged 3 to 17 years. No overall differences have been observed between pediatric and adult subjects.

**Geriatric Use:** No overall differences in safety and effectiveness have been observed between elderly and younger adult subjects.

**OVERDOSAGE**

No deaths due to acute poisoning with phentolamine have been reported. Overdosage with parenterally administered phentolamine is characterized chiefly by cardiovascular disturbances, such as arrhythmias, tachycardia, hypotension, and possibly shock. In addition, the following might occur: excitation, headache, sweating, visual disturbances, nausea, vomiting, diarrhea, or hypoglycemia. There is no specific antidote; treatment consists of appropriate monitoring and supportive care. Substantial decreases in blood pressure or other evidence of shock-like conditions should be treated vigorously and promptly.

**Carcinogenesis, Mutagenesis, IMPAIRMENT OF FERTILITY**

**Carcinogenesis:** Carcinogenicity studies with RYZUMVI have not been conducted.

**Mutagenesis:** Phentolamine was not mutagenic in the in-vitro bacterial reverse mutation (Ames) assay. In the in-vitro chromosomal aberration study in Chinese hamster ovary cells, numerical aberrations were slightly increased after a 4-hour exposure to phentolamine without metabolic activation, and structural aberrations were slightly increased after a 4-hour exposure to phentolamine with metabolic activation only at the highest concentrations tested, but neither numerical nor structural aberrations were increased after a 20-hour exposure without metabolic activation. Phentolamine was not clastogenic in two in-vivo mouse micronucleus assays.

**Impairment of Fertility:** The effect of phentolamine on female fertility has not been studied. Male rats treated with oral phentolamine for nine weeks (four weeks prior to mating, 3 weeks during the mating period and 2 weeks after mating) were mated with untreated females. At doses up to 648-times human therapeutic exposure levels at the Cmin, no adverse effects on male fertility parameters or on reproductive parameters in the untreated females mated with the treated males were observed.

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“It’s a skill I tend to be bullish about,” he says. “I’ve taught courses both at the American Academy of Ophthalmology and ASCRS meetings for many, many years on the skill of performing corneal-relaxing incisions. The best time to use this technique is if a patient has a postoperative spherical equivalent near plano, then you can go ahead and try to correct the astigmatism with peripheral corneal relaxing incisions. LRI s can be used to correct low errors, up to 2 D of astigmatism, he continues. “It’s usually rare to have postop patients who have more than that. Usually, you’re correcting 1 to 1.5 D of astigmatism with a spherical equivalent near plano. It’s a very effective technique. It can be done as an office-based procedure. Some people do this at the slit lamp. “The technique and how much to cut is based on a nomogram, which requires an adequate refraction,” explains Dr. Rubenstein. “I’d refract the patient more than once at two separate visits to make sure I have a stable refraction. You can use a number of nomograms that are available in the literature and identify the amount of correction that needs to be performed. The level of treatment is based on the amount of astigmatism, the location of the astigmatism and the age of the patient. First, calculate how much astigmatism needs to be corrected and then it’s a minor surgical setup. I use the operating microscope with the patient supine, topical anesthetic, topical Betadine and then a diamond blade to create corneal incisions near the limbus at the peripheral cornea. You can either measure the peripheral corneal thickness with ultrasonic pachymetry and set your diamond knife to the thinnest of your measured thicknesses or use a preset 600 micron diamond blade.”

• IOL exchange. Thresholds for determining when it’s better to exchange the IOL differ.

For Dr. Rubenstein, an IOL exchange would be reserved for large residual refractive errors of 3, 4 or 5 D. “In general that’s unusual,” he says. “The misses are usually smaller and within 1 D. For these small refractive errors, I tend not to want to go back and exchange the lens.”

Dr. Berdahl says, “For those surgeons that don’t have access to an excimer laser, an IOL exchange or a piggyback or rotation of an IOL is a very reasonable option. There are many tools out there to help you figure out how to rotate the IOL to the proper location to minimize the amount of astigmatism. In my mind I philosophically moved away from thinking about an IOL exchange as a failure. It’s simply one more tool in our toolkit to get the patient to a happy spot.

“This is especially true as we..."
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pushing the limits of technology in eyes that are less pristine,” he continues. “This of course warrants careful informed consent with the patient’s understanding that their eyes aren’t pristine. But if they’re hoping for vision that’s free of spectacles or diminished use of spectacles and we think there’s a reasonable chance of achieving their visual goals, I offer this to the patient and we talk about the increased likelihood of an IOL exchange should they not be happy.”

Dr. Rubenstein prepares for a few scenarios as he proceeds with an exchange. “If you’re doing an IOL exchange, you’re not sure what’s going to happen when you get into surgery,” he advises. “You don’t know if that lens is going to come out smoothly or not. Your intent is to try to dissect the lens implant out of the capsular bag without any injury to the capsular bag or any injury to the lens zonules. That’s your number-one game plan. If you can do that, and you preserve the integrity of the capsular bag and zonules, you can put a replacement lens implant of the appropriate power back into the capsular bag. But that may not always be the case so you have to be prepared for scenario number two.”

Scenario number two is implanting a lens into the ciliary sulcus and capturing the optic with anterior capsular capture, he continues. “The optic stays in the capsular bag and the haptics are in the sulcus—that’s a very stable way of fixing the lens,” Dr. Rubenstein says. “The lens implant power ends up being basically the same as if the lens implant was fully in the bag.”

However, if the lens is out and the surgeon is worried about the bag and the zonules, they can try to put the lens implant into the sulcus alone and orient the lens implant in the position that gives the greatest amount of support with the existing zonules. “You usually have to change the lens implant power and decrease the lens implant power by 0.5 D to 1 D when you put the implant in the sulcus,” Dr. Rubenstein says.

“And then the fourth option, after you take the lens out and it turned out to be quite traumatic and you don’t have a good bag or sulcus, then you have to do some sort of fixation of the lens implant, either intra-scleral haptic fixation or some sort of sutured fixation to the sclera,” he says. “When I take these patients in for lens implant exchange, I have all four options planned for. I have all the instrumentation for those four options lined up in the operating room and I’ll do whatever is necessary to produce a stable lens implant depending on what I’m encountering intraoperatively.”

• Repositioning the lens. Another scenario that can occur is if a lens implant is the correct power, but it’s out of position.

“For a toric lens, you may have to change the position of the lens implant so that it corrects the full amount of astigmatic power,” notes Dr. Rubenstein. “There’s a tool called AstigmatismFix.com, which allows you to assess the position that the lens sits in postop, and compares that with the intended position. The formula then calculates the anticipated reduction in the astigmatism if you rotate the lens and what position to rotate the lens to. You can also adjust the position of the IOL that’s currently in the eye in order to change the spherical power, such as bringing the optic outside of the capsule in a reverse optic capture. There are various manipulations of the existing lens implant that can sometimes give you a refractive change without having to exchange the lens entirely.”

• Piggyback. If the refractive error produced hyperopia in the patient, a piggyback lens may be considered.

“A piggyback lens implant can go on top of the lens if the intraocular situation is deemed to be safe: an adequate anterior chamber; a healthy cornea and corneal endothelium; and a well-placed initial lens implant that allows you to piggyback the new lens implant in the ciliary sulcus on top of the existing lens implant,” says Dr. Rubenstein.

Patient Relationships

Dr. Epitropoulos says if these measures don’t resolve a patient’s problem, then they should be thoroughly evaluated, including topography, followed by an OCT to rule out macular edema.

Often, these challenging patients can be identified and counseled ahead of surgery. “During discussions with patients, I emphasize that while we employ advanced equipment and techniques, the human body’s response to surgery can be unpredictable despite our best efforts,” she says. “This perspective helps to provide context for surgical outcomes and underscores the fact that results aren’t solely determined by the surgeon’s skill. I also highlight the remarkable healing and adaptive capabilities of the human body, reassuring patients that their bodies have the capacity to respond positively to treatment with time.

“I train my staff to be vigilant in identifying patients who may have unrealistic expectations or whose needs we may not be able to fully meet,” continues Dr. Epitropoulos. “This proactive approach helps ensure that we can manage patient expectations effectively and provide the best possible care for each individual. By identifying such patients early on, we can have open and honest discussions with them about what they can realistically expect from their treatment, thereby minimizing the likelihood of dissatisfaction or misunderstanding later.”

The number of treatments in the U.S. Food and Drug Administration pipeline for dry-eye disease is staggering. Each novel pharmaceutical is going through different phases of clinical trials all with the same goals: Effectiveness and market approval.

“I think that the realities of cost and regulatory approval and the complexity of trying to meet both clinical sign and symptom endpoints for these is hard,” says Rebecca Petris, the president of the Dry Eye Foundation and a dry-eye disease patient. “But the market is continually growing, so it’s clearly a very attractive area for the industry.”

This article will review several dry-eye disease treatments undergoing Phase III trials along with treatments nearing market availability.

Never Giving Up
Aldeyra submitted its New Drug Application for its drug Reproxalap in 2023. The FDA responded with some discrepancies over the clinical trials. According to the company, the FDA stated that the NDA didn’t demonstrate efficacy in treating ocular symptoms associated with dry eye and that the pharmaceutical company would need to conduct at least one additional efficacy trial to receive market approval.

“[Aldeyra] came to an agreement with the FDA about a new mini trial with a really interesting structure,” says Ms. Petris. “Once they’ve presented that with their resubmission, then it’s expected to be another six-month review period from the FDA. So, it’s definitely not dead. They’re heading into their next phase of it.”

In April, researchers for Aldeyra presented the results for a pivotal dry-eye disease chamber crossover trial at ASCRS 2024. The researchers tested the efficacy of 0.25% Reproxalap ophthalmic solution compared to a vehicle in dry-eye patients. A total of 63 patients were selected for the trial, receiving four doses of Reproxalap or the vehicle daily for about one to two weeks. Researchers observed the primary endpoint of ocular redness during the chamber and Schirmer test 10 minutes after the fourth dose.

Lacrifill is a one-time disposable prefilled syringe containing sterile hyaluronic-acid gel. It can be administered in the canaliculi in both eyes if needed. The most common adverse event presented in the original Lacrifill study (n=63) was epiphora (7.8 percent).
According to the report, Reproxalap demonstrated statistically significant diminished ocular redness and increased Schirmer score by ≥10mm in subjects. Compared to the vehicle, Reproxalap statistically significantly lowered symptoms assessed in the chamber following treatment. Patients treated with Reproxalap experienced mild adverse events, the most common being mild, transient irritation upon instillation, which lasted approximately one minute for each individual.

In a company statement, Aldeyra states that the FDA didn’t have issues with safety or manufacturing. The company says that data from their Phase IIb clinical trial proved that Reproxalap effectively reduced patients’ symptoms leading to ocular surface improvement. They say that drug improved symptoms such as ocular discomfort, dryness, grittiness, stinging and burning, as well as provided better osmolarity and Schirmer test scores compared to vehicle.

On the Cusp of Release
Nordic Pharma’s Lacrifill has 510(k) approval but isn’t yet available. Nordic says it’s set to release the treatment in the coming months. Lacrifill is a canalicular gel dermal filler used to block tear drainage that has been given labeling from the FDA to stay resident in the eye for up to six months before irrigating and readministering the treatment.

“The reason for that is that when we did the study, the FDA wanted us to do a much longer study,” says Mark Packer, MD, the founder of Packer Research Associates and former chief medical officer for Visant Medical, the pharmaceutical company originally developing Lacrifill before Nordic acquired the product. “We wanted to do six months. We thought that would be sufficient. They wanted us to do longer. We weren't really sure at the time how long the stuff would last. We were pretty confident at about three months based on prior clinical work we had done but we didn't know beyond that.

“In the negotiation with the FDA, they said, 'Fine, you can do it for six months, but at six months you’ve got to wash it out. You’ve got to remove it from everybody. We don’t want people out there with this investigational gel in their canaliculus,’” continues Dr. Packer. "So, at six months you’ve got to wash it out. That was kind of the negotiation, so that’s what we did and that’s why it’s temporary. But it absolutely lasts six months. There’s no question about that.

“Basically, [Visant was] a small startup company,” Dr. Packer explains. “We wanted to move forward. We didn’t want to be studying for a whole year or two, which the FDA would’ve been happy with. So, we do have plans around that because we don’t even know how long it would last if you didn’t wash it out in six months. I think it might be a year, but I don’t really have any basis for that. It’s just a gut feeling. So, that’s a really interesting study and that’s definitely a part of the plan.”

When it was originally developed, the clinical research for Lacrifill only supported up to three months with speculation for use up to six months. John P. Fezza, MD, a facial cosmetic surgeon who developed Lacrifill and owns the patent behind it, first proposed the idea of using cross-
linked hyaluronic acid gel to treat dry eyes. In his published research, he explained how the gel can be placed in the lower canaliculus, which would block tear drainage similar to punctal plugs.

Although the final follow-up period for Dr. Fezza’s study was set at six months after treatment, he focused on observing the three-month follow-up period to assess the safety and efficacy of the gel. A total of 63 patients completed the study, all of which demonstrated an improvement in corneal fluorescein staining. Dr. Fezza noted that Schirmer’s tests demonstrated an average increase over baseline of 3.67 mm after three months of treatment. Both breakup time and tear meniscus height at baseline over the three-month period increased (87 percent and 57 percent, respectively).

At the time of writing this article, the latest data for six-month follow-up hasn’t been published, but Dr. Packer notes that this information will be made public in the coming months.

Dr. Packer mentions that the procedure is very easy to perform. “It’s like doing a lacrimal irrigation, which I think was probably the first procedure I ever learned in residency to determine the patency of the lacrimal system,” he says. “So, it’s just like squirting some saline down through the punctum, through the canaliculus, and ultimately into the nose. You get a prefilled sterile syringe that has 0.6 mL, [of solution], and that is enough if you needed to actually occlude all four canaliculi, but in the study that we did, it was just the inferior.”

**Further Analysis**

RegeneRx Biopharmaceuticals is awaiting market approval for its moderate-to-severe dry eye treatment, RGN-259 (also indicated for neurotrophic keratitis). RGN-259 is an eye-drop solution containing the regenerative protein thymosin β4.

In a company statement from 2021, the ARISE-3 Phase III clinical trial has been completed. Although the drug didn’t meet the primary endpoint, it did meet the secondary endpoint of improvement of ocular grittiness. This improvement was statistically significant and was observed at one and two weeks after treatment, the company says. No serious adverse events were reported, although mild-to-moderate events were analyzed in both the RGN-259 group and placebo group. The most common adverse event was mild pain upon instillation, which was reported in 6.6 percent of RGN-259 patients and 4.6 percent of placebo recipients.

According to a post-hoc analysis by GtreeBNT using the exact cohort from the Phase III trial, patients showed significant improvement in...
fluorescein staining scores after two weeks of treatment.

“While the trial didn’t meet its primary outcome measures, there was a statistically significant symptom effect in favor of RGN-259 in a short period of time in addition to its safety,” stated J.J. Finkelstein, the RegeneRx president and chief executive, in the official statement. “Statistically significant clinical improvements in various signs and symptoms of dry-eye syndrome have now been observed in all three Phase III clinical trials, ARISE-1 -2 and -3, and further analyses are ongoing.”

Both RegeneRx and GtreeBNT will continue their efforts towards achieving market approval and are exploring the possibility of a pre-Biologics License Application with the FDA using the results from the three ARISE clinical trials.

**Smooth Sailing (So Far)**

Alcon acquired AR-15512, a topical transient receptor potential melastatin 8 (TRPM8) agonist, after the acquisition of Aerie Pharmaceuticals in 2022. In January of this year, Alcon announced that its Phase III COMET trials for AR-15512 had achieved positive topline results. “I saw on their results announced in January that they were talking about a 10-mm increase in the Schirmer’s score,” points out Ms. Petris.

According to Alcon, subjects from the COMET-2 and COMET-3 trials met the primary endpoint of the proportion of subjects with at least a 10-mm increase in Schirmer’s score at day 14 of the trials, which was statistically significant. Additionally, data from the secondary endpoints in the trials demonstrated the rapid onset and sustained tear production associated with AR-15512 compared to the vehicle. Some patients met this secondary endpoint at day one, while others were persistent up until day 90 of the trials. No serious ocular events were reported.

**Moving Forward**

A Phase III clinical trial for ST-100, Stuart Therapeutics’ vezocolmitide drug candidate, has begun, with an enrollment of 320 subjects in a randomized, placebo-controlled trial aiming to evaluate the safety and efficacy of the drug. According to Stuart Therapeutics, this novel treatment is based on the company’s PolyCol technology, a collagen mimetic platform, and used to restore disease-damaged collagen.

In 2022, Stuart Therapeutics announced the success of its Phase II clinical trial for ST-100. A total of 160 subjects were enrolled for the study, each receiving either 20 μg/mL ST-100, 50 μg/mL of ST-100 or a placebo twice daily. The primary endpoint observed, similar to previously mentioned trials, was a statistically significant difference between the percentage of patients achieving a ≥10 mm increase in Schirmer’s score at 28 days. Other points assessed were the ocular surface staining scores, which were statistically significant at treatment day seven, and overall ocular discomfort graded on the Ora Calibra Scale which the company says improved at treatment day 14.

**Reviewing and Reassessing Trials**

According to Palatin, the company is expected to meet with the FDA to discuss a regulatory approval path for their dry-eye treatment, PL9643, a melanocortin agonist. After not meeting its Phase III co-primary sign endpoint and secondary sign endpoints, Palatin is moving forward to the next stages of development.

“Our comprehensive data analysis is ongoing, and upon completion, we plan to meet with the FDA to discuss and get feedback on the design of the next pivotal Phase III clinical trial,” mentioned Carl Spana, PhD, the president and CEO of Palatin, in a company statement.

The company says that, in its Phase III MELODY-1 trial, the co-primary symptom endpoint was met as well as multiple secondary symptom endpoints. Symptom endpoints assessed pain while sign endpoints assessed conjunctival staining. As initially stated, the sign endpoints weren’t met, but PL9643 demonstrated a clinically meaningful visual analog score reduction of >10 points from baseline and other statistically significant results for the co-primary symptom endpoint.

After analyzing PL9643 for safety, the researchers

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**Slit lamp images of a cornea undergoing treatment with RGN-259.** (A) Image of a prominent epithelial defect at onset of treatment. (B) Image of healed epithelial defect 31 days after treatment.
If you identify new or changing signs or symptoms, consult with an eye doctor who specializes in TED right away.1,7

For patients with Graves’ disease (GD), Thyroid Eye Disease (TED) may be hiding in plain sight.1,2

Up to 50% of patients with GD may develop TED, a separate and distinct disease which can progress if left untreated. Look out for the early signs and symptoms3-6:

- Proptosis
- Sensitivity to light
- Diplopia
- Grittiness
- Dry eyes
- Pain or pressure behind the eyes

If you identify new or changing signs or symptoms, consult with an eye doctor who specializes in TED right away.1,7

Visit TEDimpact.com to find a TED Specialist

indicated that the treatment was well-tolerated with fewer ocular adverse events in the PL9643 group (5.6 percent) compared to the vehicle (6.3 percent). Additionally, some subjects discontinued treatment during the trial, which resulted in a lower number of patients in the PL9643 group discontinuing treatment (7 percent) compared to the vehicle group (11.1 percent).

**Another Treatment Indication**

“If Dompé could get an indication for Sjogren’s for Oxervate [cenegermin-bkbj], that would be a real coup to have something specific for Sjogren’s,” comments Ms. Petris. “It’d be a coup for them. It would definitely be a coup for the Sjogren’s world.”

In 2022, Dompé announced it had enrolled the first patient in the Phase III trial for Oxervate with an indication for severe Sjogren’s dry eye. Now, the PROTEGO-1 PHASE III trial has completed enrollment and is actively undergoing investigation. The study will determine the safety and efficacy of cenegermin ophthalmic solution at 20 μg/mL versus a vehicle over four weeks.

According to Clinicaltrials.gov’s listing of Clinical Trial NGF0121, Oxervate will need to achieve the co-primary endpoint of >10 mm/5 min. in Schirmer’s tests along with a co-primary endpoint for change from baseline in SANDE global score. Secondary endpoints will assess a change from baseline in Schirmer’s test, change from baseline in cornea and conjunctival vital staining with fluorescein, change from baseline in tear-film breakup time, change from baseline SANDE scores for severity and frequency, number of patients experiencing a worsening in SANDE scores as well as an Impact of Dry Eye in Everyday Life questionnaire.

In conclusion, dry-eye treatments will continue to develop, especially since there’s no perfect solution to mitigate the disease’s symptoms. Both Dr. Packer and Ms. Petris agree that physicians need to work with their patients to help them better understand their symptoms and explain that there will be more options as treatments are approved.

“I think in the mass for the patient world, knowing how much is in the pipeline is very important, because when you have a disease that has so much impact on someone’s daily life, and often gets labeled with terms like ‘chronic’ and ‘progressive,’ people struggle with hope,” says Ms. Petris. “They struggle to find hope that things can get better. And the pipeline is that promise that there’s hope that there are things being worked on.”

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nandropper, Inc., an ophthalmic device company announced publication of “An Evaluation of the Efficacy and Safety of Timolol Maleate 0.5% Microdrops Administered with the Nanodropper” in the journal Ophthalmology. The Nanodropper® Adaptor has been shown to reduce eyedrop size by 62% on average. A smaller drop extends the number of doses yielded per medication bottle (up to 100 drops/mL).

The study found that timolol microdrops had an improved safety profile in the form of less heart rate reduction yet did not significantly differ from conventional drops in intraocular pressure (IOP)-lowering efficacy.

**Study Design**
The study employed a prospective, non-inferiority, parallel, multicenter, single-masked, active-controlled, randomized trial design. Treatment-naïve subjects received either one commercially available drop (28 μL) or one microdrop (12.5 μL) of timolol — IOP, resting heart rate, and blood pressure were measured at baseline and 1, 2, 5, and 8 hours after administering the drop.

**Findings**
Nanodropper established IOP non-inferiority to conventional drops at three of four timepoints, and the average heart rate decrease with Nanodropper was around three beats per minute less than in the conventional drops group, meaning heart rate fluctuated less and thus remained more stable with administration of microdrops.

The conclusion supports the Nanodropper Adaptor as a tool for optimizing topical management of ophthalmic conditions, particularly in enhancing safety profiles and reducing waste.

We are thrilled, albeit not surprised, by these encouraging results demonstrating the Nanodropper Adaptor’s capacity to improve patient safety.

-Jennifer Steger, PhD CSO of Nanodropper

**Bring Nanodropper to Your Practice**
Thousands of eyecare clinics in the U.S., and tens of thousands of patients worldwide, are already utilizing the Nanodropper Adaptor.

Join the Nanodropper partner clinic network and the movement towards reducing the waste and cost of eyedrop medications while improving patient outcomes. As a partner clinic, you can utilize Nanodropper on in-office drops and dispense to patients for home medications.

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Beyond the Blurred Lines

Common children’s eye conditions such as myopia and amblyopia may signal deeper issues.

ALINA V. DUMITRESCU, MD
IOWA CITY, IOWA

Myopia and amblyopia are among the most common conditions in pediatric ophthalmology practice. While the diagnoses are relatively easy and the conditions are treatable, knowing when to suspect an underlying cause or a genetic disorder contributing to myopia or masquerading as amblyopia is less clear. Here, I’ll discuss some of the signs and clues for cases where myopia and amblyopia are manifestations of a more severe condition.

Myopia
We know that myopia can result from an elongated axial eye length, an abnormal intraocular lens, an abnormal corneal curvature or a combination. Usual symptoms are decreased distance vision, squinting—or adopting a head position for distance viewing—for pinhole purposes. Some children can be asymptomatic, and the suspicion arises during vision screening.

The final diagnosis is made with an eye exam and cycloplegic refraction. The treatment is glasses or contact lenses. Most children will tolerate the correction and will have normal visual acuity with correction. A certain degree of progression of the myopic correction is expected in most children, and using diluted atropine drops, glasses with peripheral defocus, and special contact lenses (orthoK) can mitigate myopia progression in most patients.

Amblyopia
Amblyopia represents decreased vision in one or both eyes due to abnormal vision development in infancy or childhood. The most common cause of amblyopia is uncorrected refractive error in one or both eyes, resulting in poor development of the visual function in the affected eye(s). Another common cause is strabismus or eye misalignment, in which the two eyes aren’t used simultaneously. Rarely, a structural anomaly that impairs vision, such as visually significant eyelid ptosis, media opacity, cataract or corneal scar, is the cause of amblyopia.

In all these situations, addressing the cause of amblyopia (with glasses and/or surgery) and using the penalization of the better-seeing eye (with patching or atropine) or binocular stimulation treatments (NovaSight or Luminopia) improves vision. Each treatment modality has its indications and limitations but is effective when applied correctly. (To learn more about binocular stimulation treatments, check out “New Ways to Address Amblyopia” from the February issue of Review.)

Retinopathy of prematurity is often associated with the development of progressive high myopia.

This article has no commercial sponsorship.

Dr. Collinge is an assistant professor in the Department of Pediatrics of the University of Connecticut School of Medicine. She can be reached at jcollinge@connecticutchildrens.org. She has no financial interest in any of the products discussed in the article.
SYFOVRE® (pegcetacoplan injection)

15 mg / 0.1 mL

**INDICATION**

SYFOVRE® (pegcetacoplan injection) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

- SYFOVRE is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation.

**WARNINGS AND PRECAUTIONS**

- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

- **Retinal Vasculitis and/or Retinal Vascular Occlusion**
  - Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.

- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

**ADVERSE REACTIONS**

- **Intraocular Inflammation**
  - In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves, patients may resume treatment with SYFOVRE.

- **Increased Intraocular Pressure**
  - Acute increase in IOP may occur within minutes of any intravitreal injections, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

Please see Brief Summary of Prescribing Information for SYFOVRE on the adjacent page.

**Trial Design:** SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=627), multi-center, 24-month, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE EOM, sham monthly, or sham EOM for 24 months. Change from baseline in the total area of GA lesions in the study eye (mm²) was measured by fundus autofluorescence (FAF). **References:** 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc. 2. Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. JAMA Ophthalmol. 2020;138(10):1026–1034. 3. Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. JAMA Ophthalmol. 2014;132(3):338–345. 4. Data on file. Apellis Pharmaceuticals, Inc.

SYFOVRE achieved continuous reductions in mean lesion growth rate* vs sham pooled from baseline to Month 24.**

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<th>Monthly</th>
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SE in trials (monthly, EOM, sham pooled):

OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17.

* Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.

**Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.

The CMS-assigned permanent J-code for SYFOVRE is J2781—effective 10/1/23. **

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**CONTRAINDICATIONS**

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SYFOVRE® (pegcetacoplan injection), for intravitreal use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see SYFOVRE full Prescribing Information for details.

INDICATIONS AND USAGE

SYFOVRE is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

CONTRAINDICATIONS

Ocular or Pericocular Infections

SYFOVRE is contraindicated in patients with ocular or pericocular infections.

Active Intraocular Inflammation

SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

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Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intracocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.

Neovascular AMD

In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

Intraocular Inflammation

In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreous cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.

Increased Intraocular Pressure

Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

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.

A total of 830 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nine (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.

The most common adverse reactions (>5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>PM (N=419)</th>
<th>PEOM (N=420)</th>
<th>Sham Pooled (N=417)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular discomfort*</td>
<td>13 (3%)</td>
<td>10 (3%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Neovascular age-related macular degeneration*</td>
<td>12 (3%)</td>
<td>7 (3%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>10 (3%)</td>
<td>7 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>8 (3%)</td>
<td>8 (3%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>4 (3%)</td>
<td>6 (3%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>4 (3%)</td>
<td>5 (3%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Punctate keratitis*</td>
<td>5 (3%)</td>
<td>3 (&lt;1)</td>
<td>&lt;1 (&lt;1)</td>
</tr>
<tr>
<td>Posterior capsule opacification</td>
<td>4 (3%)</td>
<td>4 (3%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Intraocular inflammation*</td>
<td>4 (3%)</td>
<td>2 (&lt;1)</td>
<td>&lt;1 (&lt;1)</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>2 (3%)</td>
<td>3 (&lt;1)</td>
<td>&lt;1 (&lt;1)</td>
</tr>
</tbody>
</table>

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:
Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye
Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization
Punctate keratitis included: punctate keratitis, keratitis
Intraocular inflammation included: vitritis, vitreous cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

Endophthalmitis, retinal detachment, hyphema and retinal tears were reported in less than 1% of patients. Optic neuropathy was reported in 1.7% of patients treated monthly, 0.2% of patients treated every other month and 0.0% of patients assigned to sham. Deaths were reported in 6.7% of patients treated monthly, 3.6% of patients treated every other month and 3.8% of patients assigned to sham. The rates and causes of death were consistent with the elderly study population.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of SYFOVRE. 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. Eye disorders: retinal vasculitis with or without retinal vascular occlusion.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.

Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.

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

Lactation

Risk Summary

It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when SYFOVRE is administered to a nursing woman.

Females and Males of Reproductive Potential

Contraception

Females

It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose.

For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.

Pediatric Use

The safety and effectiveness of SYFOVRE in pediatric patients have not been established.

Geriatric Use

In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥65 years of age and approximately 72% (607/839) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is recommended based on age.

PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing endophthalmitis, retinal detachments, retinal vasculitis with or without retinal vascular occlusion and neovascular AMD. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopia, instruct the patient to seek immediate care from an ophthalmologist.

Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured for:

Apellis Pharmaceuticals, Inc.

110 Fifth Avenue
Walsham, MA 02451

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Going Beyond the Surface
Myopia and amblyopia can sometimes be associated with ocular or systemic conditions or be symptoms of an underlying condition. Rapid myopia progression, i.e., progression greater than 1 D per year in older children or 2 D or more per year in younger children, raises a red flag. It's common to recheck vision and refraction in one year for older children and in six months for younger children. If there's progression of 1 D or more in those six months, progression is considered rapid.

Be on guard for amblyopia cases in which the patient's vision is out of proportion to expectations for amblyopia. Examples include four or more lines of difference in vision for a minimum of anisometropia (0.5 D) or a patient with intermittent exotropia or monofixation syndrome. If no other signs are present, standard treatment is recommended first. If the patient fails to improve as expected (i.e., vision improves with glasses and/or patching or atropine), additional work-up should be considered for an underlying condition.

When your suspicion is raised, consider these conditions:
• **Retinopathy of prematurity.** Especially when requiring laser therapy, ROP is commonly associated with developing progressive high myopia with debut in infancy. The prevalence of myopia seems to vary with the severity of ROP; reported in 0 percent to 16 percent of preterm infants with no ROP and up to 21 percent to 100 percent for children whose ROP was treated with laser photocoagulation.1

  • **Juvenile and congenital glaucoma.** These are both associated with childhood myopia. In patients with primary congenital glaucoma, myopia correlates with IOP and cup-to-disc ratio.2 Approximately 70 to 80 percent of patients with juvenile primary open-angle glaucoma are myopic at presentation, and myopia less than -1 D correlates with disease progression.3

  • **Inherited retinal dystrophies.** Dystrophies like congenital stationary night blindness (CSNB) present with early childhood myopia with rapid progression with a normal fundus exam and a normal optical coherence tomography. Children will usually not complain of night blindness (because they have no comparison). Parents may not recognize that children have difficulties with dark adaptation unless pointed out or asked specific questions. In some cases, a history of improved or resolved early childhood nystagmus can be elicited from parents.

  • **Connective tissue disorders.** Disorders such as Stickler Syndrome, Marfan, Knobloch, Wagner syndrome, etc., can present with early onset progressive high myopia and/or subluxation of the intraocular lenses before other systemic symptoms are noted.

  • **Other retinal dystrophies.** Dystrophies like Leber congenital amaurosis associated with RPE65, X-linked retinitis pigmentosa associated with RPGR variants, and many others can be associated with progressive high myopia. Retinal dystrophies affecting bipolar cells and cones seem to be more commonly associated with early-onset progressive myopia.4

  • **Chromosomal abnormalities.** Like Down syndrome, other chromosomal issues can be associated with high myopia.

The diagnostic workup differs with the condition, however, and might include full-field electroretinogram (pathognomonic for retinal dystrophies), macula optical coherence tomography (retinal dystrophy, foveal hypoplasia), and ultimately genetic testing with pre- and post-test counseling.

Consequences
In the majority of these cases, the myopic refractive error starts early in childhood and tends to progress, resulting in high myopia in childhood. Depending on the underlying condition and the magnitude of myopia, there’s an increased risk of retinal detachment primarily associated with trauma but also nontraumatic.5 It’s unclear if the mechanism of myopia development is the same in these conditions as in “regular myopia” and if the same progression mitigation methods are effective. The studies that show the efficacy of diluted atropine and peripheral defocus lenses didn’t include (or analyzed separately) children with high myopia associated with an underlying condition.

Conditions like optic pathway gliomas associated with neurofibromatosis type I, slow-growing intracranial or orbital tumors, unilateral or asymmetric optic nerve hypoplasia, inherited optic neuropathies (Leber hereditary optic neuropathy or Dominant optic atrophy), or retinal conditions with onset in later childhood (like Stargardt disease) can present with asymmetric decreased vision and strabismus that can be diagnosed as amblyopia when clinical findings are subtle or absent. Bilateral amblyopia secondary to high refractive errors or deprivation is possible, but vision should improve with timely and correct treatment.

When an underlying condition is present, visual loss tends to be progressive or doesn't respond to treatment as expected. Failure to improve or worsening vision in the amblyopic eye with reported good compliance with treatment should raise concerns.
that can be missed while focusing on the eye exam, glasses prescription and amblyopia treatment.

The diagnostic workup differs for each condition; however, it might include brain and orbit MRI, optic nerve and/or macula OCT and genetic testing. Family history, review of systems, complete physical and ocular exam, and a high index of suspicion and awareness can help initiate the workup and diagnose an underlying condition associated with myopia or masquerading as amblyopia. A complete and correct diagnosis may change the treatment and the visual and overall prognosis for patients and families.

The Bottom Line
While most childhood myopia cases are considered “simple myopia” and have a relatively benign course, certain features may suggest an underlying genetic disorder:

- **Early onset.** Myopia that presents in early childhood, particularly requiring correction before age 6, may indicate a genetic disorder.

- **High myopia.** Severe myopia with high refractive values at onset or rapidly progressive early in life may also be associated with underlying genetic disorders.

As with myopia, certain features of amblyopia may suggest an underlying genetic disorder:

- **Severe.** Amblyopia that is more severe than expected for the risk factor may indicate an underlying disorder.

- **Refractive to treatment.** Amblyopia that’s not responding as expected to adequate therapy may indicate an underlying disorder.

- **Bilateral.** Bilateral amblyopia may suggest there’s an underlying genetic disorder causing the high refractive error or the deprivation, driving inadequate response to therapy. Examples include oculocutaneous albinism associated with high hyperopia or myopia, and congenital cataracts associated with systemic conditions (e.g., PAX6-related disorders).

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**Janssen/Centocor Trials for Retinitis Pigmentosa and AMD**

Cell therapy research has a broader scope beyond hESCs. Janssen/Centocor trials have attempted to determine the efficacy and immunogenicity of human umbilical tissue-derived RPE cells (hUTC-RPEs; named palucorcel, or CNTO 2476) in degenerative retinal diseases.

Unlike hESCs, these cells are derived from adult stem cells which are multipotent, meaning that they’re able to differentiate into different cell types that can promote repair to damaged tissues. First clinically tested in 2007, Centocor’s Phase I CNTO 2476 trial was geared towards patients with retinitis pigmentosa, a group of genetic disorders causing photoreceptor degeneration and gradual vision loss. After seven patients were enrolled and treated, the trial was terminated early in 2013 due to the development of RDs in two subjects. This RD rate was mostly attributed to the surgical delivery method used in the trial, which was transvitreal delivery of the cell line into the subretinal space. The treatment itself (CNTO 2476) was considered “possibly related” to the RDs. In addition, this hUTC trial didn’t use immunosuppressive therapies, and a closer histological study of an epithelial membrane sampled from one of the RD cases on the trial was unable to confirm the immunological safety of CNTO 2476.32

Once acquired by Janssen Research & Development, a Phase I/IIa study was initiated in 2010 to test the safety, tolerability and efficacy of the CNTO 2476 line in GA patients. CNTO 2476 was administered in 33 patients enrolled in the CR017548 trial, and while there were no observed cases of immune response or

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**REFERENCES**


rejection, the high rate of RDs and retinal tears noted (17.1 and 37.1 percent, respectively) emphasized the need for further modifications to the surgical approach. Nevertheless, visual gain data for eyes treated in this study was optimistic, with 24.1 percent of eyes sustaining a ≥15-letter gain at one year postoperatively, and 34.5 percent showing an improvement of ≥10 letters in the same timeframe.34

The Janssen PRELUDE study followed in 2015, and was conducted with the hope that a suprachoroidal to subretinal approach would reduce the risk of complications noted in earlier trials.34

In this Phase IIb trial, 21 patients received suprachoroidal to subretinal delivery of approximately 300,000 hUTC-RPEs through an updated surgical approach using a custom delivery system for the cell suspension. While adverse events with the new surgical approach were less extreme and the utility of the custom delivery system proved to be successful, data regarding vision and GA progression was confounding, and pointed towards no apparent benefit of the hUTC-RPE treatment.35 The delivery system evolved into the FDA-approved Orbit Subretinal Delivery System.

Kobe Trials of iPSC-RPE Sheets And Retinal Organoids
In addition to hUTCs, the safety and efficacy of induced pluripotent stem cell (iPSC) treatments for retinal diseases has also been an area of major interest. In 2017, a study from the Kobe Center for iPSC Cell Research and Application (CiRA) in Japan assessed the feasibility of autologous iPSC-derived RPE cells in two patients with wet AMD.36

As opposed to allogeneic cells such as hESCs, autologous cell therapy derives valuable, differentiable stem cells from the patients themselves, which reduces the risk of transplant rejection, and provides an easier cell harvesting method.37

Two patients were enrolled in this study, where iPSCs were made from their own skin fibroblasts, then successfully prepared into RPE sheets ex vivo. Only one patient was treated with the autologous iPSC-RPE sheet, due to gene deletions detected in the second patient that posed unforeseen risks. For the treated patient, removal of the neovascular membrane was performed prior to subretinal transplantation of the RPE sheet. No signs of graft rejection, failure or any serious adverse events were noted at one year post-transplant, and the presence of RPE cells appeared to grow over time on OCT images.

Unlike hESCs, [hUTC-RPE] cells are derived from adult stem cells which are multipotent, meaning that they are able to differentiate into different cell types that can promote repair to damaged tissues.

Retinal sensitivity and visual acuity remained stable in the treated eye, at 20/200 throughout the follow-up study period.

Recently, the Kobe City Eye Hospital group published a report following the first clinical trial using iPSC-derived retinal organoid sheets.38 As described, retinal organoids may have more promise than stem cell suspensions or “patches” due to their ability to account for more than just RPE loss in retinal degenerative diseases.

Early animal models demonstrate potential for these organoids to help restore further visual function due to their ability to differentiate into viable photoreceptors, accounting for the deterioration of photoreceptors that occurs in advanced disease.

Subretinal implantation of three organoid sheets was performed in two patients with advanced RP. Intentional shallow retinal detachments were induced in the selected eye, and implantation was localized at sites displaying RPE retention to maximize opportunity for synaptic connections to the host retina. Silicone oil was used as tamponade, while intravitreal triamcinolone and oral cyclosporine were provided to suppress potential inflammation.

There were no reports of intraocular inflammation, graft rejection, or serious systemic adverse events noted through two years of follow-up. While exploratory endpoints demonstrated no significant change to visual functioning outcomes in either patients, the treatment was well-tolerated in both cases.

The Future of Cell Research
Research into cell therapy continues to broaden the scope of its use in ophthalmology and beyond. In 2018, a Phase I trial researching a patch of hESC-RPEs provided hopeful results after treating two patients with severe wet AMD.39 A single-center study in California is applying these new technologies to retinal vein occlusions, testing the safety and viability of CD34+ stem cells in a Phase I/II trial, enrolling 16 patients following Phase I data.40,41

Human retinal progenitor cells (hRPCs) are also being more closely studied for their potential to reactivate photoreceptors in retinitis pigmentosa patients. Recent results of a Phase II safety trial by iCyte demonstrated the safety of intravitreal hRPC injections for RP in 30 patients, with a larger Phase II/III trial anticipated to follow in late 2024.42 Entities such as Astellas and the NIH also plan on continuing the pipeline of iPSCs for retinal disorders due to their efficiency, scalability and potential for treatment.43,44

In conclusion, there is vast potential for cell therapies as a treatment option for a myriad of retinal diseases and degenerations. Although cell therapy retina trials to date have been small, promising safety and tolerability data has emerged even at long term.
intervals. Current cell therapy trials continue to build on previous studies and we expect this quickly growing field of research to offer us insight into how our treatment approaches may change in the near future.


15. ASP3716, Stargardt’s Macular Dystrophy. [Accessed February 1, 2024].
Dear CSE 3rd-Year Resident Program Director and Coordinator,

We would like to invite you to review the upcoming 3rd-Year CSE Ophthalmology Resident CME Programs and Wet Labs for 2024 in Fort Worth, Texas. The programs offer a unique educational opportunity for third-year residents by providing the chance to meet and exchange ideas with some of the most respected thought leaders in ophthalmology. The programs are designed to provide your residents with in-depth didactic program and state-of-the-art wet lab experience with one-on-one wet lab guidance from faculty. The courses also serve as an opportunity for your residents to network with residents from other programs.

After reviewing the material, it is our hope that you will select and encourage your residents to attend one of these educational activities, which are CME accredited to ensure fair balance.

Best regards,
Kendall Donaldson, MD, MS, Yousuf Khalifa, MD, and Mitchell P. Weikert, MD, MS

CME courses are restricted to 3rd-year residents enrolled in an ophthalmology residency program at the time of the course. There is no registration fee for this activity. Air, ground transportation in Forth Worth, shared hotel accommodations, and modest meals will be provided through an educational scholarship for qualified participants.

Joint Accreditation Statement
In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Review Education Group. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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For more information visit the registration site above by scanning the QR code or call Denette Holmes at 866-627-0714 or email dholmes@postgradhealthed.com

Registration Open: www.ReviewEdu.com/CSE3rdYr2024
Aqueous Outflow Mechanisms

An introduction to the pulsatile flow motion model and its implications for developing future procedures.

MURRAY A. JOHNSTONE, MD
SEATTLE

In the 1870s, Leber proposed a model of IOP regulation that most ophthalmologists today are familiar with, one in which a passive flow-filter mechanism governs aqueous outflow. The model posits an obstruction in the juxtacanalicular space caused by extracellular matrix, which acts as a filter to impede fluid flow. Ultimately, fluid passes through endothelium via pores with the extracellular matrix regulating the filter’s function. However, this theory was formulated based on observations from enucleated eyes lacking normal intraocular pressure and normal ciliary body tone, and preserved ex vivo with fixative—a stark departure from physiological conditions in living organisms.

Our understanding of aqueous outflow today takes a different shape, reminiscent of the lymphatics mechanism proposed by Leber’s contemporary, Schwalbe. The model presented here is a pulsatile flow motion model based on frameworks that have evolved over the last century since 1942, when dynamic pulsatile flow out of the anterior chamber and into the episcleral veins was first demonstrated. Here, I’ll provide an overview of this system and its implications for clinical practice and surgical management.

Pulsatile Flow Motion Model

The trabecular meshwork along with the inner wall endothelium and Schlemm’s canal are in constant motion, dependent on pressure gradients. Fluid is forced into this valve system, i.e., the Schlemm’s canal inlet valve, which then pumps fluid into the Schlemm’s canal. The fluid is then driven out of the canal into collector channels and ultimately into the episcleral veins.

The ocular pulse and intraocular pressure undergo oscillatory changes, typically fluctuating by about 3 mm on average with each pulse wave. At the slit lamp, you can watch the mires oscillate when performing tonometry. These oscillations reflect the pressure gradient changes occurring within the anterior chamber. That pressure is transmitted to the trabecular meshwork, which undergoes dynamic motion in response to the intraocular pressure changes.

The underlying power behind this process is the heart. The pressure generated by the heart drives the trabecular meshwork, causing it to move outward. The trabecular meshwork’s elastic properties allow it to stretch, store elastic energy and then recoil when pressure decreases, releasing its stored energy. It’s a highly dynamic system. The trabecular meshwork responds in a similar manner to the heart undergoing oscillatory compression of a chamber, driving fluid.

Valved Distal System

Before more recent advances in OCT imaging, we’ve known that the trabecular meshwork is the wall of Schlemm’s canal, and that Schlemm’s canal is a chamber whose volume changes with intraocular pressure. Aqueous-containing endothelial-lined conduits arise from the inner wall of the canal. These conduits have a tubular shape. They cross the canal and attach to the external wall.

Over the last 12 years, in my lab and in Dr. Ruikang K. Wang’s lab, we’ve demonstrated that a Schlemm’s canal inlet valve apparatus is functionally present using various techniques, including dissecting microscopy, bright-field microscopy, bright-field blockface, scanning electron microscopy, confocal native fluorescence, Nomarski DIC, nanoparticle tracers and high-definition OCT, both static and phase-based (See Further Reading).

Here’s a rundown of the system (Figure 1):

- Schlemm’s canal inlet and outlet valves. Schlemm’s canal has both inlet valves and outlet valves, which can be visualized at the dissecting microscope. The inlet valves are flow pathways to Schlemm’s canal that also connect the trabecular meshwork to the collector channel valves. Inlet valves attach to the outlet valves at collector channel entrances. There are approximately 70 inlet valves around the circumference of the canal. These require canal dilation to be seen.

Inlet valves permit aqueous flow and prevent blood reflux. Sch-
lemm’s canal inlet valve structure has been documented by light, scanning and transmission electron microscopy, and microsphere and red blood cell tracer studies have documented inlet valves’ function as conduits. When we unroof Schlemm’s canal, the inlet valves break and discharge aqueous. During gonioscopy, inlet valves discharge oscillating waves of aqueous into the canal.

• **Septa.** Between Schlemm’s canal and the outer canal lie the septa. Still images of the dynamic motion of a septum controlling distal flow are pictured in Figure 2.

• **Collector channels.** The collector channels leave the eye in a remarkably regular fashion, all in the same plane, exiting from Schlemm’s canal, then entering a circumferential set of vascular channels, also known as the circumferentially oriented deep scleral plexus or the outer canal, before reaching the surface episcleral veins. Basically, the fluid must pass through these circumferential vascular channels before moving into the radial channels and reaching the surface.

  Using *ex vivo* high-resolution OCT, we’ve observed that the collector channel valve entrances have collagen flaps attached only at one end. These hinged flaps undergo pressure-dependent changes in position, which allow the hinged flaps to open and close the collector channels, acting also as Schlemm’s canal outlet valves.

• **Circumferentially oriented deep scleral plexus.** These channels are adjacent to Schlemm’s canal, separated from it by thin septa. They move by pressure-dependent mechanisms, opening and closing like a second pressure-dependent chamber.

  Real-time imaging of tissue motion using *ex vivo* high-resolution OCT shows that the trabecular meshwork beams, Schlemm’s canal inlet and outlet valves, and the circumferentially oriented deep scleral plexus all undergo rapid cyclic pulsatile movement. The motion of these structures’ volume changes is all synchronous, made possible by cellular attachments between the structures. The amplitude and motion velocity of the pulsatile movement can account for all of the aqueous outflow.

  Interestingly, an independent embryogenesis study of 61 eyes preserved with clarification and microvascular casting, reported five gestational intervals, with collector channels developing at six weeks of gestation, sprouting from Schlemm’s canal. These developed into circumferential channels, joining one another to create the circumferential vascular plexus. This ultimately joins with the episcleral and intrascleral vessels to form a complete system.

### Under Pressure

As glaucoma worsens, fluid movement into and out of the canal slows. This indicates a change in the pulsatile motion. You can see this in the clinic by pressing on the gonio prism to apply light pressure to the episcleral veins. In healthy patients, the pressure on the episcleral veins drives blood rapidly into Schlemm’s canal and fills it.
GLAUCOMA MANAGEMENT | Aqueous Outflow Mechanisms

completely. As pressure is released, the blood escapes rapidly, indicating that the trabecular meshwork is capable of rapid motion in response to pressure changes.

Homeostatic responses in the trabecular meshwork are well documented and can be observed in the clinic with tests such as the water drinking test, which involves having the patient drink a quart of water very quickly, driving up the fluid pressure within the eye. This rise in pressure occurs due to osmotic changes that draw fluid from the bloodstream into the eye to maintain osmotic balance, ultimately elevating intraocular pressure.

The example in Figure 3 shows video screen captures of visible pulsatile flow at an intraocular pressure of 10 mmHg. As the pressure gradually rises during the water drinking test, new regions begin to exhibit pulsations, indicating an increase in the stroke volume of pulsatile flow. At 12 mmHg, the pulsatile flow is notably larger, driving fluid farther along the vein into the episcleral veins on the surface. Even more pronounced pulsatile behavior is seen with each pulse wave at 14 mmHg. The larger stroke volume of aqueous drives fluid into a more distal region, entering a larger episcleral vein.

This provides clear evidence of pulsatile aqueous outflow, which serves as a regulatory mechanism. When intraocular pressure rises, so does the ocular pulse, along with pulse pressure and oscillatory flow. This leads to an increased volume of aqueous pumped out of the eye with each cardiac pulse wave, subsequently lowering intraocular pressure and ultimately returning it to its pre-water drinking test level.

This homeostatic return of flow to its normal level also occurs with medications such as miotics, adrenergics and prostaglandins such as latanoprost and travoprost. When the patient is at a homeostatic setpoint for pressure, upon initiating medication (typically within five minutes for adrenergics and 15 minutes for prostaglandins and miotics) the stroke volume of aqueous starts to rise and continues to rise for about an hour or so. As the stroke volume rises, the pressure begins to drop as aqueous is pumped out of the eye. Finally, the pressure moves to a lower homeostatic setpoint.

The eye is one of many vascular loops of the heart, along with the arterial, venous and lymphatic systems. In these systems, the principle remains the same: Return is regulated by valves and a pulsatile mechanism. With each systolic pulse wave, aqueous is discharged from the intrascleral channel into the episcleral vein, driving the episcleral venous blood backwards. As that wave progresses, it drives fluid along the aqueous vein, discharging farther.

Thanks to in vivo phase-sensitive-OCT developed by Dr. Wang’s Imaging Lab, we’re now able to see the response to intraocular pressure gradient changes in patients in real time. Compared to the limited sensitivity of spectral domain-OCT systems using a 810-nm wavelength, a 1,310-nm PhS-OCT system resolves motion of approximately 20 nm and quantifies trabecular meshwork velocity and displacement. Figure 4 shows video screen captures of a PhS-OCT heat map of the trabecular meshwork’s outward motion in red and recoil in blue.

TM-Ciliary Muscle Complex
Pinpointing the causes of glaucoma remains challenging. We hypothesize at least two fundamental pathways: 1) The ciliary body moves forward with age, but pathologically so in glaucoma; and 2) the trabecular meshwork stiffens with age, like other collagen tissues of the body. This stiffening may be accentuated in glaucoma, however. Taken together, these changes in stiffness and elastance of the trabecular meshwork-ciliary muscle complex may underlie intraocular pressure abnormalities.

The ciliary muscle maintains uniform tension throughout the outflow system, from the trabecular meshwork to the septa and collector channels. When the ciliary muscle contracts, it increases tension on the scleral spur and trabecular meshwork lamellae, causing the trabecular meshwork to move away from the external wall of Schlemm’s canal. This increase in stress on the trabecular meshwork changes its elastance and allows it to distend and recoil in a homeostatic range. Loss of ciliary muscle tension and increased intraocular pressure result in Schlemm’s canal collapse.

The trabecular meshwork possesses mechanisms to maintain homeostasis and repair tissue. Like the aorta, which is fairly analogous to this system, elastin provides recoil while collagen maintains stability and resistance. As we age, particularly between ages 40 and 70, elastin fragments and is replaced by collagen. This age-related process leads to tissue stiffening and likely affects the trabecular meshwork lamellae similarly, imped-
ing its ability to move back and forth. The aorta undergoes a 50-percent enlargement with age. As the trabecular meshwork stiffens, it distends into Schlemm’s canal, narrowing its lumen. This change may contribute to Schlemm’s canal wall apposition and closure.

Shear stress issues with age are a fundamental problem in this area, much like in the cardiovascular system. The aorta experiences approximately 31 million distension and recoil cycles annually. So does the trabecular meshwork. Basically, the lumen of Schlemm’s canal is constantly oscillating, also around 31 million times a year, exposing it to significant stresses. As we age, every cardiac pulse wave is driven at a much higher speed because it’s a stiffer system.

The endothelial walls of these vascular pathways are constantly sensing and adjusting shape in response to pressure gradient changes. The vasculature is highly dependent on maintaining a tightly regulated flow pattern, which regulates the dimensions of the vessel walls. Disruption of this flow pattern, such as with the removal of a normal regulatory system (e.g., the trabecular meshwork and Schlemm’s canal inlet valves), results in exposure to abnormal shear stresses, which over time leads to cytokine release, fibrotic changes and involution or closure of the vessel walls.

**A Role in Surgical Planning**

Studying pulsatile flow patterns in the clinic to check for potential outflow structure damage may assist with surgical planning when it comes to identifying MIGS placement locations. While pulsatile flow from the aqueous to episcleral veins is visible at the slit lamp, this approach (i.e., the water drinking test) is time consuming and of limited clinical use. On the other hand, hemoglobin imaging, a new technique that can be employed at the slit lamp in the clinic, offers noninvasive, real-time quantification of flow rate by differentiating aqueous and episcleral venous blood.

Alex S. Huang, MD, PhD, and colleagues reported that injecting a fluid bolus into the anterior chamber during MIGS surgery will displace blood in the episcleral veins, resulting in a pulsatile episcleral vein bolus and regional blanching that indicates the openness of structural pathways from the anterior chamber to the aqueous and episcleral veins. Another approach studied in primates and humans involves injecting dyes into the anterior chamber of Schlemm’s canal to visualize pulsatile behavior. These approaches may assist with MIGS placement.

It’s important to note that MIGS don’t work by a physiologic mechanism since they disrupt the outflow system structures. Nevertheless, they’re an important component in the surgical management of glaucoma and reduce patients’ medication burden as well as the need for trabeculectomies.

**Restoring Normal Pump Function**

Cataract surgery is one procedure that restores normal pump function and avoids structural damage to the outflow system, potentially by improving scleral spur traction. A 2010 paper by Susan A. Strenk, MD, and colleagues...
sugggests that cataract surgery’s intraocular pressure reduction mechanism is related to anterior chamber deepening and the residual lens capsule positioned posterior to Schlemm’s canal. This alignment causes the trabecular meshwork and scleral spur attachments to rotate backward in response to ciliary muscle tension, increasing tension on the trabecular meshwork and enlarging Schlemm’s canal.

As long as there’s ciliary muscle tone, pilocarpine temporarily restores pulsatile flow in glaucoma by increasing ciliary muscle tension. This miotic response may explain some of the effects of transscleral micropulse laser, which induces heat, tightening the ciliary muscle and opening the proximal and distal outflow pathways. The effects of laser trabeculoplasty such as SLT and ALT also induce heat, resulting in collagen shrinkage and potentially increasing trabecular meshwork tension to restore pulsatile outflow.

In summary, the aqueous outflow system is a vascular loop of the circulatory system, where pulsatile tissue motion, chambers and valves work together to control the stroke volume of aqueous discharge and regulate IOP. As a system with collagen- and elastin-containing tissues, its motility decreases with age. It’s believed this stiffness occurs pathologically in the setting of glaucoma. Further research on the restoration of normal pump function may hold clues to developing future glaucoma procedures and therapeutics.  

Further Reading


ABOUT THE AUTHOR

Dr. Johnstone is a clinical professor of ophthalmology at the University of Washington School of Medicine in Seattle. He leads the Johnstone Lab, which studies regulation of aqueous outflow in glaucomas through studies of tissue biomechanics and related morphology. He is a consultant for Alcon and Elsio Vision.
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A chalazion masquerader presents at Wills’ ER.

TALIA N. SHOSHANY, MD, SIWEI ZHOU, MD, PRISCILLA A. LAO, MD, THEODORE S. BOWE, MD, AND JACQUELINE R. CARRASCO, MD

Presentation
A 36-year-old female presented with two weeks of right upper eyelid swelling fluctuating in severity. She endorsed mild itching, tearing and injection, but denied decreased vision, diplopia or pain with extraocular movements. She had no fevers, chills or headaches. These symptoms began several days after returning from a trip to Costa Rica, during which she swam in fresh water and hiked in a muddy swamp. She reported wearing mosquito repellent, sleeping with a mosquito net for the entirety of the trip, and having no known insect bites or direct contact with wild animals. On the trip, she developed two ‘pimple-like lesions’ on her right temple and medial lower eyelid associated with mild itching that had since resolved.

History
Her past medical history is notable for oral herpes simplex virus. Her past ocular history is positive for contact lens wear, false-eyelash use and occasional chalazia. She lives at home with her child, one male partner and two dogs. She gardens outdoors frequently and lives and works indoors in a major Northeast metropolitan area.

She had been using warm compresses and tobramycin-dexamethasone ophthalmic ointment for a presumed chalazion without much improvement and was later prescribed cefalexin by her primary care provider for preseptal cellulitis, which she had self-discontinued after three days due to worsening symptoms. She had also tried a course of trimethoprim-sulfamethoxazole and oral prednisone as well as valacyclovir given to her by a local urgent care. Despite these treatments, the eyelid swelling continued to progress and she began noticing spontaneous bleeding from the lesion which prompted her to seek care at the Wills Eye Emergency Room.

Examination
At this presentation, her vitals were within normal limits and she was afebrile. She had 20/20 vision in each eye, normal intraocular pressures and full extraocular movements. Her external exam was notable for a large, firm, non-tender pre-auricular node on the right as well as moderate right upper eyelid swelling (Figures 1A, 1B). On closer examination she had a small nodule on the right upper eyelid with a 1- to 2-mm opening on the lash line that produced serosanguinous discharge on expression (Figure 1C). The remainder of the slit lamp and dilated exam in both eyes was normal.

What’s your diagnosis? What management would you pursue? The case continues on the next page.
Work-up, Diagnosis and Treatment

Given the lack of improvement with several antibiotics and antivirals and her recent tropical exposure, parasitic and less commonly encountered fungal and bacterial pathogens were considered. The serosanguinous drainage was sent for culture, and peripheral blood testing for several of the above infections was obtained with the help of infectious disease specialists (ultimately yielding no causative microorganism). She was discharged on doxycycline and tobramycin-dexamethasone ophthalmic ointment with close follow-up.

Over the following days the patient noticed worsening right upper lid swelling and returned to the ER. Her exam was similar to prior. She continued to have fullness of the lateral right upper eyelid, which was now visible from the palpebral conjunctiva on lid eversion (Figure 1D). Computed tomography imaging of the orbits with contrast showed right preseptal soft tissue swelling with a small fluid/gas collection (Figure 2).

Decision was made for transconjunctival incision and drainage of the lesion. A white, string-like material was expressed first, followed by a 0.5-cm foreign body with black spines, consistent with the appearance of botfly larva (Figure 3A). The specimens were sent to pathology which eventually confirmed the diagnosis of botfly fragments with surrounding granulomatous inflammation (Figures 3B, 3C). Clindamycin and dexamethasone were injected into the lesion and the patient was continued on her course of doxycycline and ointment and started on oral methylprednisolone with taper. At one week, the lid swelling and other symptoms had improved significantly (Figure 4A); she was found to have an additional raised nodule below the medial canthus. Further incision and drainage was performed of the nodule which revealed two cystic lesions, confirmed as additional larvae fragments on pathology (Figure 4B).

Discussion

Infestation with the human botfly (Dermatobia hominis) is an uncommon cause of skin swelling. Ophthalmomyiasis externa is human botfly larval infestation of the external eye which is a rare cause of eyelid swelling. The human botfly is endemic to Central and South America, however North American botfly myiasis has also been reported with the Cuterebra, or North American botfly, larvae. Once transferred to the human skin, the abrupt change in temperature causes the eggs to hatch. The larvae bury deeper into the skin causing an inflammatory reaction that produces encapsulation and helps the larvae evade the human immune system. Patients infected with botfly larvae will often describe a slow growing nodule which may be confused with a chalazion or preseptal cellulitis. On close examination the nodule is usually found to have a small opening or central pore consistent with the breathing hole, which produces serosanguinous expression when palpated, as was seen in this case. This breathing hole is required for the larvae to stay alive under the skin and if blocked can cause botfly death and worsening focal inflammatory reaction. Patients often have no other systemic symptoms, but peripheral blood may show leukocytosis with eosinophilia. Treatment may be achieved non-surgically with suffocation by obstructing the breathing hole with ointment, injecting lidocaine, or by manual extraction with incision and drainage. Oral anti-helminthics such as ivermectin have been reported to be useful in severe cases or when surgical extraction is not possible. Expectant manage-
ment is also plausible as the larvae eventually expel themselves, as mentioned above. 5

Although the skin is the most common location for botfly infestation, they can also be found inside the globe.5,10 In ophthalmomyiasis interna, the larvae enter the posterior segment. Most commonly they burrow under the retina, where they can be seen on dilated fundus exam. They leave characteristic appearing ‘tracks’ when they move within the subretinal space, and rarely can even be found within the vitreous cavity. The treatment options include observation if the larva is dead or near the fovea, laser photocoagulation if outside the macula, or vitrectomy (with or without administration of intraocular steroids) if the larva is within the vitreous cavity.5 In cases of ophthalmomyiasis interna treated with laser, careful follow up is required as death of the larvae can lead to a rampant intraocular inflammatory response.10 Ophthalmomyiasis interna is often diagnosed late in the disease course with resultant significant visual morbidity.9

Although rare, Dermatobia hominis infestation should be considered in a patient with skin lesions not responding to conventional treatment, especially in patients who have had recent travel to endemic areas. Infestation with the Cuterebra species may be seen more frequently in North America, particular in the Northeast or Pacific Northwest in the summer months, and may present similarly.2,3

Figure 4. (A) Improvement in upper lid swelling one week after incision and drainage. (B) Incision and drainage of medial canthal nodule revealing two additional cystic lesions with botfly fragments at one week follow-up.

HIghlights of Prescribing Information

This brief summary does not include all the information needed to use IYUZEH safely and effectively. See full prescribing information for IYUZEH.

Initial U.S. Approval: 2022

Indications and Usage

IYUZEH is a prostaglandin F2α analogue indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

contraindications

Known hypersensitivity to latanoprost or any other ingredients in this product.

Warnings and Precautions

pigmentation: Topical latanoprost ophthalmic products, including IYUZEH have been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered.

The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of latanoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

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

EyeLash Changes: Latanoprost ophthalmic products, including IYUZEH may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: IYUZEH should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation because inflammation may be exacerbated.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost ophthalmic products, including IYUZEH. IYUZEH should be used with caution in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Herpetic Keratitis: Reactivation of herpes simplex keratitis has been reported during treatment with latanoprost. IYUZEH should be used with caution in patients with a history of herpetic keratitis and should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Contact Lens Use: Contact lenses should be removed prior to the administration of IYUZEH and may be reinserted 15 minutes after administration.

—Adverse Reactions—

The following adverse reactions have been reported with the use of topical latanoprost products and are discussed in greater detail in the prescribing information:

• Iris pigmentation changes
• Eyelid skin darkening
• Eyelash changes (increased length, thickness, pigmentation, and number of lashes)
• Intraocular inflammation (iritis/uveitis)
• Macular edema, including cystoid macular edema

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.

In the two clinical trials conducted with IYUZEH (latanoprost ophthalmic solution 0.005%) comparing it to XALATAN the preserved 0.005% latanoprost reference product, the most frequently reported ocular adverse reactions were conjunctival hyperemia and eye irritation (Table 1).

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of topical latanoprost products. 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. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ophthalmic latanoprost products, or a combination of these factors, include:

• Nervous System Disorders: Dizziness; headache; toxic epidermal necrolysis
• Eye Disorders: Eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes); keratitis; corneal edema and erosions; intraocular inflammation (iritis/uveitis); macular edema, including cystoid macular edema; trichiasis; periorbital and lid changes resulting in deepening of the eyelid sulcus; iris cyst; eyelid skin darkening; localized skin reaction on the eyelids; conjunctivitis; pseudopterygium of the ocular conjunctiva.
• Respiratory, Thoracic and Mediastinal Disorders: Asthma and exacerbation of asthma; dyspnea
• Skin and Subcutaneous Tissue Disorders: Pruritis
• Infections and Infestations: Herpes keratitis
• Cardiac Disorders: Angina; palpitations; angina unstable
• General Disorders and Administration Site Conditions: Chest pain

Drug Interactions

The combined use of two or more prostaglandins, or prostaglandin analogs including IYUZEH is not recommended, and administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical IOP elevations.

Use in Specific Populations

Pregnancy: There are no adequate and well-controlled studies of IYUZEH administration in pregnant women to inform drug-associated risks.

Lactation: It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when IYUZEH is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IYUZEH and any potential adverse effects on the breastfed child from IYUZEH.

Pediatric Use: The safety and effectiveness of IYUZEH have not been established in pediatric patients.

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

Overdosage

Intravenous infusion of up to 3 mcg/kg of latanoprost in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment with latanoprost ophthalmic solution and no adverse reactions were observed. IV dosages of 5.5 to 10 mcg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea, and sweating.

Handling the Container

IYUZEH is a sterile solution that does not contain a preservative supplied in a single-dose container. The solution from one individual container is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be maintained after the individual container is opened, the remaining contents should be discarded immediately after administration. Open a new single-dose container every time you use IYUZEH.

Manufactured by: Thea Pharma Inc. Waltham, MA. All rights reserved. U.S. Patent No. 8,637,054. Revised: 04/2023 ©2023 Laboratoires Théa. All Rights Reserved. IYUZEH™ is a trademark of Laboratoires Théa.

Table 1. Adverse Reactions

<table>
<thead>
<tr>
<th>Symptom/Finding</th>
<th>IYUZEH (n=378)</th>
<th>XALATAN (n=358)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hyperemia</td>
<td>129 (34)</td>
<td>133 (37)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>72 (19)</td>
<td>112 (31)</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>57 (15)</td>
<td>58 (16)</td>
</tr>
<tr>
<td>Abnormal sensation in eyes</td>
<td>51 (14)</td>
<td>52 (19)</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>44 (12)</td>
<td>36 (10)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>28 (7)</td>
<td>30 (8)</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>19 (5)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>13 (3)</td>
<td>17 (5)</td>
</tr>
</tbody>
</table>
I prescribe IYUZEH because it has no preservatives, and the data clearly showed that it lowered IOP at rates comparable to XALATAN®. That makes IYUZEH a go-to treatment for my patients.

Jason M. Bacharach, MD
Dr. Bacharach is a paid consultant of Thea Pharma Inc.

INDICATIONS AND USAGE
IYUZEH™ (latanoprost ophthalmic solution) 0.005% is a prostaglandin F2α analogue indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
Known hypersensitivity to latanoprost or any other ingredients in this product.

WARNINGS AND PRECAUTIONS
IYUZEH may cause changes to pigmented tissues. Most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as IYUZEH is administered. Iris pigmentation is likely to be permanent. Eyelid skin darkening and eyelash changes may be reversible.

IYUZEH may cause gradual change to eyelashes including increased length, thickness, and number of lashes. These changes are usually reversible upon discontinuation of treatment.

IYUZEH should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

IYUZEH should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Reactivation of herpes simplex keratitis has been reported during treatment with latanoprost. IYUZEH should be used with caution in patients with a history of herpetic keratitis.

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

ADVERSE REACTIONS
The most common adverse reactions (5% to 35%) for IYUZEH are: conjunctival hyperemia, eye irritation, eye pruritus, abnormal sensation in eye, foreign body sensation in eyes, vision blurred, and lacrimation increased.

DRUG INTERACTIONS
The combined use of two or more prostaglandins or prostaglandin analogs including IYUZEH is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

Please see full Prescribing Information at www.iyuzeh.com and Brief Summary on the next page.